Jacques Bernier
Editor

Head and Neck Cancer

Multimodality Management

Second Edition

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Preface

Throughout the last decade, advances in head and neck cancer management mainly resulted from breakthroughs in translational research and closer interactions among specialists, in both the diagnostic and therapeutic domains. The last 5 years were particularly rich in novel approaches ranging from functional imaging to radiotherapy optimization and from targeted therapies to innovations in surgery and reconstruction. A better understanding of factors influencing the natural history of the disease and tumor response to treatment was also shown to impact the decision-making processes.

In this perspective, the second edition of *Head and Neck Cancer: Multimodality Management* is an essential guide which encompasses the most recent evidence relating to contemporary management of this disease. Its preparation required a critical appraisal of what had been done before, by boosting the positive aspects and avoiding redundancy between chapters. Each domain of knowledge has therefore been updated and new issues as, for instance, transoral robotic surgery, dental oncology, and psycho-oncologic aspects are now addressed in the Textbook. Moreover, the content of a significant number of chapters is illuminated with clinical images and illustrations.

The first part revisits the most recent data on the epidemiology and etiology of head and neck carcinomas and covers the biomolecular bases of future treatment strategies and highly personalized medicine in this domain of oncology.

The second part is mainly dedicated to key diagnosis modalities, not only in terms of refinement of morphological imaging but also with respect to preclinical and clinical research on tumor metabolism.

In the third part of the Textbook, a systematic account of the current management of individual cancers in function of their site of origin is organized to provide an exhaustive analysis of organ-oriented strategies.

The fourth and last part addresses a number of more specific issues not always traceable in other textbooks, including quality assurance programs, patient rehabilitation, salvage treatments.

Thanks to their very high expertise level, the authors once again provide a timely account of our present knowledge in all facets of the head and neck cancer management. A comprehensive approach representing a wide spectrum of specialists including surgical, radiation, and medical oncologists, as well as dentists, pathologists, radiologists, and nurses, this textbook actually shows how considerable are the efforts put forth in translational and clinical research to optimize our ways to plan and deliver our treatments.

With expanded and revitalized coverage of newest concepts and novel clinical applications, this Second Edition is an essential reference and source of knowledge for both entrusted oncologists and practitioners less experienced in head and neck oncology. We want to express all our gratitude to the scientists and clinicians who accepted our invitation: all preeminent in their area of expertise, they have once again reaffirmed their attachment to the mission of promoting a truly interactive multidisciplinary approach to treat head and neck cancer patients and, as importantly, their full commitment to education.

Genolier, Switzerland — Jacques Bernier

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About the Editor

Jacques Bernier, MD, PhD After obtaining his degree in Radio-Oncology at the University of Liege, Belgium, Jacques Bernier completed his training at the MD Anderson Cancer Center, Houston, and the Curie Institute, Paris. In 1988, he moved to Switzerland, where, in 1995, he received a Privat-Docent Chair from the Geneva University. In 2006, he joined the Swiss Genolier Medical Network, where since then he has been chairing the Radio-Oncology Department. Throughout most of his career, Jacques Bernier has been heavily involved with translational and clinical research. In 1993, he received the Yalow-Berson Award, in St Louis, USA, for his laboratory work on interferons and interleukins. In the recent past, he has been instrumental in introducing the concept of postoperative chemo-radiation in head and neck cancers and leading a seminal EORTC study, the results of which were published in the New England Journal of Medicine. From 2000 to 2006, Jacques Bernier was Chairman of the Head and Neck Group of the EORTC. In 2009, he pioneered in Switzerland the use of intra-operative radiotherapy (ELIOT). He served as an Editorial Board member of "Journal of Clinical Oncology" till 2012 and an Associate Editor of "Annals of Oncology" till 2013. He is currently Associate Editor of "Oral Oncology." Author of more than 130 publications in peer-reviewed international Journals, he was awarded, in 2010, the "Claudius Regaud Medal" by ESTRO. A Course Director at the European School of Oncology since 1990 and, in the nineties, a member of the Quality Assurance Committee of the EORTC, he is currently the Chairman of the International Conference on Translational Research in Radio-Oncology—ICTR, organized every two years in Switzerland. He is currently a member of a Quality Assurance Group within one of the European Commission Initiatives. Department of Radio-Oncology, Genolier Swiss Medical Network, Genolier, Vaud, Switzerland

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Epidemiology and Aetiology of Head and Neck Cancers

1

Newell W. Johnson and Hemantha K. Amarasinghe

Abstract

Malignant neoplasms of the head and neck are among the most common in the world and constitute a major public health problem in most countries. Over 90 % of these are squamous cell carcinomas arising in the mucous membranes of the upper aerodigestive tract (UADT). Their epidemiology and aetiology are considered in detail. We separate nasopharyngeal cancer, because it has a specific aetiology related to Epstein–Barr virus (EBV) infection and dietary carcinogens. We then add those sites with the common major risk factors of alcohol, tobacco (including betel quid/areca nut habits), poor dentition and diets poor in antioxidants and vitamins and an increasingly recognised role for human papillomavirus (HPV). By simplistically adding age-standardised rates together, collectively these UADT sites of the oral cavity (including the tongue), nasopharynx, other pharynx and larynx have a male incidence/mortality of 14.3/7.9 and for females of 4.4/2.3 cases per 100,000 pa. This ranks UADT cancer as the sixth most common site for men and eighth for women across the world. If the oesophagus were to be included as another alcohol- and tobacco-related cancer, the rates add to 23.3/15.6 and 7.5/5.0, respectively. These cancers—which might be termed cancers of the mouth, pharynx, throat and gullet—then rank second only to lung cancer in men, and fourth after breast, uterine cervix and large bowel in females, worldwide.

Detailed data are presented on geographical, ethnic, gender and time differences. The highest rates in the world are found in Melanesia, South Asia, parts of France and much of Eastern Europe and the former Soviet republics. Whilst the rates are now trending downwards for the "traditional" alcohol- and tobacco-related cancers in much of the developed world, the numbers remain high and constitute a considerable personal and public health burden. Many areas are showing rising trends, particularly for oropharyngeal cancer, with a shift to involvement of younger individuals. This, and the fact that survival rates have improved little, except for the most sophisticated multidisciplinary treatment centres, emphasises the need for effective primary and secondary prevention strategies—and for improved public policy to implement these.

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Cancer • Head and neck (H&N) • The upper aerodigestive tract (UADT) • The mouth • The larynx • The nasopharynx • Oral potentially malignant disorders (OPMD) • Tobacco • Alcohol • Nutrition • Human papillomavirus (HPV)

Abbreviation List

EBV	Epstein–Barr virus
GATS	Global Adult Tobacco Survey
H&N	Head and neck
HHV	Human herpesviruses
HN	Head and neck
HO	Hydroxyl radical
HPV	Human papillomavirus
IARC	International Agency for Research on Cancer
IIPS	International Institute for Population Sciences
INHANCE	International Head and Neck Cancer Epidemiology Consortium
KS	Kaposi sarcoma
MNPN	Methylnitrosaminoproprionitrile
NNK	Nicotine-derived nitrosamine ketone
NNN	Nitrosonornicotine
NPC	Nasopharyngeal cancer
OPC	Oropharyngeal cancer
OPMD	Oral potentially malignant disorders
OSF	Oral submucous fibrosis
OSCC	Oral squamous cell carcinoma
PAH	Polycyclic aromatic hydrocarbons
PNG	Papua New Guinea
ROS	Reactive oxygen species
SCCs	Squamous cell carcinomas
SEER	Surveillance, Epidemiology, and End Results program
ST	Smokeless or chewing tobacco
TSNA	Tobacco-specific nitrosamines
UADT	Upper aerodigestive tract
WHO	World Health Organisation

1.1 Introduction and Scope

The term *head and neck [HN] cancer* is usually taken to cover the range of malignant neoplasms of soft tissue origin that develop in the oral cavity including the lips, nasal cavity, paranasal sinuses, pharynx, larynx and salivary glands. The skin will be included in many descriptions, but not usually ocular and intracranial neoplasms nor those of endocrine or lymphatic origin—thus excluding thyroid and parathyroid cancers and lymphomas. Sarcomas, though more rare, must be included among these soft tissue neoplasms of the head and neck, be they of connective tissue, neural or vascular origin.

Summary data will be given on primary bone "tumours" and on those of odontogenic origin, though their pathology and management are not covered in detail in this volume. Readers are referred to the several excellent modern textbooks of surgical pathology and of oral and maxillofacial pathology: especially recommended are Fletcher DEM, Ed, Diagnostic Histopathology of Tumours, 4th Edn., Elsevier 2013 and Gnepp DR, Ed., Diagnostic Surgical Pathology of the Head and Neck, 2nd Edn., Elsevier 2009. Reliable concise accounts created by a team of international experts appear in the series of WHO "blue books", viz. Pathology and Genetics of Head and Neck Tumours, Brown L et al. Eds., IARC Press, 2005.

Metastases from distant primaries to the jaws (and occasionally to mucous membranes) must always be considered.

Most head and neck cancers, indeed 90 % or more, are squamous cell carcinomas (SCC) and variants thereof, originating from the epithelium of the mucosal lining of the upper aerodigestive tract (UADT), and adenocarcinomas from associated secretory glands. Carcinomas everywhere in the head and neck spread readily to the lymph nodes of the neck, and this is often the first (and sometimes only) manifestation of the disease at the time of presentation. Head and neck SCC is strongly associated with environmental and lifestyle risk factors, particularly tobacco use, both smoked and "smokeless", the chewing of areca nut (aka betel nut), regular alcohol consumption, diets poor in antioxidant vitamins and minerals, UV light from the sun, indoor and outdoor air pollution, occupational exposures to radiation or chemical carcinogens and, increasingly, to certain viruses, perhaps sexually transmitted, notably "high-risk" genotypes of the human papillomavirus family (particularly HPV 16 and 18, particularly when originating in the tonsil, base of tongue and elsewhere in the oropharynx), and some human herpesviruses (HHVs: Epstein–Barr virus with nasopharyngeal carcinoma and HHV-8 with Kaposi sarcoma at all sites and some lingering possibilities of HHV-1 as a "hit and run" agent). There is a modest inherited susceptibility. Chronic trauma and chronic inflammation are re-emerging as significant cofactors.

Around the world, with the exception of HPV-related cancers, HNSCC is predominantly a disease of the poor: inequalities and contributing factors are analysed by Johnson et al. [1].

SCCs of the H&N are frequently aggressive in their biologic behaviour: patients with many of these types of cancer have very destructive disease above the clavicle, develop local (cervical) lymph node metastases early and develop distant metastases over time—even following effective local therapy—and a high proportion have recurrence of the primary lesion and/or develop a second primary neoplasm. This is especially so if risky lifestyles continue: UADT cancers ought in fact to be considered systemic diseases; not only is there "field of change" with molecular lesions involving much or all of the regional mucosae but also damage to the immune system and host defences generally and damage to key organs especially the liver. Indeed comorbidities are common—especially respiratory and cardiovascular—resulting from common risk factors, especially tobacco and alcohol abuse and poor nutrition.

HNSCC is curable if detected early, usually with some form of surgery. For more advanced lesions, in modern best practice, surgery is usually accompanied by preceding or subsequent radiotherapy, with or without adjuvant chemotherapy. We are now entering an era of individualised biotherapies for many cancers, based on understanding of the precise molecular aberrations within a given neoplasm and of the patient's individual genetic polymorphisms, though more clinical trials of such approaches need to be completed. Indeed, at the time of writing for this second edition, directing monoclonal antibodies at blocking the family of epidermal growth factor receptors on the surface of malignant keratinocytes, in neoplasms with overexpression of these molecules, is the only biotherapy approved by the US Food and Drug Administration for HNSCC.

The evidence base, with a focus on cancer of the oral cavity and the oropharynx, is exhaustively presented in Shah JP and Johnson NW, Oral Cancer, CRC Press | Taylor & Francis Group, 2nd Edition, In Press, 2016.

1.2 History

Evidence of head and neck malignancies has been found in ancient skulls. The oldest known tumour is contained in a fossil found in East Africa by Leakey that dates back more than 500,000 years. Some historians speculate that a high incidence of nasal cancer may have been present in some ancient populations because of the inhalation of wood smoke in poorly ventilated huts. In approximately 400 BC, Hippocrates described a common chronic ulcer at the edge of the tongue that he attributed to the presence of sharp teeth rubbing against the tongue: a challenge to differential diagnosis which is still real today!

Even earlier, in the sixth century BC, the classical Sanskrit text on surgery, Sushruta Samhita (सुश्रुतसंहिता), described the removal of tumours from the head and neck. Modern Western Medicine received its foundation from early Roman medical writings. Nevertheless, real advances in the management of head and neck cancers had to wait until the advent of comparatively safe and effective anaesthesia and surgical excision in the eighteenth century.

1.3 Cancer Registries

Cancer registries play a vital role in monitoring the incidence of and mortality from cancers. However, the quality of data available is highly variable. Many parts of the world produce no data at all, in others (often among the most populous), the data may come from localised, atypical regions. Hospital-based cancer registries naturally gather biased information—those cases which present to hospital only; thus, in many developing countries, cases may not come to attention at all, either because of fear or the inability of poor people to access hospital services. Data may be even more unreliable because, in many resource-poor countries, follow-up, even of treated cases, is impossible. Death certification is not always compulsory, and there is limited international standardisation in the categories for cause of death, let alone calibration of those signing death certificates.

Fortunately, many nations have high-quality national, often incorporating regional, population-based cancer registries, with compulsory reporting of all malignancies. These are guided by, and quality-assured by, both national authorities and the positive influence of the World Health Organisation (WHO), mostly through its constituent body, the International Agency for Research on Cancer headquartered in Lyon, France. Data from all over the world are collated and are available from the websites of both these bodies: this includes free access to programmes that allow online interrogation of the databases. Many of the tables and graphs in this chapter have been generated in this way. Within the USA, the SEER website provides similar sophisticated opportunities to registered users (SEER is the Surveillance, Epidemiology, and End Results program of the National Cancer Institute. It is based on data from, nowadays, 20 population-based registries, but these by no means cover the whole nation. See http://seer.cancer.gov/registries/list.html).

1.4 Why Collect Detailed Epidemiological Data?

Cancer epidemiology is a demanding but essential science. Some acquaintance with epidemiological method and data is required by all who participate in cancer care, from politicians, public health officials, hospital managers, individual clinicians in both general and the wide range of specialist

practitioners concerned with diagnosis and treatment, those providing palliative care, nurses, speech and swallowing therapists, dieticians, social workers to spiritual advisors. *Descriptive epidemiology* provides the fundamental evidence base, but its value is dependent on the accuracy and completeness of the information therein: reliable, sufficiently detailed and safely stored hospital-based information is sine qua non. Increasingly, hospital records contain information on lifestyle and other known or suspected risk factors. The growth of biological "tumour banks" or "tissue banks" from which molecular markers and indeed molecular mechanisms can be researched is encouraging: this needs co-ordinated international action. There are several large, often international, consortia using such banks to unravel the genome of all cancers: notably the International Cancer Genome Project which has several collaborating centres dealing with head and neck (https://icgc.org/), the Cancer Genome Atlas in the USA (http://www.genome.gov/17516564) and the Wellcome Trust Sanger Institute Cancer Genome Project in the UK (https://www.sanger.ac.uk/research/projects/cancergenome/).

Population-based registries, as described above, are of even greater value. These permit *analytical epidemiology* and thus the ability to address essential questions such as: Why is the incidence of a particular type or site of neoplasm rising or falling over time or in a particular ethnic group or age group? How should this inform government and public health policy? Are existing public awareness and screening campaigns effective and efficient? How do different treatment modalities compare? How does my hospital or my personal clinical practice compare to the national average or world's best practice? In respect of the latter, there is an ethical imperative for every clinician to keep detailed records, using standardised measures, of the outcomes of his or her care. Guidelines for care pathways and "minimum data sets" to facilitate quality control and recording of outcomes are available: those from the British Association of Head and Neck Oncologists (http://www.bahno.org.uk/docs/) and from the American Head and Neck Society (http://www.headandneckcancer.org/) can be recommended. In many countries, cancer is a notifiable disease, and both the registration of all cases and the provision of information on the patient, on the care provided and on the outcomes—not just survival rates but information on complications and on quality-of-life measures—are mandatory. The guidelines from the National Comprehensive Cancer Network in the USA are invaluable (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site). There remains, however, a continuous need to evaluate the quality and strength of the evidence base for all published guidelines, preferably using the strict criteria of the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation: http://www.gradeworkinggroup.org/intro.htm).

1.5 The Global Scenario of Head and Neck Cancer: Differences by Country

Depending on the number of anatomical sites and subsites included, head and neck cancer (ICD-10: C00–C14) is the seventh most common type of cancer, representing about 4.3 % of all cases and accounting for an estimated 599,637 new cases and 224,834 cancer deaths worldwide every year. Figure 1.1 compares several H&N cancers with cancers affecting other body sites: the number of new cases and of deaths attributed to cancer at these anatomical sites are given for males and females, in which males predominate in all H&N sites.

Head and Neck Cancers Are Among the Top Ten in the World Most malignancies of the head and neck are squamous cell carcinomas of the lip and oral cavity (ICD-10: C00–C06), of the oro- and hypopharynx (C09–C10, C12–C14) and of the larynx (C32). These share common risk factors of tobacco and alcohol, diets poor in antioxidants and vitamins and a role for human papillomavirus. Although having a different aetiology, malignant neoplasms of the major salivary glands (ICD-10: C07–C08) are often grouped with these sites. Together these sites rank men sixth in the world and women thirteenth. It is important to record nasopharyngeal cancer (C11) separately because it has a specific aetiology related to EBV infection and dietary carcinogens. Adding nasopharynx pushes head and neck cancer higher up the scale. If the upper two-thirds of the oesophagus were to be included as another alcohol- and tobacco-related cancer, the rates increase dramatically. These cancers—which might be termed **cancers of the upper aerodigestive tract**—then **rank third after lung and prostate cancer in men, and seventh after breast, colorectal, lung, uterine cervix, stomach and corpus uteri in females**, worldwide.

According to GLOBOCAN 2012, the highest incidence of oral cancers (ICD C00–C08) is found in Melanesia (astounding rates of 22.9 per 100,000 in men and 16.0 per 100,000 in women, though there are caveats about the quality of these data) [2]. In India alone over 100,000 cases of oral cancer are registered every year, and the numbers are rising. Though men predominate overall, among females a very high incidence is found throughout South Central Asia (4.7 per 100,000). In terms of countries, Maldives and Sri Lanka have the highest incidence of oral cancer in the South Asian region. Poor access to health services contributes to high mortality.

Data extracted from the Cancer Incidence in Five Continents Database for the period 2003–2007 [3] also facilitate a global overview. When considering oral and pharyngeal cancer, the annual estimated incidence is around 300,373 cases for lip and oral cavity (ICD-10: C00–C08) and 142,378

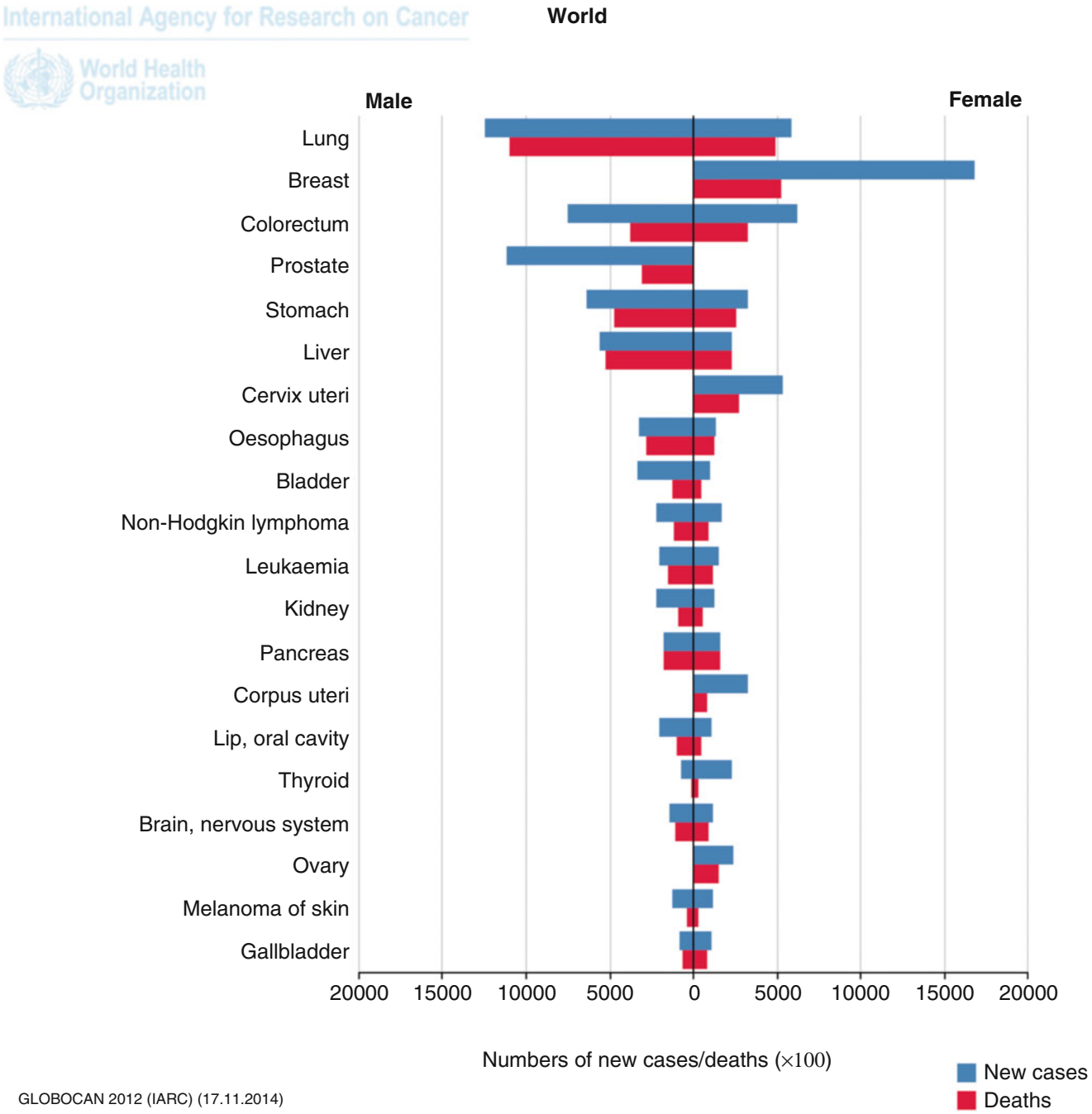


Fig. 1.1 Global scenario of the burden of cancer: new cases and deaths per annum, in 2012, for the top 20 cancers

for other pharyngeal cancers (C09–C10, C12–C14) *excluding nasopharynx*: two-thirds of these cases occur in developing countries [2]. There is a wide geographical variation in the incidence of oral cancer, of nasopharyngeal cancer, of "other pharynx", of the larynx and of the oesophagus (Table 1.1).

For oral cancer, the highest crude rates in the world are found in Melanesia, Maldives, Sri Lanka, Bangladesh, France and Hungary [2]. There are marked differences between countries in the same geographical region. The extremely high rates in the relatively small populations of the Melanesian Islands have not been comprehensively researched, but data from Papua New Guinea (PNG) (see below) define the importance of areca nut [betel] chewing [called Buai in PNG] and smoking habits as the major risk factors.

Table 1.1 World standardised *incidence* rates per 100,000 for upper aerodigestive tract cancers

	Mouth (ICD-10: C00–C08) Being lip, all of tongue, all of mouth and major salivary glands		Nasopharynx (ICD-10: C11) Data for C30, malignant neoplasm of nasal cavity and middle ear For C31, malignant neoplasm of accessory sinuses For C32, malignant neoplasm of larynx *are not included here*		Remainder of pharynx (ICD-10: C09–C10 plus C12–C14) Being tonsil, remainder of oropharynx, pyriform fossa, hypopharynx and sites not otherwise specified among C00–C13		Larynx (ICD-10: C32)		Oesophagus (ICD-10: C15) This code *excludes* cancers arising at the gastro-oesophageal junction which are included in stomach cancers, the majority of which are adenocarcinomas. *Included here*, therefore, are mostly SCC sharing common risk factors with the mouth	
Country	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
World	5.5	2.5	1.7	0.7	3.2	0.7	3.9	0.5	9.0	3.1
More developed	7.0	2.6	0.6	0.2	4.7	0.8	5.1	0.6	6.4	1.2
Less developed	5.0	2.5	2.0	0.8	2.8	0.7	3.5	0.4	10.1	4.1
Africa	3.3	2.0	1.5	0.8	1.1	0.6	2.7	0.3	5.6	3.5
Eastern Africa	4.5	2.8	1.9	1.1	1.0	0.6	2.3	0.3	11.9	7.8
Middle Africa	3.5	1.8	1.3	0.6	1.7	0.6	1.4	0.2	4.2	2.0
Northern Africa	2.8	1.8	2.3	1.0	0.8	0.7	4.2	0.4	2.4	1.5
Southern Africa	6.3	2.3	0.4	0.2	3.9	1.5	5.0	0.9	13.7	6.7
Western Africa	1.7	1.4	0.7	0.4	0.6	0.1	1.4	0.1	0.8	0.4
Caribbean	4.8	1.8	0.4	0.2	3.6	0.9	7.9	0.9	4.6	1.2
Central America	2.6	1.7	0.2	0.1	1.0	0.3	4.0	0.6	1.7	0.6
South America	5.3	2.4	0.5	0.2	3.0	0.5	5.2	0.7	7.0	2.0
Northern America	7.2	3.2	0.7	0.3	4.2	1.0	4.0	0.9	5.4	1.1
Asia	5.2	2.5	2.3	0.9	3.1	0.7	3.3	0.4	11.4	4.3
Eastern Asia	2.4	1.1	2.5	1.0	1.3	0.2	2.2	0.2	16.9	5.4
Southeastern Asia	4.0	2.5	6.4	2.4	2.6	0.7	2.7	0.5	3.6	1.0
South Central Asia	9.9	4.7	0.6	0.2	6.2	1.4	4.6	0.6	6.5	3.9
Western Asia	2.7	1.6	1.3	0.5	0.8	0.4	6.5	0.9	2.9	2.1
Europe	7.5	2.5	0.6	0.2	5.2	0.9	6.2	0.6	5.8	1.2
Central and Eastern Europe	9.1	2.0	0.6	0.2	5.3	0.5	7.9	0.4	5.6	0.8
Northern Europe	5.9	3.1	0.4	0.2	3.4	1.0	3.4	0.6	8.1	2.7
Southern Europe	5.8	2.1	0.7	0.3	3.4	0.5	7.2	0.6	3.2	0.6
Western Europe	7.9	3.2	0.5	0.2	7.5	1.6	4.9	0.7	6.8	1.6
Australia	8.8	3.9	0.6	0.3	3.3	0.7	3.1	0.3	5.4	1.7
New Zealand	5.5	2.7	0.9	0.3	2.4	0.4	2.3	0.4	5.6	1.8
Melanesia	22.9	16.0	0.4	0.1	3.4	0.4	2.7	0.6	3.6	1.4
Micronesia	4.9	0.0	3.3	2.0	0.0	0.0	0.0	0.0	3.3	0.0
Polynesia	4.1	1.8	2.0	0.8	3.8	0.0	3.2	0.4	3.0	0.3

Data derived from the Globocan 2012 database: anatomic descriptors derived therefrom [2]

1.6 Territory Size Shows the Global Burden of Deaths from Oral Cancer and the Relationship to the Proportion of who Smoke and Live There

The prevalence of smoking increased dramatically during the world wars, mainly due to the policy of providing free cigarettes to allied troops as a 'morale boosting' exercise. (The Cancer Council, 2006 (Fig. 1.2))

It is important to realise that the above data relate only to smoking and do not include the many forms of oral smokeless tobacco (ST) in common use around the world. The Global Adult Tobacco Survey (GATS) is the global standard for systematic monitoring of adult tobacco use (smoking and smokeless) in the world. In India alone, the GATS (India) survey, conducted in 2009–2010 by the International Institute for Population Sciences (IIPS) Mumbai, covered about 99.9 % of the total population of India. This revealed that more than one-third (35 %) of adults in India used tobacco in

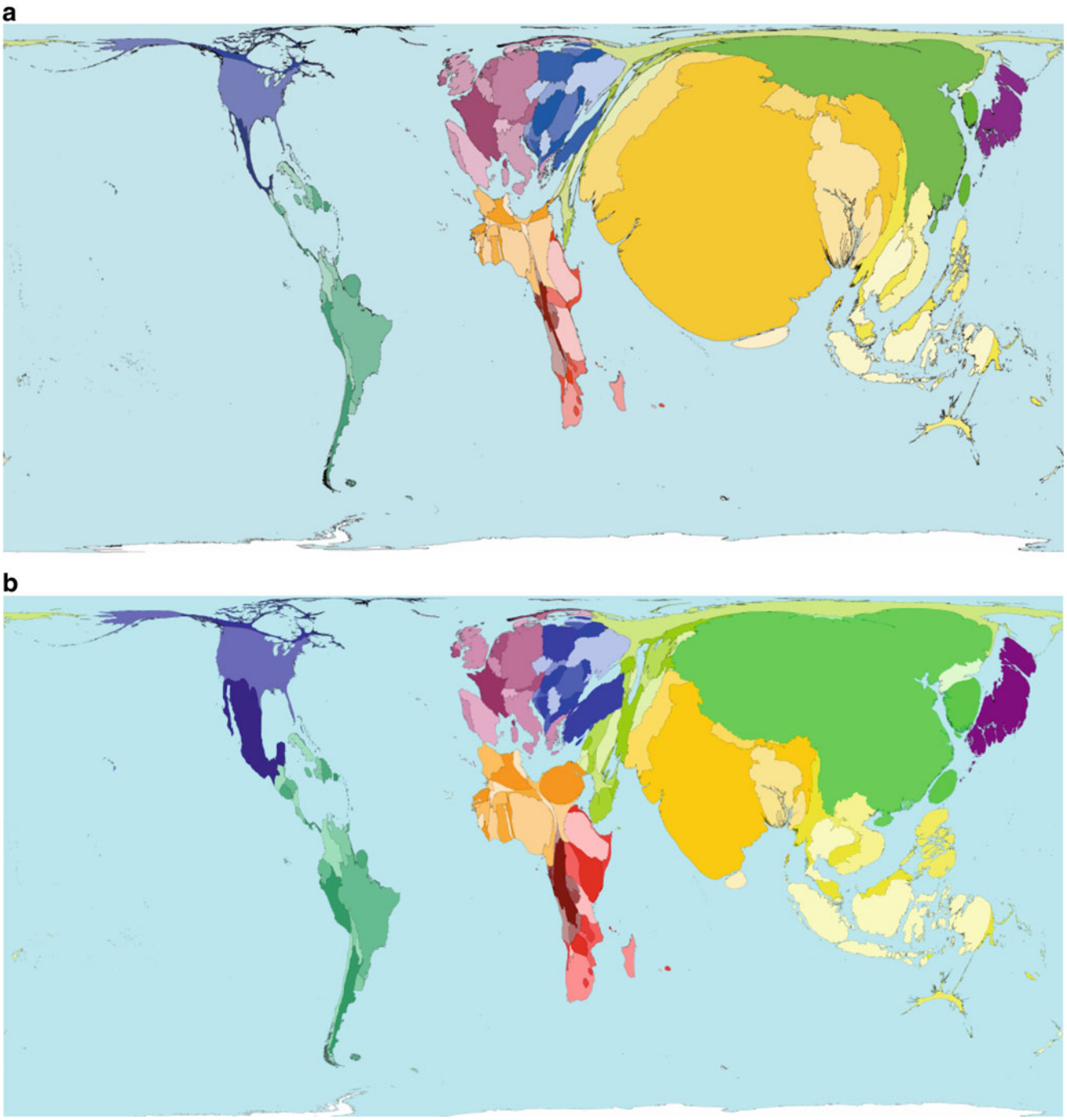


Fig. 1.2 Mouth cancer deaths, IARC 2002 International Classification of Diseases-10 codes: C00–C14. http://www.worldmapper.org/display_extra.php?selected=419. Accessed November 2014. These two maps (shown only for males here) distort countries on the basis of the number of deaths by mouth and pharynx cancer (**a**) and the number of men smokers (**b**). They show that the public health burden is borne by Eastern Europe, Central and Eastern Asia and South Asia. China is the major storehouse of tobacco-related morbidity and mortality in the world, a nation where more than half the population continues to smoke. Yemen, Indonesia and Mongolia and Armenia followed by Kenya are the top five-ranked countries for smoking prevalence, at 77 %, 69 %, 68 % and 67 %, respectively. Territory size shows the proportion of men who smoke and live there. (**a**) Number of deaths by mouth and pharynx cancer in males. http://www.worldmapper.org/display_extra.php?selected=419 Accessed on 20-11-2014. (**b**) Number of male smokers. http://www.worldmapper.org/display.php?selected=242 Accessed on 20-11-2014. (**a** and **b**): [© Copyright Sasi Group (University of Sheffield) and Mark Newman (University of Michigan)]

some form or the other (48 % of males and 20 % of females): 21 % adults used only smokeless tobacco, 9 % only smoke and 5 % smoke and use smokeless tobacco. Thus, in India, there are ~275 million tobacco users, 164 million users of only smokeless tobacco, 70 million only smokers and more than 42 million users of both smoking and smokeless tobacco. The distribution of tobacco use in India has been well mapped by Bhawna Gupta [4].

Worldwide there are four times more men that smoke than women. In 2002 there were 941 million male smokers, which was 43 % of all men aged over 15 years old. The largest population of male smokers lives in China—where men are more likely to smoke than not to smoke. Even Puerto Rico and Sweden, with the lowest percentages of men who smoke, still have 17 % who are smokers.

When smoking is this widespread, smokers do not just damage their own health but also collectively damage the health of people around them. Passive smoking by children can increase the risks of asthma, cot deaths and chest infections.

The world maps reproduced below (Figs. 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9 and 1.10), though simplifying data by aggregation to national averages, contain important information. As with the tables, maps are shown for each of the important head and neck sites. It has been apparent for decades that the global picture for head and neck cancer is dominated by the incidence of oral cancer in Southern Asia and of oral cavity plus nasopharyngeal cancer in East Asia. In the 1980s, in India, Bangladesh, Pakistan and Sri Lanka, oral cancer was the most common site and accounted for about one-third of all cancers: it is still the most common cancer among men in Sri Lanka [5–7]. The proportion is falling, partly due to increased detection of other cancers by more extensive screening programmes and improved techniques [7]. Even within the subcontinent, there are striking differences in incidence rates. The highest rate for tongue and mouth cancer is reported for men living in South Karachi, Pakistan, and the second highest from Trivandrum city in Kerala, India. Extremely high rates of cancer for women are seen in the Tamil community in Malaysia—higher even than in Tamil Nadu itself: the second most common cancer sites in Indian females in Peninsular Malaysia are the upper aerodigestive tract, behind the breast and above the uterine cervix [8].

Oesophageal cancer is a significant public health problem in all continents. It is important to draw a distinction between SCC of the upper two-thirds of the oesophagus, which is associated with tobacco and alcohol abuse, and adenocarcinomas of the lower third/gastric junction, frequently arising out of long-standing metaplasia towards secretory mucosa—the potentially malignant condition of Barrett's oesophagus, associated usually with chronic gastro-oesophageal reflux. Cancers of the junction and the cardia are included with those of the stomach in ICD-10. [An excellent, up-to-date and evidence-based set of guidelines for the management of this condition can be seen at <http://wiki.cancer.org.au/australia/Guidelines:Barrett%27s>, accessed 10 December 2014.]

More than 126,000 cases of oral cancer (ICD: C00–C08) occur every year in South and Southeast Asia alone, with poor prospect of survival: about 90 % of these cases are attributable to smoking and chewing habits. It is encouraging that overall rates in India are showing a decreasing trend in successive birth cohorts; declining trends were observed for mouth (ICD-10: C03–C06) and tongue (C01–C02) cancers among females and tongue cancers among males between 1982 and 2000 [9], and this has continued. However, population growth in the subcontinent means that the disease burden continues to rise (Fig. 1.11): better primary prevention is essential [10]. There is growing concern that commercial areca nut and tobacco products will contribute to future rises in the incidence of oral submucous fibrosis (OSF) and of subsequent oral cancer [11].

Data from Japan show a dramatic increase in oral and pharyngeal cancer incidence (ICD-10: C01–C14) for both sexes; there was a 4.4-fold increase for males and 3.8-fold increase for females in the total numbers between 1965 and 1999—noted from data retrieved from the Osaka Cancer Registry [12]. There is also an upward trend for both males and females in Australia and among the non-Maori population in New Zealand. Lip cancer in fair-skinned populations, particularly due to ultraviolet light, is a growing problem [13]. In Europe, Hungary has the highest incidence and mortality of oral and pharyngeal cancer for both sexes [14]. Between 1984 and 1994, the Hungarian mortality rates for oral cancers rose by 83.5 and 72.3 % in males and females, respectively, but this has now stabilised. Trends in the mortality rate among Italian and French males peaked in the 1980s and have decreased after 1990 [15]. However, some persisting upward trends were registered for Belgium, Denmark, Greece, Portugal and Scotland [16].

In the USA, the estimated number of incident cancer cases for tongue, mouth and other oral cavity in 2008 was 15,250 cases for men and 7650 for women; for the pharynx, the number of incident cases for men is 10,060 and 2350 for women (3 % of all cancer cases in men). For cancer of the larynx, 12,250 incident cases were estimated, of which 9680 were men. In the USA, the mortality rates per 100,000 population pa for cancer of the oral cavity and pharynx for men was 5.61 in 1990 and 3.98 in 2004, the absolute decrease being 1.63 per 100,000, contributing to a 3 % reduction in mortality of all sites. For women, the decrease across the same period was 0.56 contributing to a 2.5 % reduction of all sites [12]. The incidence rates of cancers of the oral cavity and pharynx-throat were stable or declining for men and

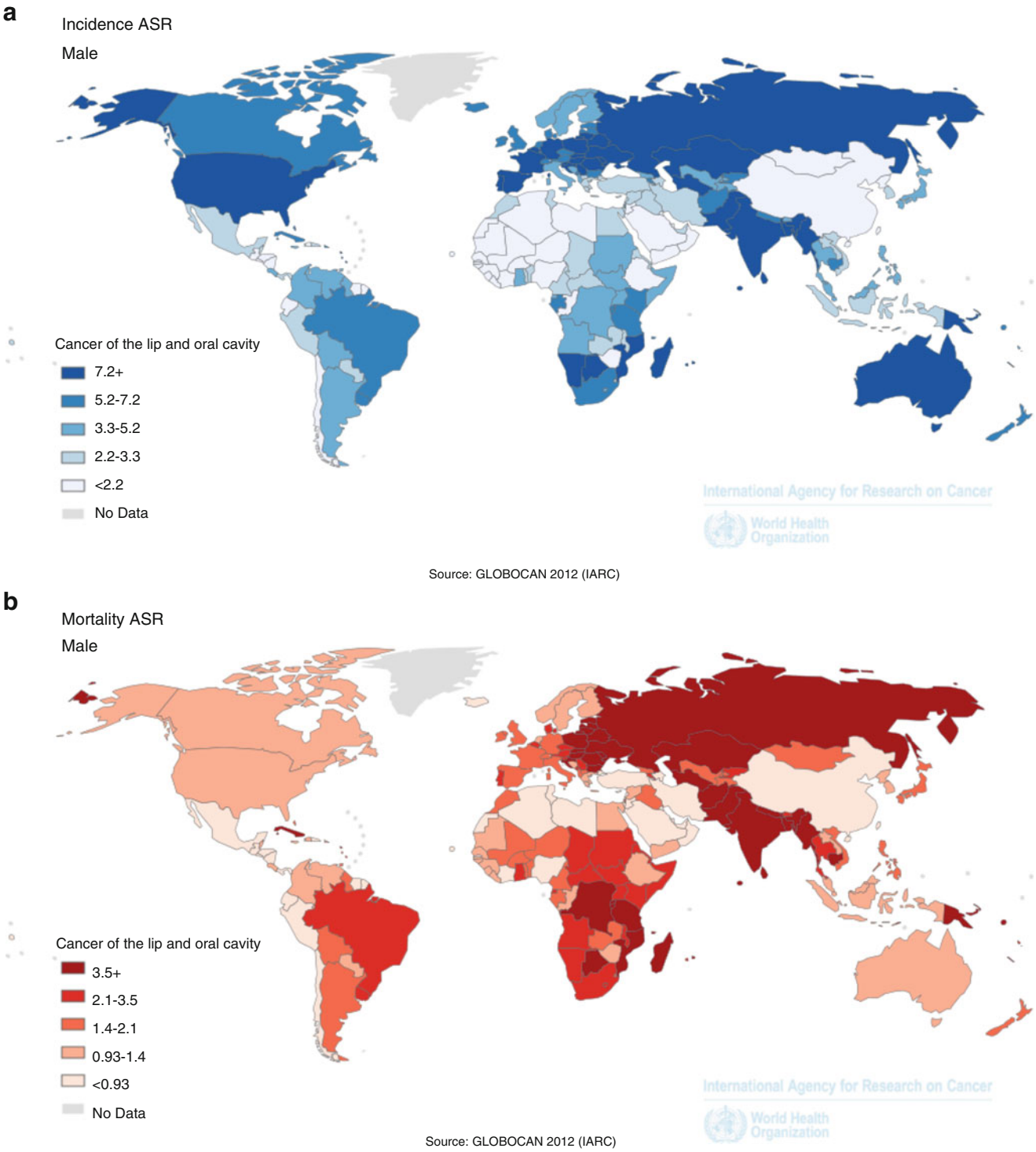


Fig. 1.3 (**a**) Incidence ASR male—lip and oral cancers. (**b**) Mortality ASR male—lip and oral cancers. Incidence (**a**) and mortality (**b**) rates for lip and oral cavity cancer in males, in quintiles, by country. A quick comparison of these maps makes a number of points. The "traditional" high incidence areas of central Asia and the Indian subcontinent stand out: much of this is due to betel quid use, with or without smokeless tobacco, plus smoking, sometimes alcohol abuse and poor diet. Note that parts of both Western and Eastern Europe remain in the top quintile—see text. The African data are not particularly robust. Australia shows a high incidence, due to ultraviolet light-induced lip cancer in a fair-skinned population: mortality rates are not comparably high because lip cancer is comparatively easily treated. Eastern Europe and the former Soviet republics have high mortality, partly related to low socioeconomic status, limited treatment facilities and the fact that many patients have substantial comorbidities. As already mentioned, Papua New Guinea and surrounding Melanesian islands of the Western Pacific are in the top quintile both in incidence and mortality: indeed Melanesia has the highest recorded rates in the world at the beginning of this millennium—associated with chewing of areca nut and tobacco use

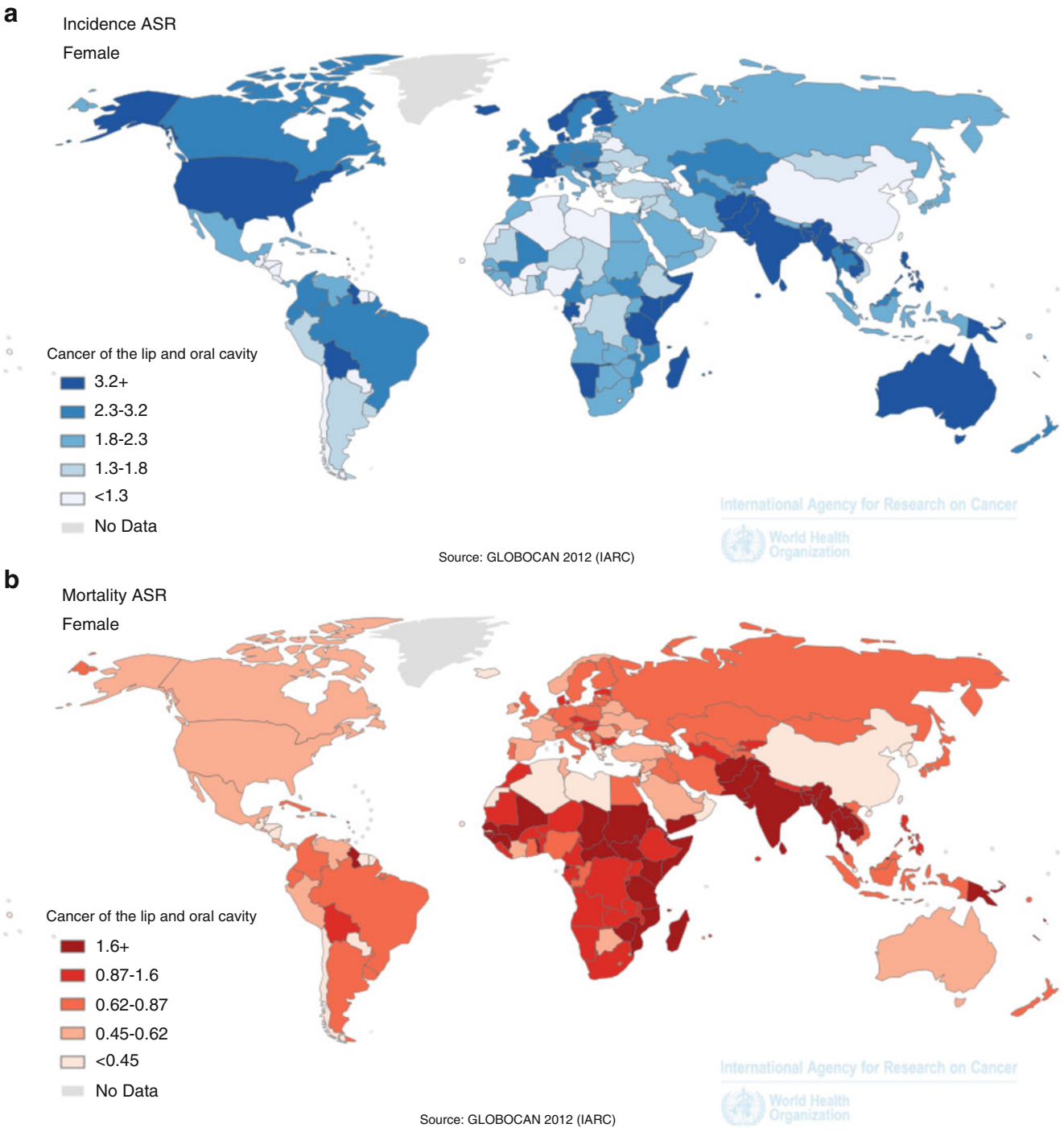
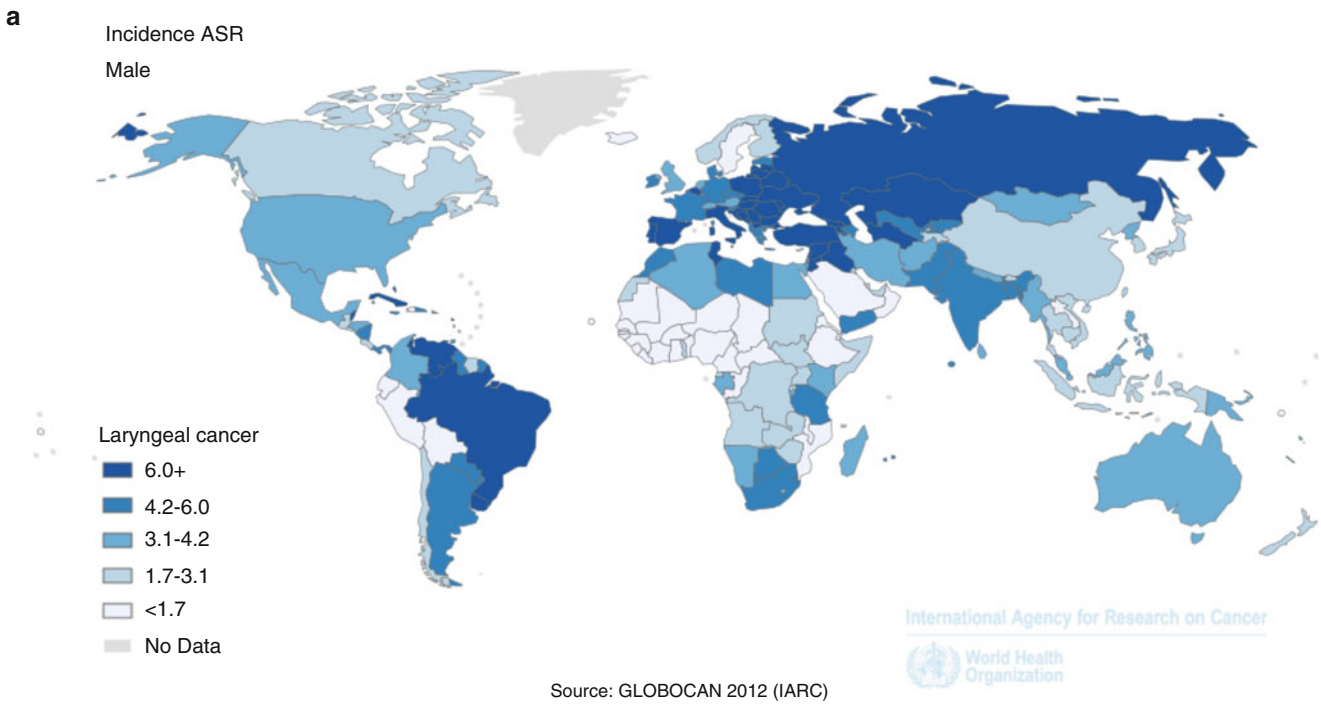


Fig. 1.4 (**a**) Incidence ASR female—lip and oral cancers. (**b**) Mortality ASR female—lip and oral cancers. Similar explanations relate to the national incidence (**a**) and mortality (**b**) data for women for cancers of the lip and oral cavity. Note the serious situation in the Indian subcontinent, much of northern Asia, South America and parts of the Middle East including the southern provinces of Saudi Arabia and Yemen. In parts of India, oral cancer is the leading cancer among women, because of heavy use of betel quids. Indeed emigrant Tamil women working on rubber and palm oil estates in Malaysia have among the highest rates, by population group, in the world



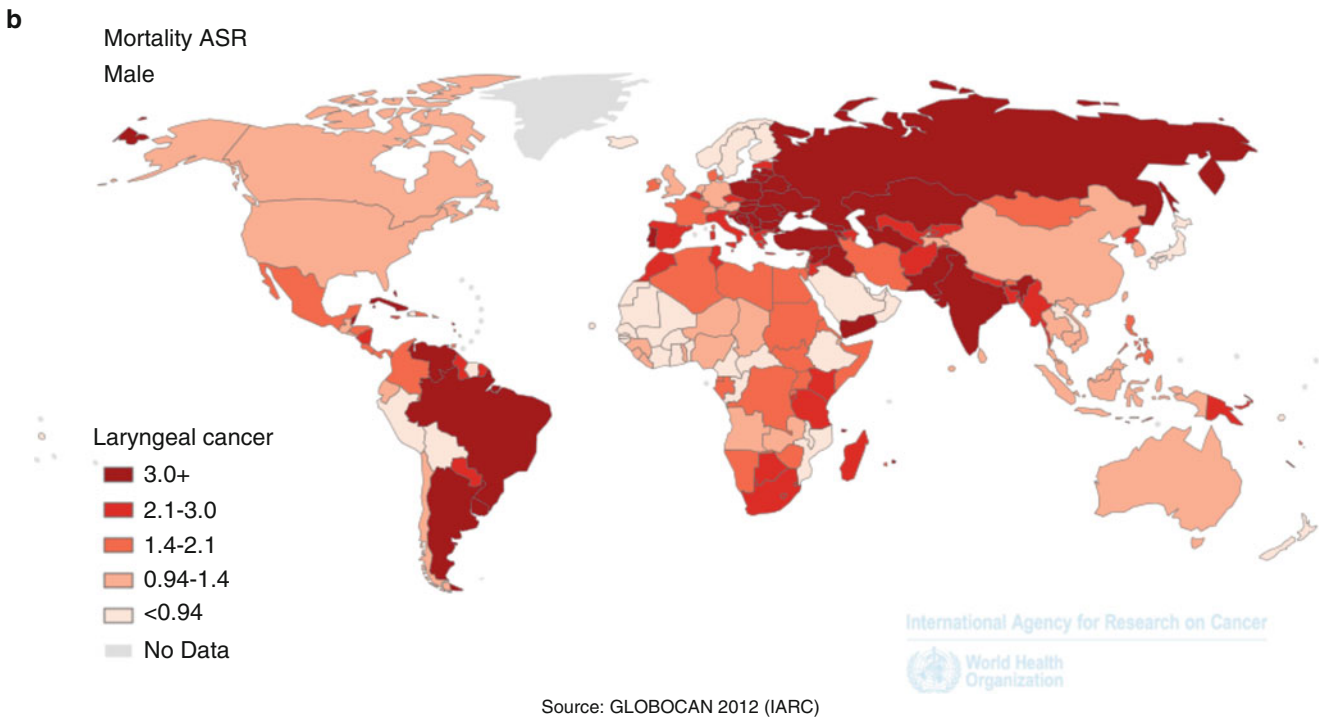


Fig. 1.5 (**a**) Incidence ASR male—laryngeal cancer. (**b**) Mortality ASR male—laryngeal cancer. Rates of laryngeal cancer largely reflect male smoking rates around the globe, with the surprising exceptions of China and Japan who have comparatively low incidence (**a**) and mortality (**b**), in spite of male smoking prevalence being 50 % or above: however, as noted earlier, Japanese rates are on the rise. The proportionately higher death rate in Eastern Europe, Russia and the former Soviet Republics is again related to late stage at diagnosis and high comorbidities associated with low socioeconomic status and difficulties with access to care

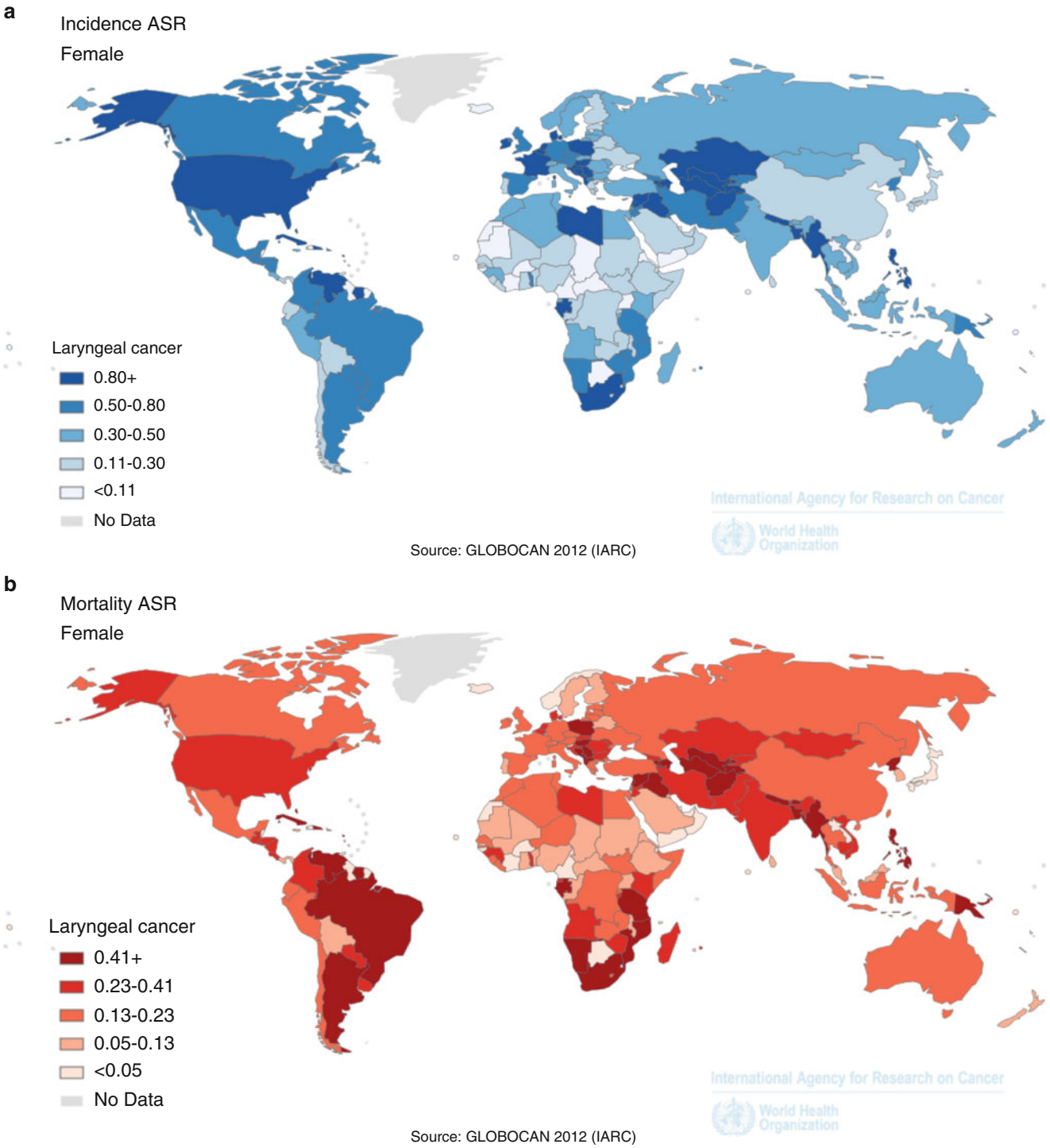


Fig. 1.6 (**a**) Incidence ASR female—laryngeal cancer. (**b**) Mortality ASR female—laryngeal cancer. (**a** and **b**) Because smoking is far less prevalent in women than men in most societies, the laryngeal cancer rates are low worldwide, and less can be read into this aspect of "geographical pathology". Nevertheless, there are clear challenges to be met in much of the continent of South America, in Central Europe and in the USA

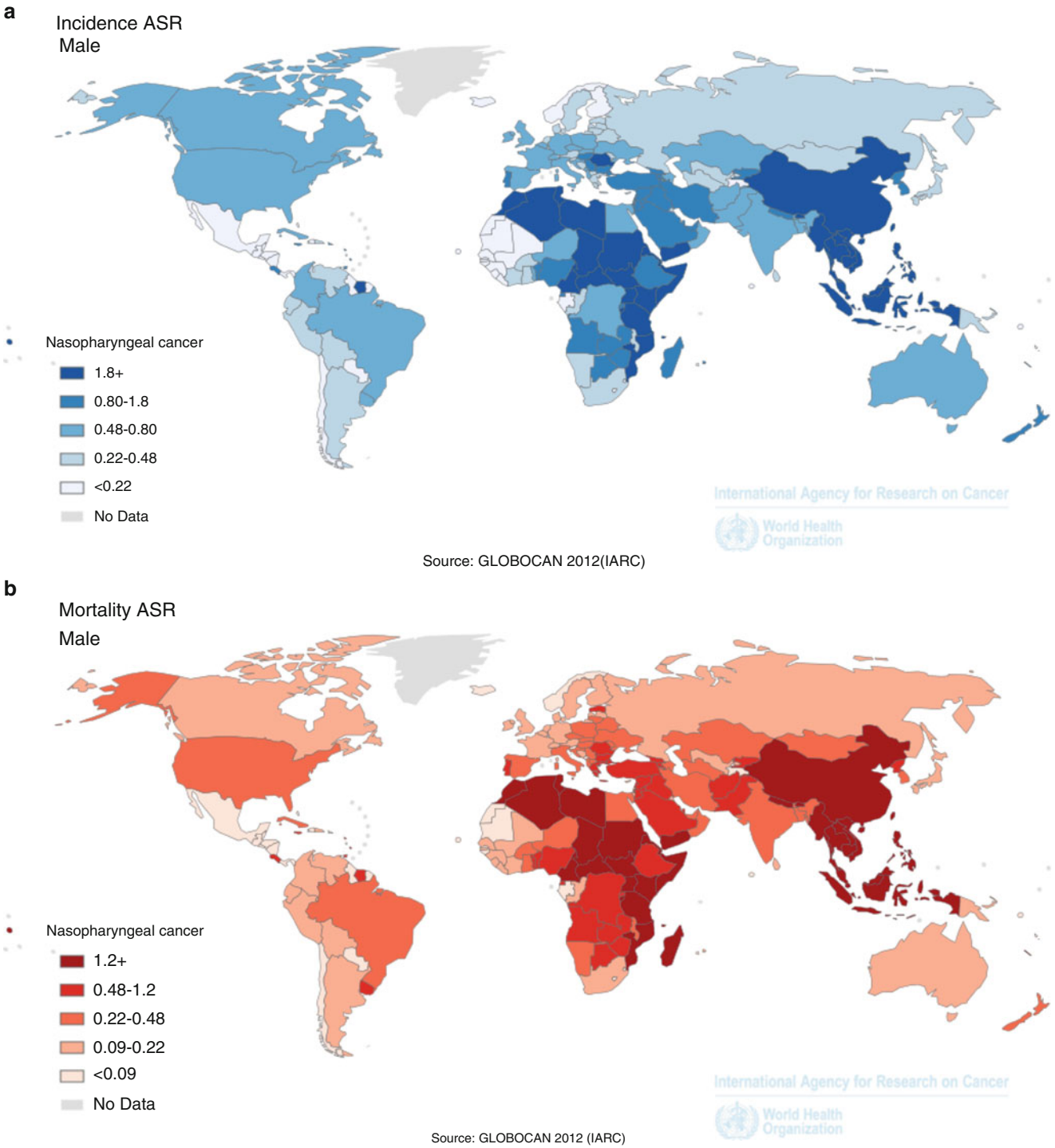


Fig. 1.7 (**a**) Incidence ASR male—nasopharyngeal caner. (**b**) Mortality ASR male—nasopharyngeal caner. Risk factors for nasopharyngeal cancer are comparatively well understood. It is a biologically distinct disease, driven by Epstein–Barr virus, in subjects with genetic susceptibility, compounded by toxins in particular cultural dietary practices. Both incidence (**a**) and mortality (**b**) rates are historically high in North, Central and East Africa, in Indonesia and in China—particularly Guangdong Province—the Hong Kong SAR and emigrant communities therefrom

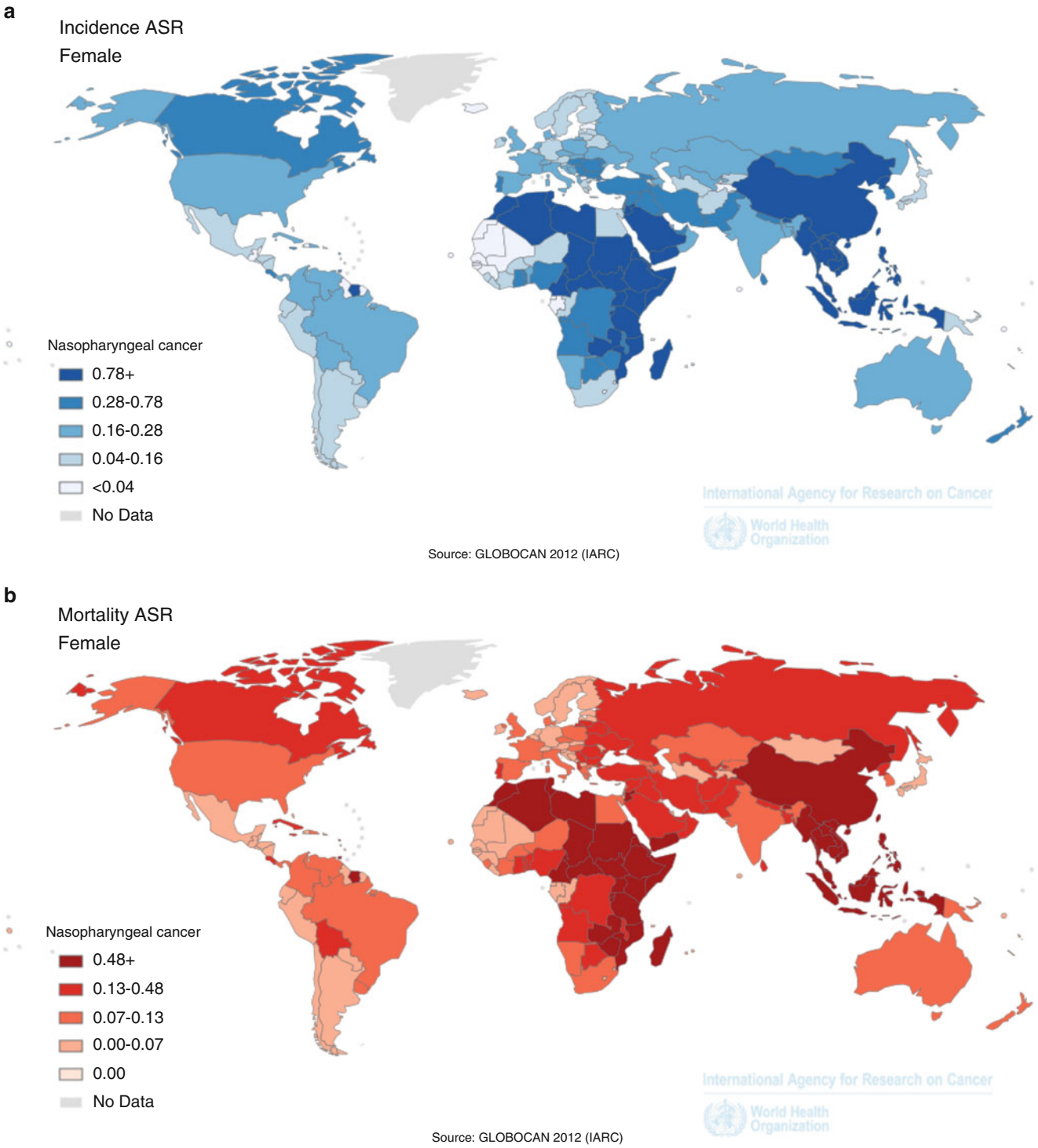


Fig. 1.8 (**a**) Incidence ASR female—nasopharyngeal cancer. (**b**) Mortality ASR female—nasopharyngeal cancer. (**a** and **b**) Female rates for NPC are lower than for men but show the same geographical distribution

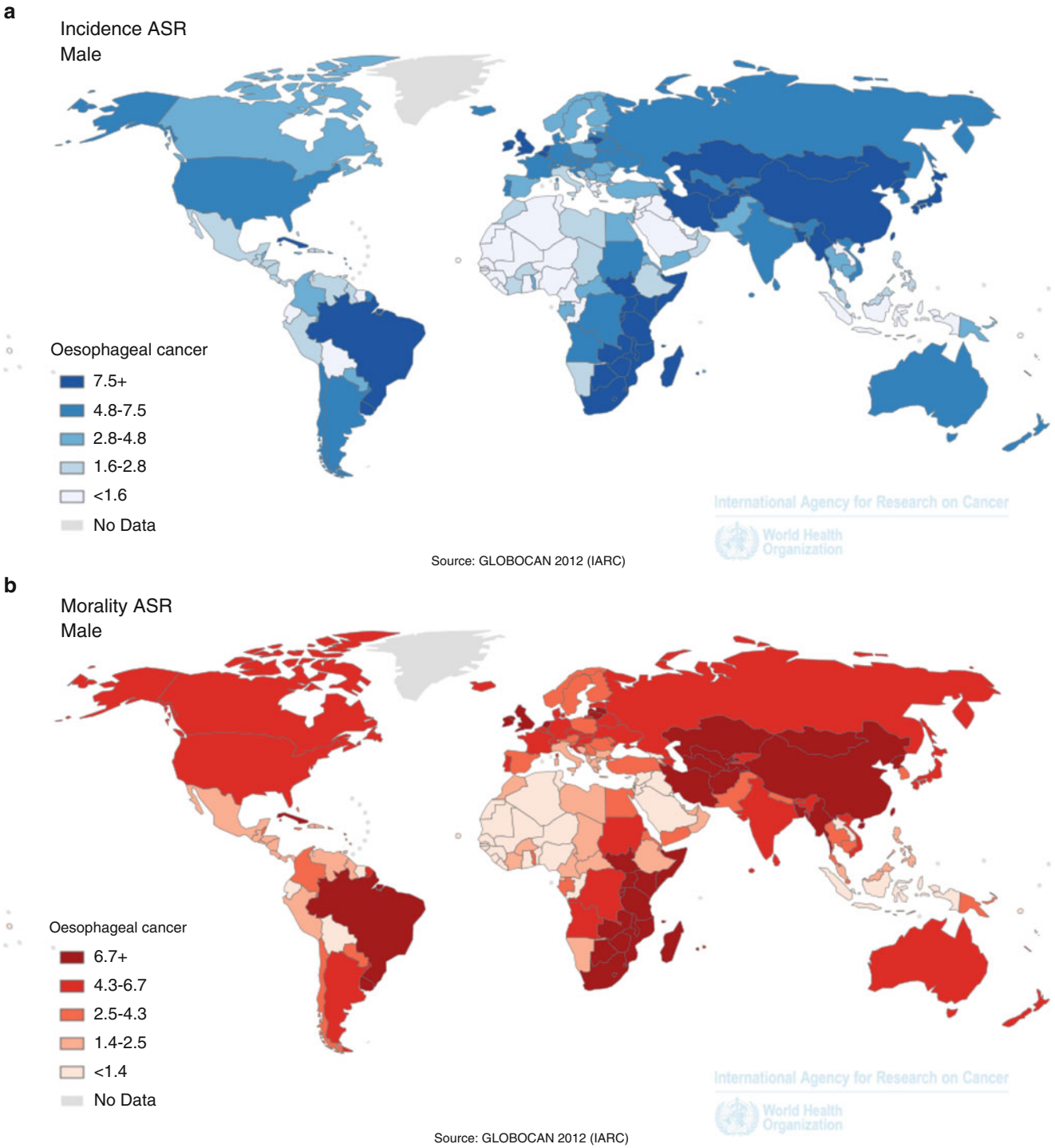


Fig. 1.9 (**a**) Incidence ASR male—oesophageal cancer. (**b**) Mortality ASR male—oesophageal cancer. Oesophageal cancer incidence (**a**) and mortality (**b**) data for men. Highest rates in Central Asia, Brazil and in Eastern/southern Africa

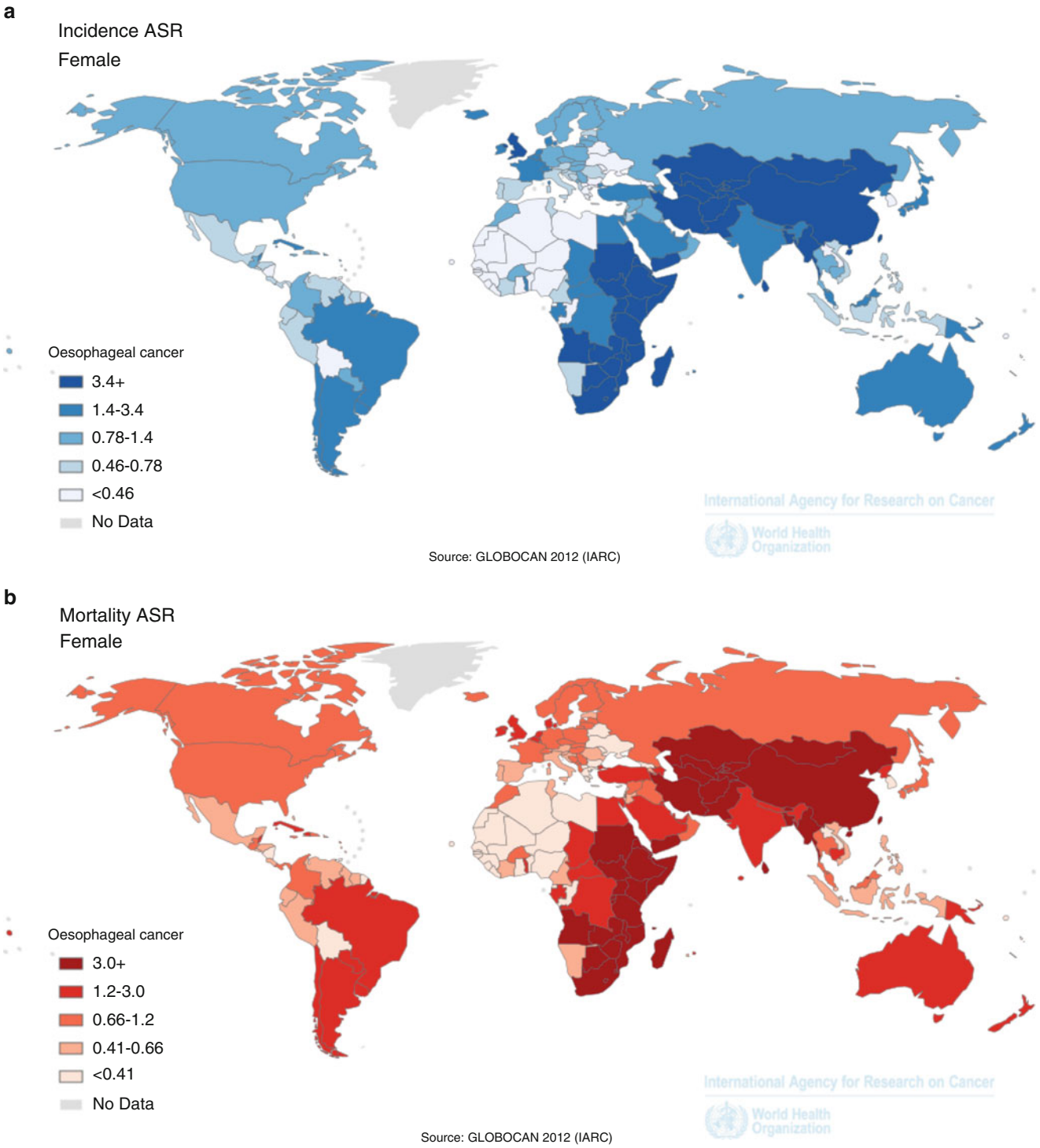


Fig. 1.10 (**a**) Incidence ASR female—oesophageal cancer. (**b**) Mortality ASR female—oesophageal cancer

women in most age groups during the period 1973–2003 in the USA, probably related to changes in tobacco and alcohol consumption. This is a highly pleasing situation, common to many countries with advanced care facilities but not reflected in most of the high incidence countries elsewhere in the world. Furthermore, as described below, black citizens of the USA fare comparatively badly.

Cancer of the larynx has always been a serious public health problem in nations with high smoking prevalence, and this remains a disaster in China and Eastern Europe and the former Soviet Republics. Differences among selected countries are shown in detail in the time and birth cohort trends reproduced below, these being the latest data available at the time of writing at the beginning of 2015.

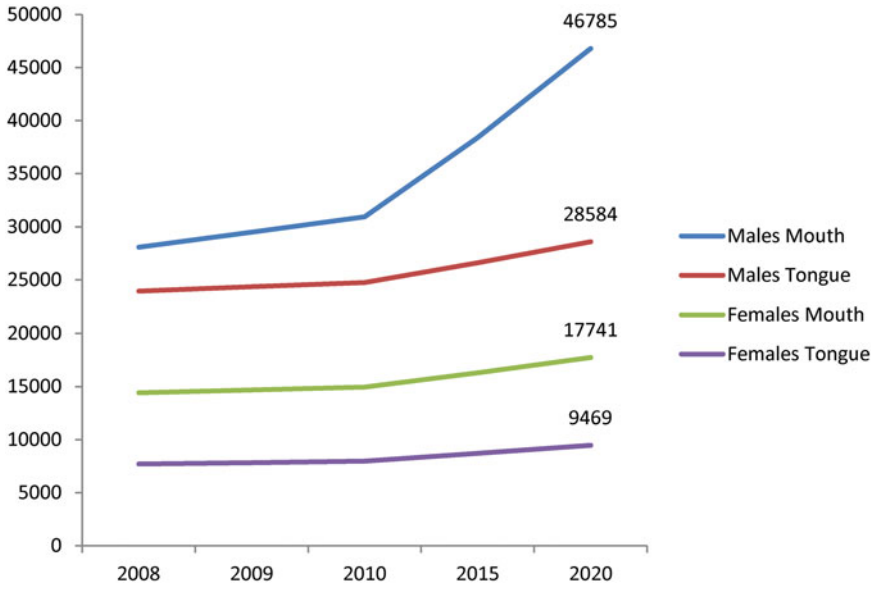


Fig. 1.11 Projected rises in the burden of mouth and tongue cancer in India in the next decade. [Reprinted Gupta B, Ariyawardana A, Johnson NW: Oral cancer in India continues in epidemic proportions: evidence base and policy initiatives. Int Dent J; 2013, 63(1): 12–25. With permission from John Wiley & Sons]

For cancers of the oropharynx and tonsils, the highest combined rate is currently seen in France, and for laryngeal cancer, it was Spain and Cuba. For hypopharyngeal cancer specifically, the highest rate in men was in France. For women, the highest ASR(W) for mouth and tongue specifically was in India [3].

1.7 Differences by Sex

As already noted, worldwide, the incidence of head and neck cancers overall is higher for males than females. According to the International Agency for Research on Cancer [2], the age-specific incidence of "oral cavity", "nasopharynx" and "other pharynx" cancers was 5.5, 1.7 and 3.2 per 100,000 population for males in 2012 and 2.5, 0.7 and 0.7 for females, respectively (see Table 1.1). This may be because of their greater indulgence in the most important risk factors, such as heavy alcohol and tobacco consumption for intra-oral cancer and sunlight for lip cancer in those who work outdoors. However, oral cancer in females is increasing in some parts of the world. For instance, a study from Argentina showed the male/female ratio to be 1.24:1 for the period 1992–2000 compared to 7.1:1 for the 1950–1970 period [17]. The incidence of tongue and other intra-oral cancers for women can be greater than or equal to that for men in high incidence areas such as India, where betel quid/areca nut chewing (and sometimes smoking) are common among women—although this varies considerably from region to region.

Early this century, within Europe, the incidence of oral cavity and pharyngeal cancers (C00–C14) among males varied substantially between 5.9 (Finland) and 32 (France) per 100,000 pa [18]. Incidence rates among females were highest in Northern and Western Europe but were consistently lower than those for males. The male/female ratio decreased during the last 10 years and recently varied between 1.5 and 2.5 in Northern Europe to 7.7 in Lithuania. Between 1990 and 1999, the UK incidence rates for oral cancers rose in males of all ages from 6.5 to 8.3 per 100,000 (an increase of 18 %) and in females from 2.6 to 3.6 per 100,000 (an increase of 30 %) and continues to be a concern [19].

In the USA, the death rate due to cancer of the oral cavity and pharynx per 100,000 population in 2007–2011 was 3.8 for males and 1.4 for females [20], down from 6.9 to 2.3, respectively, in 1975. This substantial improvement is not reflected in most of the rest of the world.

Apart from the traditional risk factors, it has been suggested that oestrogen deficiency may influence susceptibility to oral cancer in women. Significantly, younger mean age at menopause and higher rates of hysterectomy may influence the higher rates of oral cancer seen among younger females [21]. Data presented in this chapter are, whenever possible, separated by sex.

1.8 Ethnic Variations

Variations by ethnicity are largely due to social and cultural practices and the influence of dietary and genetic factors, though the latter are less well quantified. Variations in outcome are also contributed to by differences in access to healthcare. Where cultural practices represent risk factors,

their continuation by emigrants from high incidence regions to other parts of the world results in comparatively high cancer incidence in immigrant communities. This can also affect the subsites of oral cancer most commonly affected, as shown in a study from California [22]. The highest age-adjusted oral cancer rates in the USA are found among non-Hispanic men (17.5/100,000) followed by non-Hispanic women (6.6/100,000), with Asian and Hispanic populations showing lower incidence rates compared with white (Caucasian) ethnic groups. Tongue cancer was the most common type of oral cancer among every ethnicity. Asians were more likely to develop their malignancy in the buccal mucosa, a reflection of continuing areca and tobacco chewing habits. Another study showed that American Indians and Alaskan Natives overall had significantly lower incidence rates than non-Hispanic whites [23]. Several studies from the USA have demonstrated that black patients with oral cancer have poorer overall and disease-specific survival than whites, mainly because of their comparatively poor access to healthcare [24, 25]. This is especially concerning because the incidence of oral plus pharyngeal cancer for black men in the USA is so high and is the sixth most common site for malignant disease among this group [26].

In the Republic of South Africa, among Asian/Indian South Africans, oral and oropharyngeal cancer incidence was higher among females (ASIR = 4.60) than among males (ASIR = 3.80). Excluding those involving the lip, these cancers were highest among Coloureds (ASIR = 5.72) and lowest among blacks (ASIR = 3.16). Incidence rates increased significantly among Coloured South Africans over the period from 1992 to 2001 ($P<0.05$), particularly for the oropharynx (Available at http://repository.up.ac.za/bitstream/handle/2263/32412/AyoYusuf_Trends(2013).pdf?sequence=1.)

The age-adjusted incidence rate for oral and pharyngeal cancers is higher for South Asians than for other residents in England, particularly among females [27]. Interestingly, this study showed that British South Asian males have significantly better survival than their non-South Asian peers in the southeast of England, possibly a reflection of the more indolent progress of tobacco/areca nut-induced lesions [27].

1.9 Age Distributions

Oral cancer is usually a disease that occurs in males after the fifth decade of life. The mean age at presentation is in the fifth and early sixth decades in Asian populations compared with the seventh and eighth decades in the North American population [28–33]. Statistics in the USA for 1975–2011 show that the median age at diagnosis for cancer of the oral cavity and pharynx was 62 years [34].

Several studies suggest that 4–6 % of oral cancers now occur at ages younger than 40 years [35]. An alarming increase in incidence of oral cancers among younger people has been reported from many parts of the world [36–39], a trend that appears to be continuing. There was a significant increase in the incidence of cancers in the tongue and tonsil among 20–40-year-olds in the USA between 1973 and 2001 [40]. In Germany, Czechoslovakia and Hungary, there has been an almost tenfold rise in mortality from oral cancer in men aged 35–44 [41], within one generation. Robinson and Macfarlane showed a dramatic increase in incidence rates for younger males in Scotland from the 1980s to the 1990s [42]. In the high prevalence areas of the world, in many cases, patients are less than 40 years old, probably owing to heavy use of various forms of tobacco from an early age, although some recent Indian data have not shown this [43].

It is also clear that a number of cases of squamous cell carcinoma occur in both young and old patients in the absence of traditional risk factors and in which the disease may pursue a particular aggressive course, more so in the elderly. A study conducted in Southern England concluded that a substantial proportion of cases of younger people diagnosed with oral cancer occur in the absence of known risk factors [44]. This, together with the relatively short duration of exposure in users, suggests that factors other than tobacco and alcohol are implicated in the development of oral cancer in a significant minority of cases. Diets poor in fresh fruits and vegetables were identified as conferring significant risk. There is now substantial evidence that human papillomavirus infections are driving this rise in younger adults, but, fortunately, HPV-related oropharyngeal cancers respond well to radiotherapy, permitting treatment de-escalation and improved quality of life. It is also suggested that greater attention should be paid to familial antecedents of malignant neoplasms in younger patients with oral cancer [45].

Age distribution curves for the major head and neck cancer sites are given for deliberately selected countries in Figs. 1.12, 1.13, 1.14, 1.15, 1.16 and 1.17.

In the high incidence age bands, there is an approximately four- to tenfold difference in incidence with, among the countries selected here, disturbingly high rates in NW France, Brazil and South India. Note the much worse situation in American blacks cf. whites, explained by a mixture of risk factor and socioeconomic reasons. Finland does comparatively well—not surprising in view of that nation's success in reducing the prevalence of smoking, though alcohol abuse remains a social problem. What is surprising are the low rates recorded for Shanghai, in spite of high smoking prevalence in this large city. China is currently developing a more comprehensive, nationwide cancer registry system; so more cogent data will soon be available.

Fig. 1.12 Male age-specific incidence curves for mouth and pharynx for selected countries. All UADT cancers show a similar distribution. Most cases occur in the fifth to seventh decades of life, presumably because decades of exposure to tobacco, alcohol and poor nutrition take time to synergise with other agents in triggering malignant transformation—or in allowing this to survive the host response! There are, nevertheless, a significant minority of cases appearing in the third and fourth decades of life: these attract much interest as, although associations with early commencement of smoking and with unsafe alcohol use can be demonstrated, a substantial minority of cases arise without exposure to traditional risk factors. Here, dietary inadequacies and HPV infection are likely to be important, as may inherited predisposition

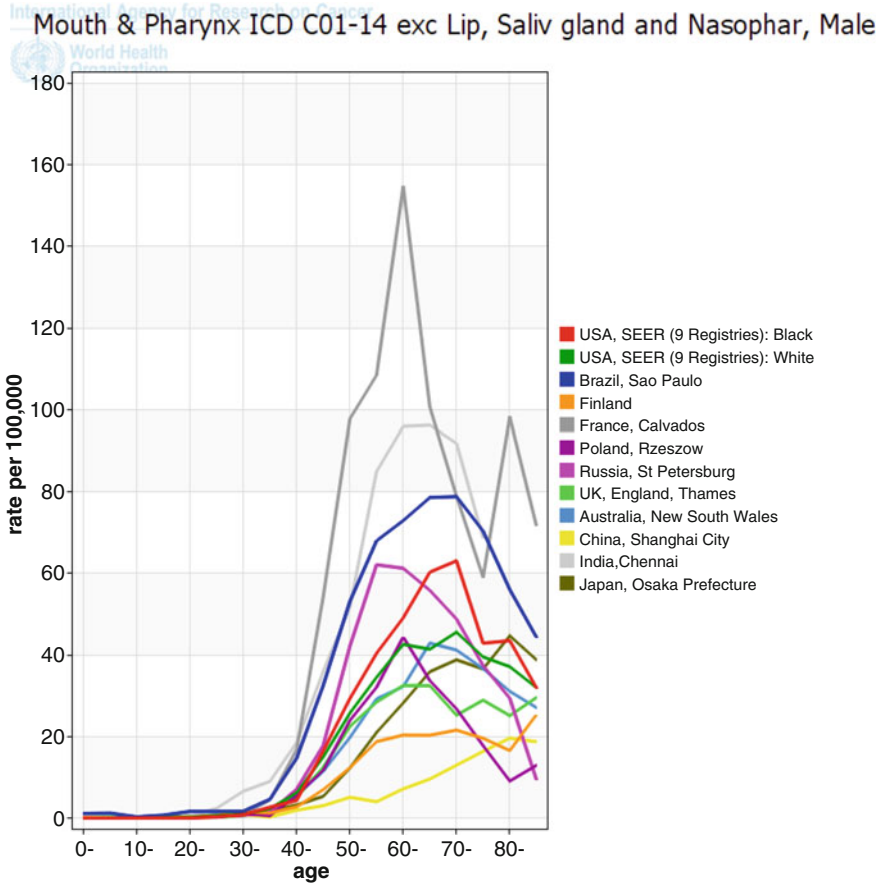
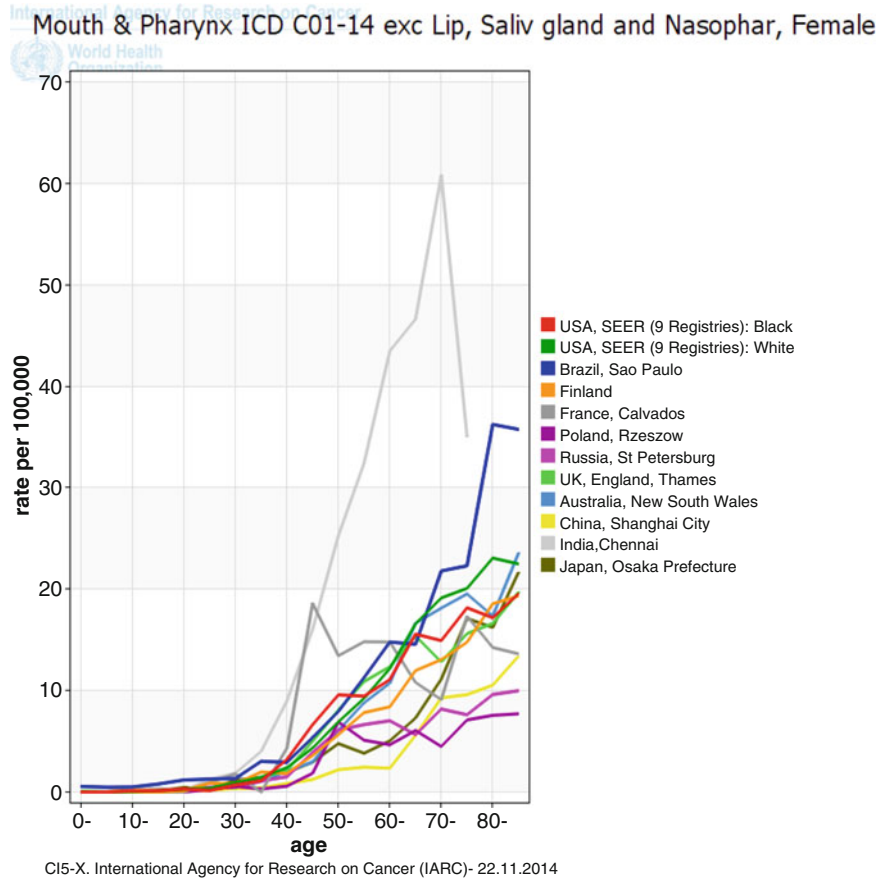


Fig. 1.13 Female age-specific incidence curves for mouth and pharynx for selected countries. Rates for females are lower and international differences are less marked. Women in South India stand out—related to use of betel quid and tobacco, together with low SES



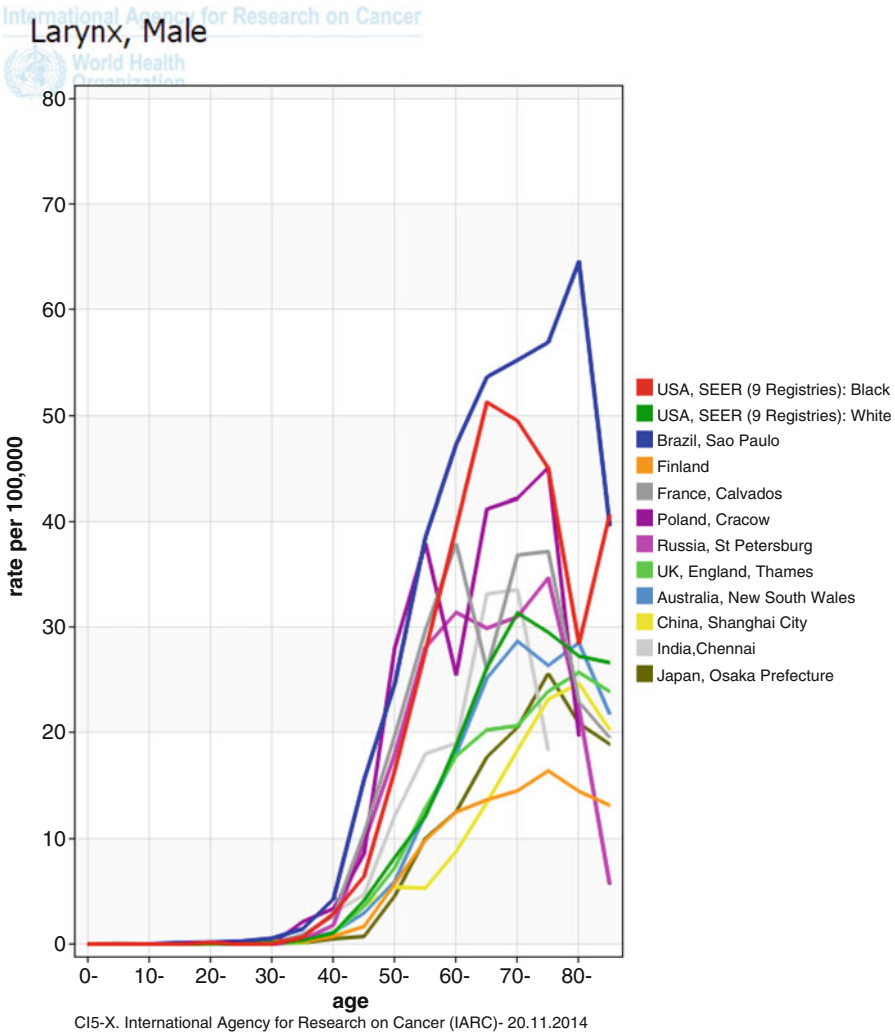


Fig. 1.14 Larynx—male. Many of the differences between populations are likely to be explained by smoking and other traditional risk factors. Serious public health challenges exist in the Brazilian example. Poland and the Russian example are consistent with the major concerns we have for Eastern Europe, Russia and the former Soviet Republics as a whole. Blacks do poorly in the USA. Finland provides encouragement: indeed this was the first country in the world to reach the WHO target for the year 2000 of having less than 20 % of the adult population smoking. Japan and China remain enigmas

1.10 Mortality Rates and Trends over Time (Table 1.2)

Trends of age-standardised (world population) mortality rates for the head and neck cancer sites of interest, within selected countries over the past 3–6 decades, are presented in Figs. 1.17, 1.18, 1.19, 1.20, 1.21 and 1.22, derived from the WHO mortality database [46].

Current male death rates for oral and pharyngeal cancer around the world are seen vividly in Fig. 1.18. There was a steady rise in oral cancer mortality in men from the 1950s to late 1980s in most Western European countries [47], but this trend has since declined in France, China and Hong Kong, which had exceedingly high rates in the past. Unfortunately, in most countries in Central and Eastern Europe, oral cancer mortality in men continued to rise, reaching exceedingly high rates in Hungary, Slovakia, Slovenia and the Russian Federation at the end of the last century. Hungary, Ukraine, Estonia and Bulgaria showed more than a 100 % increase in mortality rates for men during the 20-year period up to the turn of the Millennium. Even though the rates of oral cancer are comparatively low among women (Fig. 1.19), there was an increase in several countries in Europe (notably Hungary, Belgium, Denmark and Slovakia) over this period. These disturbing rises are thought to have been related to high drinking and smoking patterns in these societies, together with poor diet in lower socioeconomic groups. Fortunately improvements are now evident.

Trends for laryngeal cancer reflect continuing high rates of tobacco consumption in many societies (Figs. 1.20 and 1.21). Trends for nasopharyngeal cancer, both good and bad, are shown for high incidence countries (Figs. 1.22 and 1.23).

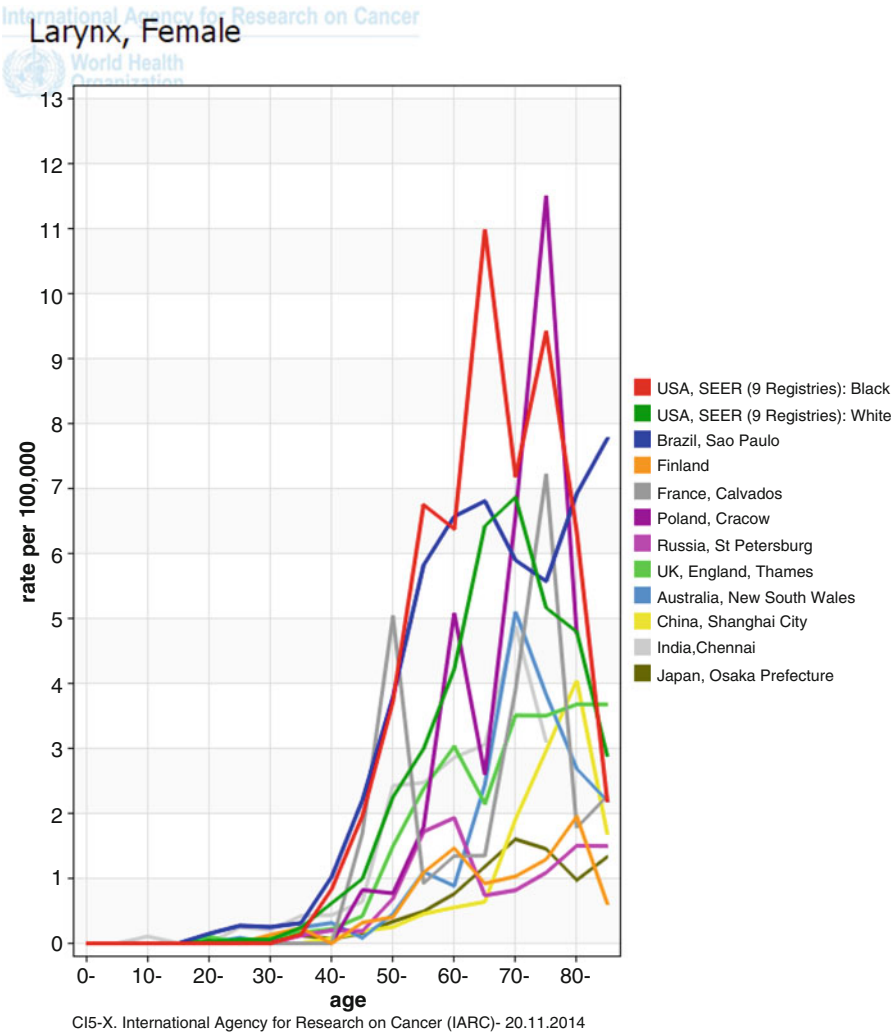


Fig. 1.15 Larynx—female. Although at first glance the spread for women looks larger, the rates are much lower than for men. Poland, as with much of Eastern Europe, American blacks and Brazil again stand out

1.11 Mortality Trends by Birth Cohort and Forward Projections

Birth cohorts are a valuable way for interpreting time trends. Cases of particular cancers are transformed back, in 5-year age groups, to the date of birth of the affected individuals. Curves derived from WHO mortality database for particularly instructive countries are given below [46]. In general these show that for most UADT cancers, in most developed countries, rates fell in the latter part of the nineteenth and the first part of the twentieth centuries. This has been continued in, for example, the USA (Fig. 1.24) and the UK (Fig. 1.25). However in Hungary (Fig. 1.26 and the same is true for most of eastern Europe, Russia and the former Soviet republics), those born in the first half of the twentieth century showed alarming rises in death rates. All of these birth cohorts have now passed on, or they are in the highest risk age groups: in these countries, we have thus seen a growing epidemic of UADT cancer. Indeed, ageing populations in many countries mean that crude rates, and thus disease burden, will continue to rise, as in the data from the USA and UK illustrated below. Encouragingly, the curves now indicate that Hungary, for example, is showing control in younger people. The success of France from the middle of the twentieth century, particularly among men, is apparent in Fig. 1.27.

The SEER programme in the USA has reported an overall fall in the mortality from oral and pharyngeal cancer, between 1975 and 2004, of 1.87 % per annum shown in Table 1.3.

Table 1.3 shows a fall in all mortality rates for oral and pharyngeal cancer in the USA between 2002 and 2011. There is a considerable fall in mortality among both black men and black women (APC of −3.7 and −2.7, respectively). Furthermore, the SEER Data show higher 5-year relative survival rates for whites (64.3 %) and blacks (43.7 %), who were diagnosed during the period 2004–2011, than rates for those who were diagnosed during the period 1974–1976 (when rates for whites and blacks were 55 % and 36.3 %, respectively) [48]. The 5-year survival rates in the SEER Registries range from a high of 72.1 % for white women in Utah to a low of 24.8 % for black men in metropolitan

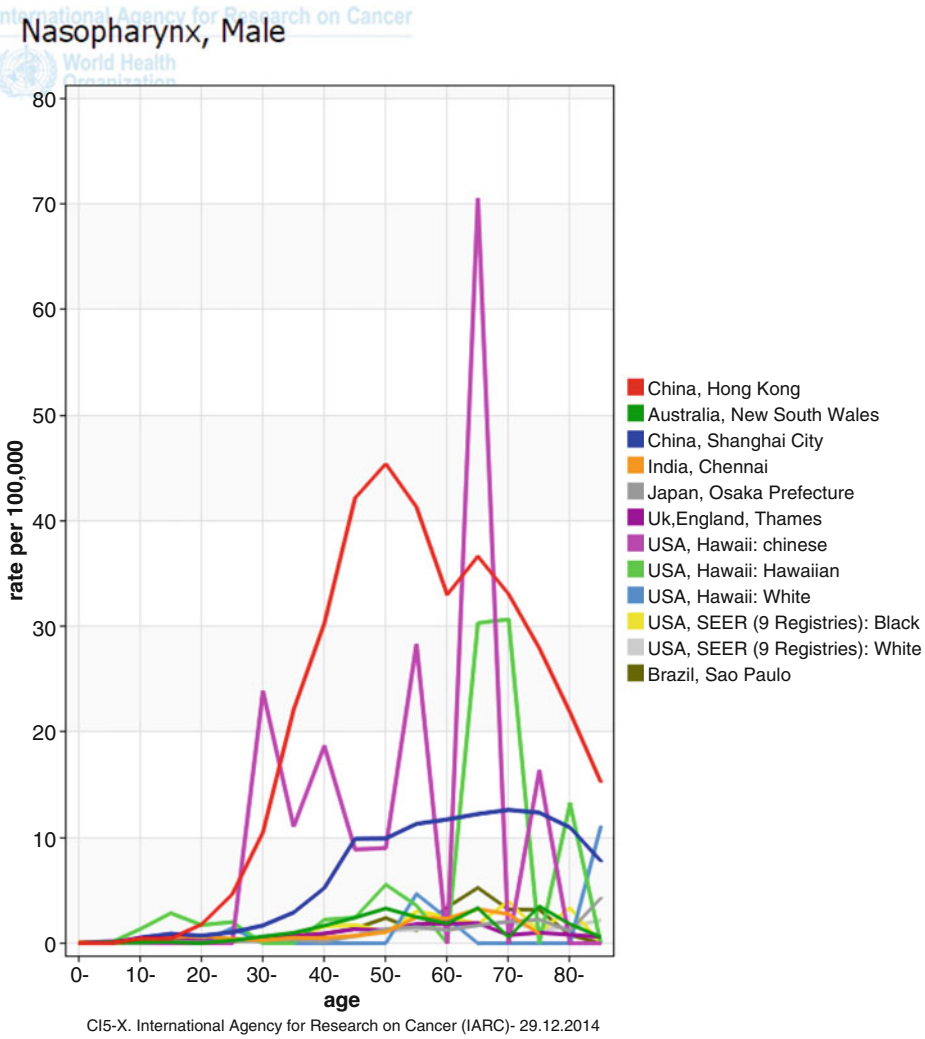


Fig. 1.16 Nasopharynx—male. NPC is a distinct disease. These countries have been chosen to reflect the differences by population. As mentioned in the legend to the cancer map, southern Chinese men are particularly susceptible: hence the alarming data from Hong Kong and to a lesser extent from Shanghai. Although the data are fragmentary, the markedly higher rates in Chinese Hawaiians than other racial groups are consistent with the ethnic bias

Atlanta. These striking differences are likely to be explained by a number of factors including socioeconomic condition, age, stage at diagnosis, continued presence or absence of environmental risk factors and access to hospital services. African-American patients have consistently poorer survival outcomes [49].

A study in Mumbai, India, indicated a decreasing trend in oral cancer incidence among Indian men, which it was suggested may be due to a decrease in the use of betel quid/pan and associated oral smokeless tobaccos over this period [50]. However, there continues to be a high prevalence of smokeless tobacco use among young adult men and women, especially in the form of Pan Parag-/Gutka-type products, and cigarette smoking is increasing. Overall, UADT will increase, as indicated earlier [10].

Population-based survival rates around the world show little evidence of improvement over recent decades, despite vast improvements in treatment modalities. Cure rates and survival rates have improved with advances in surgical and other techniques in highly specialised, high-volume treatment institutions. Regrettably, such highly expert management is not yet uniformly available, and it may be decades before these results are reflected in population trends.

1.12 Aetiology of Head and Neck Cancer

Major risk factors have been reviewed recently [51]. The majority of oral squamous cell carcinomas (OSCC) are related to tobacco in various forms, betel quid chewing, heavy alcohol drinking and dietary micronutrient deficiency. There is a clear dose–response relationship (Fig. 1.28). Nevertheless, in the West, a distinct subgroup of patients without these traditional risk factors exists: predominantly elderly females, in whom aetiological factors are not clear [52]. In the developing world, tobacco and areca nut, used either alone or in combination, account for the vast majority of oral cancers and oral potentially malignant disorders

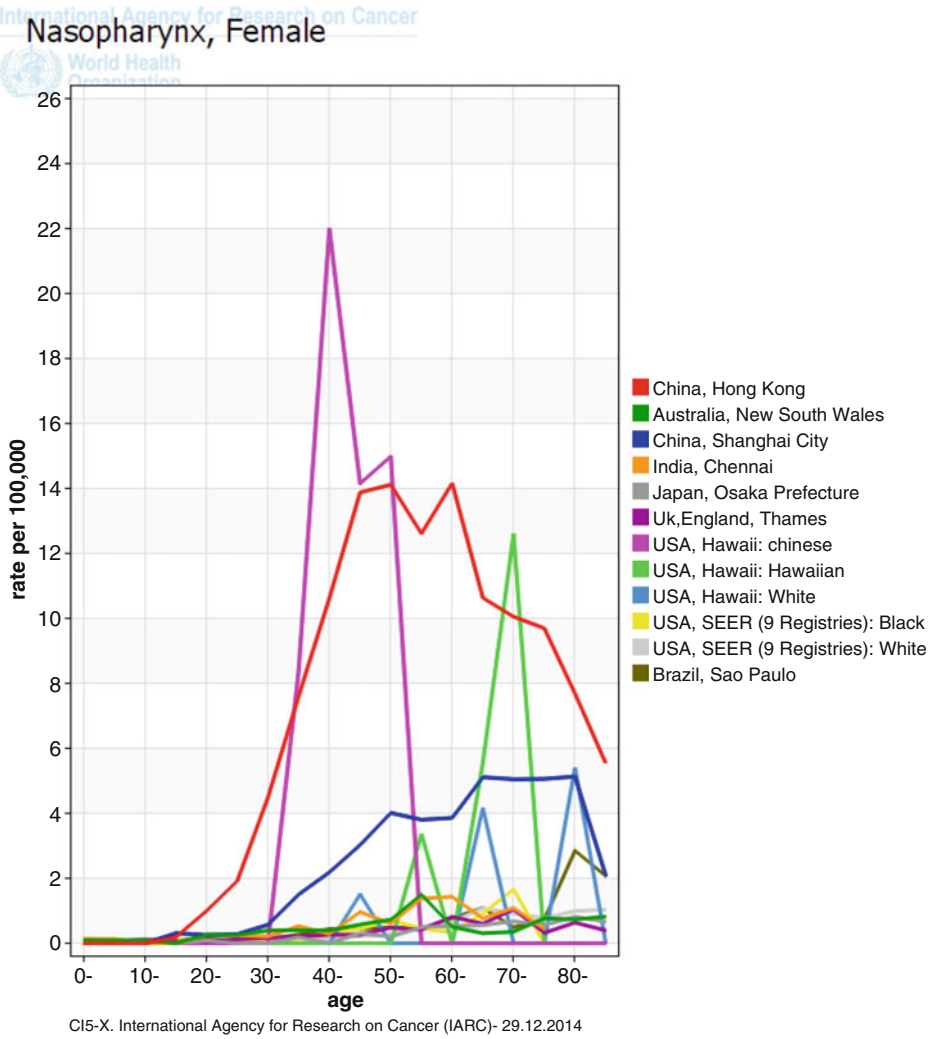


Fig. 1.17 Nasopharynx—female. The highest rates of NPC in women are again in Chinese—though only a tenth of those in males

(OPMD) [53]. The WHO has classified areca nut, a common component of many different chewing habits, as carcinogenic to humans [54–56]. UV radiation is relevant to lip cancer, and there is increasing evidence for a role for "high-risk" genotypes of the human papillomavirus family, especially for the tonsil, base of tongue and other oropharyngeal sites.

1.12.1 Betel Quid

A betel quid generally contains betel leaf, areca nut and slaked lime and may contain tobacco. Other substances, particularly spices, including cardamom, saffron, cloves, aniseed, turmeric, mustard or sweeteners, are added according to local preference [54].

1.12.2 Betel Leaf

The leaves of the *Piper betel* vine (a member of the pepper family) contain betel oil, a volatile liquid, which contains several phenols including hydroxychavicol, eugenol, betel phenol and chavicol. These compounds may, to some extent, be protective, sharing some of the antioxidant properties of many plant polyphenols. Vitamin C, a large amount of carotene and 36 trace elements have also been reported in the betel leaf—clearly beneficial micronutrients [57].

1.12.3 Betel Inflorescence

Apart from the leaf, other parts of the vine such as stem, inflorescence (the flowers or pods; catkins) are also consumed with areca nut. Consumption of the inflorescence is common in Melanesia and parts of Taiwan and in China, and it is mostly added to the quid for its aromatic flavour [54]. Betel inflorescence contains a high concentration of phenolic compounds including hydroxychavicol, eugenol, isoeugenol, eugenol methyl ester and safrole. Safrole itself, a major phenolic compound, is classified as a weak carcinogen in rats and is banned as a food and cosmetic additive by the FDA in the USA, inter alia; however, there is no direct evidence for its carcinogenicity in man.

Table 1.2 Mortality data again extracted from the Globocan 2012 database, for comparison with the incidence data in Table 1.1

	Mouth (ICD C00–C08) Being lip, all of tongue, all of mouth and major salivary glands		Nasopharynx (ICD C11) Data for C30, malignant neoplasm of nasal cavity and middle ear For C31, malignant neoplasm of accessory sinuses For C32, malignant neoplasm of larynx are *not* included here		Other pharynx (ICD C09–C10, C12–C14) Being tonsil, remainder of oropharynx, pyriform fossa, hypopharynx and sites not otherwise specified among C00–C13		Larynx (ICD C32)		Oesophagus (ICD C15) This code excludes cancers arising at the gastro-oesophageal junction which are included in stomach cancers, the majority of which are adenocarcinomas. Included here, therefore, are mostly SCC sharing common risk factors with the mouth	
Country	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
World	2.7	1.2	1.0	0.4	2.2	0.5	2.0	0.2	7.7	2.7
More developed	2.3	0.6	0.2	0.1	2.2	0.3	2.2	0.2	5.2	0.9
Less developed	2.8	1.4	1.3	0.5	2.2	0.5	2.0	0.3	9.0	3.6
Africa	2.1	1.3	1.1	0.6	0.9	0.4	1.5	0.2	5.3	3.3
Eastern Africa	3.2	1.9	1.4	0.9	0.9	0.5	1.5	0.2	11.2	7.3
Middle Africa	2.9	1.4	1.1	0.6	1.6	0.6	1.1	0.2	4.0	1.8
Northern Africa	1.3	0.8	1.4	0.6	0.6	0.6	2.0	0.2	2.3	1.4
Southern Africa	2.8	1.0	0.2	0.1	2.2	0.6	2.5	0.4	12.8	6.2
Western Africa	1.2	1.0	0.6	0.3	0.5	0.1	0.9	0.1	0.8	0.4
Caribbean	2.0	0.6	0.3	0.1	2.4	0.6	4.0	0.5	4.1	1.0
Central America	0.8	0.5	0.1	0.0	0.7	0.2	1.5	0.2	1.6	0.5
South America	2.2	0.7	0.2	0.1	2.2	0.4	3.3	0.4	5.6	1.5
Northern America	1.2	0.5	0.2	0.1	1.2	0.3	1.2	0.2	5.0	1.0
Asia	3.0	1.4	1.4	0.5	2.4	0.5	1.9	0.2	9.9	3.8
Eastern Asia	1.1	0.5	1.5	0.6	0.7	0.1	1.1	0.1	14.1	4.5
Southeastern Asia	1.9	1.2	3.8	1.4	2.1	0.5	1.3	0.2	3.3	0.9
South Central Asia	6.3	3.0	0.4	0.1	5.3	1.2	3.0	0.4	6.0	3.6
Western Asia	1.0	0.6	0.7	0.3	0.6	0.3	2.9	0.4	2.7	1.9
Europe	3.0	0.7	0.3	0.1	2.7	0.4	3.0	0.2	4.9	0.9
Central and Eastern Europe	5.1	0.7	0.3	0.2	3.8	0.3	4.9	0.2	5.0	0.6
Northern Europe	1.7	0.7	0.2	0.1	1.4	0.3	1.3	0.2	7.2	2.3
Southern Europe	1.9	0.6	0.3	0.1	1.8	0.3	2.9	0.2	2.8	0.5
Western Europe	2.0	0.6	0.2	0.1	2.7	0.5	1.5	0.2	5.0	1.2
Australia	1.3	0.6	0.2	0.1	1.2	0.3	1.0	0.1	4.7	1.3
New Zealand	1.4	0.7	0.3	0.1	1.0	0.2	0.8	0.1	4.4	1.6
Melanesia	14.4	10.2	0.3	0.1	2.8	0.4	1.9	0.4	3.4	1.4
Micronesia	2.0	0.0	1.3	1.0	0.0	0.0	1.1	0.0	3.3	0.0
Polynesia	1.4	0.0	0.6	0.0	2.0	0.3	2.0	0.7	3.0	0.3

1.12.4 Areca Nut

Areca nut is the seed of the fruit of the oriental palm *Areca catechu*. It is the basic ingredient of a variety of widely used chewed products. The consumption of areca nut is indigenous to India, Sri Lanka, Bangladesh, Myanmar, Taiwan and numerous islands in the South Pacific. It is also popular in parts of Thailand, Indonesia, Malaysia, Cambodia, Vietnam, the Philippines, Laos and China and in emigrant communities from these countries. It is believed that Areca catechu may be native to Sri Lanka, West Malaysia and Melanesia. Areca nut is used as a masticatory substance by approximately 600 million people worldwide. It is estimated that 10–20 % of the world's population chew areca nut in some form, often mixed in betel quid (pan) [54]. Patterns of use across South and SE Asia [58] and the growing public health problem across the Pacific Islands have been extensively documented recently [59]. Screening in Saipan and Guam has shown a prevalence

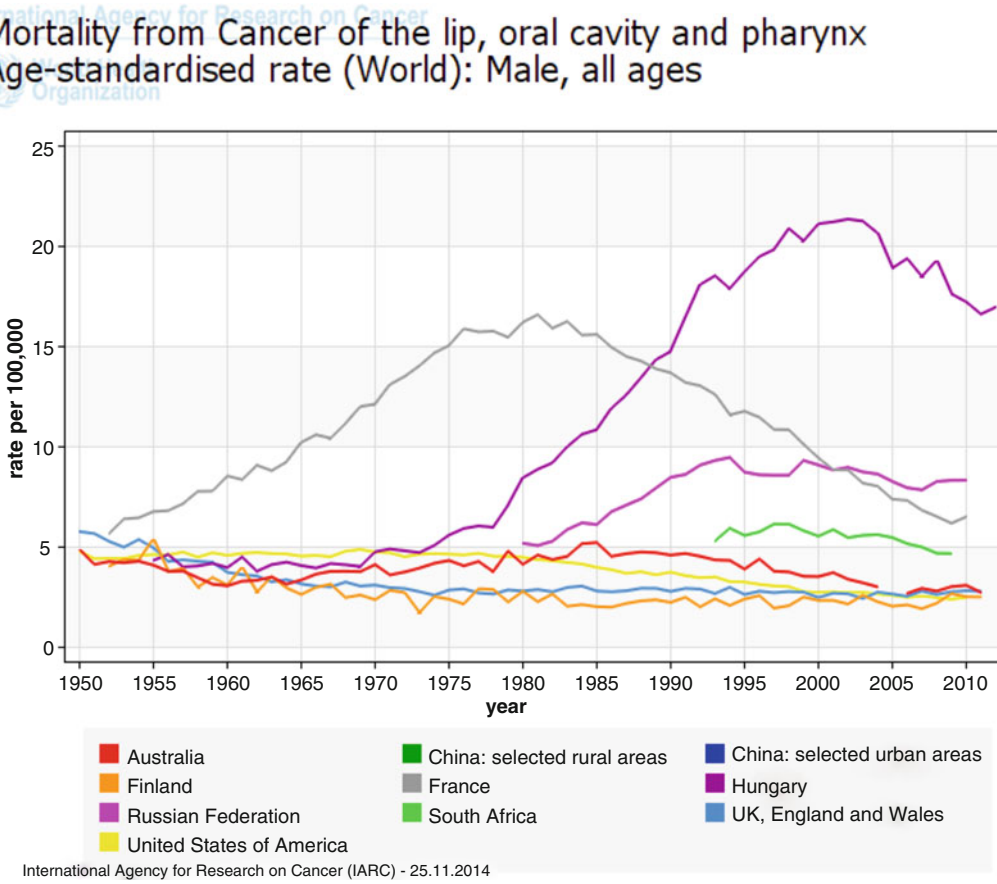


Fig. 1.18 Mortality from cancer—male. Trends in mortality over time are important to track and to understand. Hungary is a disaster, though a declining trend is evident from the year 2003. Russia remains a concern. France demonstrates what can be achieved. The overall modest downward trend in the other countries illustrated is encouraging

of OPMD of almost 20 % among users of "betel" when other ingredients were added [60].

The major constituents of the nut are carbohydrates, fat, proteins, fibre, polyphenols (flavonols and tannins), alkaloids and mineral matter. Among the chemical constituents, alkaloids are the most important chemical. The nut has been shown to contain at least six related alkaloids, of which four (arecoline, arecaidine, guvacine and guacoline) have been conclusively identified [61].

Nitrosamine derivatives from each of the four major arecal alkaloids are produced by nitrosation of the alkaloids in dried stored nuts, in the mouth and especially in the acid conditions found in the stomach, in the presence of nitric oxide generated by bacterial action. Two of these derivatives are accepted as carcinogenic in animal studies, especially MNPN (methylnitrosaminoproprionitrile). Endogenous nitrosation is significantly higher in subjects with poor oral hygiene as determined by volumes of dental plaque [62]. This implies that, on the basis of the availability of substrates from both areca nut and tobacco, there is a more extensive formation of nitrosamine in subjects with poor oral hygiene if they also chew tobacco [63]. Moreover direct evidence that reactive oxygen species, such as the hydroxyl radical (HO), are generated in the oral cavity due to autoxidation of polyphenols contained in areca nut and enhancement by the alkaline pH from slaked lime has been reported [54, 64].

1.12.5 Areca Nut-Based Industrial Packaged Products

A variety of packaged areca products are now available. These are mostly manufactured in India and Pakistan and exported worldwide where they are used by old and new habitués. The most common are *gutka* and *pan masala*. Gutka is a dry, relatively non-perishable commercial preparation containing areca nut, slaked lime, catechu, condiments and powdered tobacco. The same mixture without tobacco is called pan masala [65].

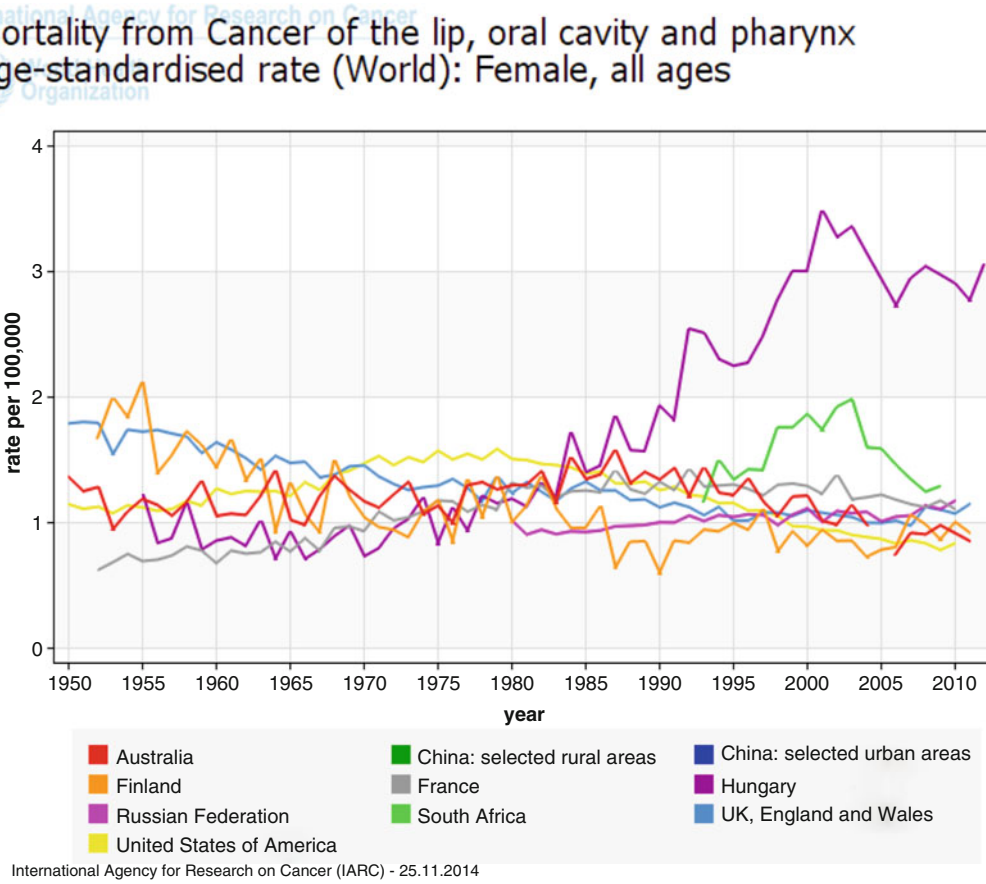


Fig. 1.19 Mortality from cancer—female. Although only ~a tenth of the male rate, Hungarian females remain a challenge

1.13 Systemic Effects of Areca Nut

Though largely outwith the scope of this chapter, it is important to realise that areca nut has widespread systemic ill effects [66]. These include psychological and behavioural disturbances due to inhibition of uptake of gamma-aminobutyric acid, neurotoxicity and addiction, cardiac arrhythmias and increased risk of myocardial infarction, hyperlipidaemia and metabolic syndrome, hypothyroidism and premature birth and infertility. Further, the IARC Monograph makes it clear that areca nut contributes not only to cancer of the mouth and oropharynx but also to cancers of the oesophagus, liver and biliary tract, lung and uterus.

1.14 Damage to Oral Soft Tissues from the Chewing of Areca Nut and Related Products

1.14.1 Lichenoid Lesions

Areca-induced lichenoid lesions, mainly on the buccal mucosa and tongue, are recognised. This is considered to be a type IV contact hypersensitivity-type lesion which resembles oral lichen planus clinically [67].

1.14.2 Betel Chewer's Mucosa

This condition was first described by Mehta et al. (1971) and is characterised by a brownish-red discoloration of the oral mucosa. It is often accompanied by encrustation of the affected mucosa with quid particles, which are not easily removed, and with a tendency for desquamation and peeling. Both chemical and traumatic effects of the betel quid on the oral mucosa are likely. The presence of tobacco in the quid is not essential for the development of chewer's mucosa [67].

1.14.3 Oral Leukoplakia

A case–control study conducted in Taiwan, where areca is chewed without tobacco, found the odds ratio for developing leukoplakia to be 7.43 (95 % CI 1.94–156.27) for areca nut chewers. These authors demonstrated that the cessation of areca chewing resulted in regression of 62 % of leukoplakias [68].

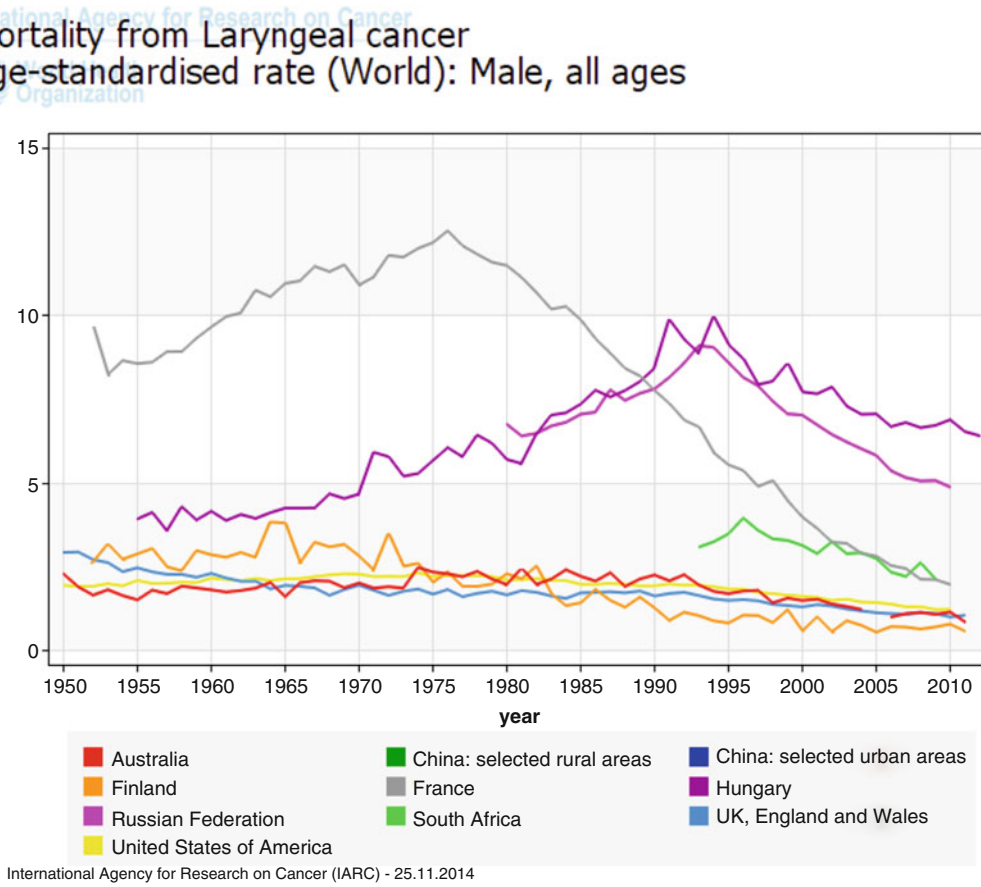


Fig. 1.20 Mortality from laryngeal cancer—male. Another success demonstrated for France, followed by healthy trends for the Russian Federation and Hungary (Y-axis = rate per 100,000 pa)

1.14.4 Oral Submucous Fibrosis

It is now accepted that chewing areca is the single most important etiological factor for the development of OSF [69–71], although the pathogenesis is not fully understood. In vitro studies have shown that areca nut alkaloids such as arecoline and its hydrolysed product arecaidine can stimulate cultured fibroblasts to proliferate and synthesise collagen. In addition flavonoids from the nut have been shown to enhance the cross-linking of collagen, thereby increasing its resistance to degradation by collagenases, as part of normal tissue homeostasis. The copper content of areca nut is high [72], and the possible role of copper as a mediator of fibrosis is supported by the demonstration of upregulation of lysyl oxidase in OSF biopsies [73]. The current state of knowledge on the molecular changes in oral tissues associated with areca nut and tobacco use is clearly laid out by Dionne et al. [74], and the pathogenesis, including familial patterns and genetic predisposition, is explored in Bengali populations by J Gopal Ray in a series of excellent so-far largely unpublished studies.

1.14.5 Oral Squamous Cell Carcinoma

Historical evidence dating back nearly a century indicates that areca nut is involved in the development of OSCC. Subsequently, many case–control studies [75, 76] have confirmed that betel quid chewing increases the risk of developing OSCC, especially when the quid contains tobacco [77, 78]. A South African study found that 68 % of cheek cancer and 84 % of tongue cancers developed in subjects consuming areca *without* tobacco [79]. A large number of animal studies have confirmed that areca products and derivatives such as arecoline and areca-derived nitrosamines have the ability to induce neoplastic changes in experimental models, and the IARC has now formally designated areca and betel quids without tobacco as carcinogenic to man [54, 56]. The role of commercial forms of areca nut and tobacco in the continuing rise in oral cancers in Ahmedabad has recently been confirmed [80].

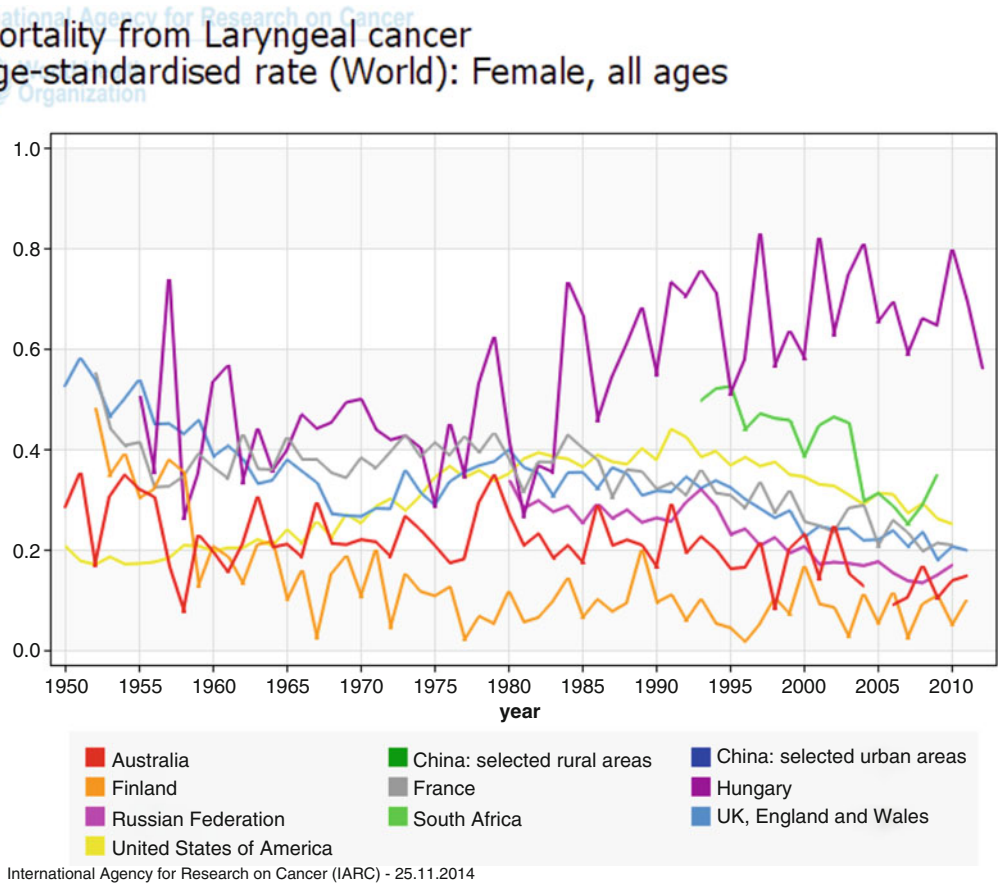


Fig. 1.21 Mortality from laryngeal cancer—female. Laryngeal cancer. This is a "noisy" curve because of the comparatively low mortality rates in women. Worryingly, but not surprisingly, it suggests an upward trend in Hungary (Y-axis = rate per 100,000 pa)

1.15 Slaked Lime

Slake lime (calcium hydroxide) is added to betel quids in most of South Asia. In coastal areas of Sri Lanka and the Pacific, it is obtained by heating sea shells or harvested from corals. In inland areas it is quarried from limestone. When added to betel quids, it causes erosions of oral mucous membranes which facilitate penetration of betel quid carcinogens through the mucosa.

1.16 Smokeless or Chewing Tobacco

Tobacco is often added to the quid mixture. Edible tobacco in the Indian subcontinent is prepared from sun-dried and partly fermented, coarsely cut leaves of *Nicotiana rustica* and/or *Nicotiana tabacum* without further processing. Chewing tobacco results in a local exposure of oral mucosa to at least 28 carcinogens, including tobacco-specific nitrosamines (TSNA) and polycyclic aromatic hydrocarbons (PAH) [81]. Unusually high levels of carcinogenic TSNAs (e.g. *N*-nitrosonornicotine (NNN) and nicotine-derived nitrosamine ketone (NNK)) were reported in saliva of oral snuff users in Sudan [82] and tobacco chewers in India [83]. NNK is a potent carcinogen, and human buccal epithelial cells (in culture) have been shown to metabolise NNK. The formation of macromolecular DNA adducts following NNK metabolism is correlated with carcinogenesis in animal models [84]. Adducts of NNN and NNK lead to mutations of oncogenes and of tumour suppressor genes [85]. The serious situation which continues in India has been comprehensively reviewed recently [86], and an exhaustive treatise was published in late 2014 by the US Department of Health and Human Services [87]. Three recent meta-analyses confirm the importance of ST across South Asia as a whole [77, 78, 88].

The form of oral ST used in North Eastern Africa and parts of the Middle East (known as Toombak in the Sudan and Shammah in Yemen and Saudi Arabia) [82, 89] is a mixture of powdered tobacco, lime, ash, black pepper, oils and

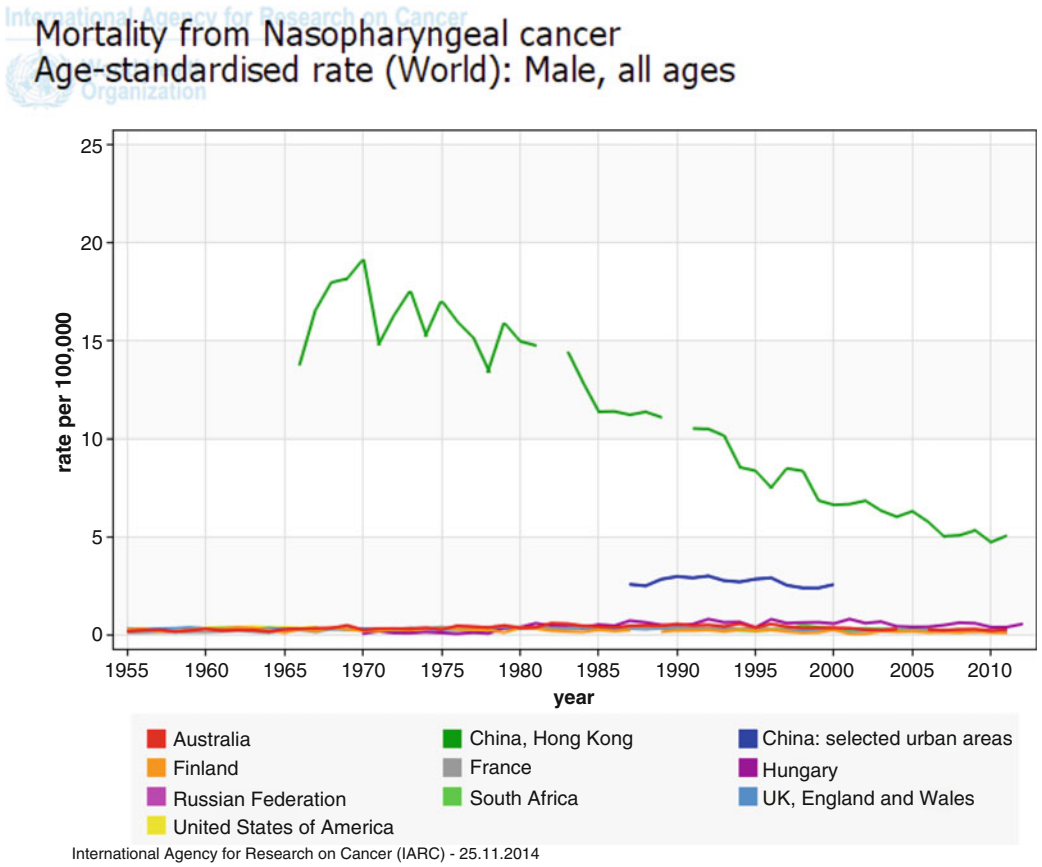


Fig. 1.22 Mortality from nasopharyngeal cancer male. One hopes the successes in Hong Kong can be replicated in other high-risk groups

flavourings. This is responsible for the epidemic of oral cancer in this region [82, 90, 91].

Betel chewing also releases large amounts of a reactive oxygen species (ROS), especially whilst the betel quid is actually present. Both TSNA and ROS are major genotoxic agents involved in chewing tobacco-associated oral cancer [54]. Clear dose–response relationships between quid use and the risk of oral cancer and of potentially malignant oral disorders have been demonstrated in many epidemiological studies.

Most forms of oral smokeless tobacco—oral snuff—consumed in Scandinavia and in North America are not fluecured and contain relatively low amounts of TSNs. Although the topic is controversial, many of these products are not highly carcinogenic, and it has even been suggested that they have a role as nicotine replacement products in achieving smoking cessation [92]. It is, however, important to remember that there is no such thing as safe tobacco: most smokeless tobaccos have high levels of nicotine and are addictive; indeed, there is evidence that they can be initiators of smoking [93]. Further, they have significant cardiovascular effects [94] and certainly produce oral mucosal lesions and local damage to the periodontium [95].

1.17 Contaminants

Areca nut can be contaminated with fungi such as *Aspergillus Flavus*, *A. Niger* and *Rhizopus* spp. Almost 40 % of samples of areca nut from India analysed using thin layer chromatography contained aflatoxins [96]. These are established carcinogens.

1.18 Tobacco Smoking

Tobacco is identified as the leading preventable cause of premature death worldwide. It is estimated that 4.9 million people died of tobacco-related illness in 2000, and by 2020, it is expected that this figure will rise to 10 million deaths per year, of which 70 % will be in developing countries [84]. Tobacco is a major independent risk factor for the development of oral and pharyngeal cancer and other malignancies of the upper aerodigestive tract. Tobacco is consumed in different ways as a form of smoking: cigarettes, cigar, beedi/bidi, reverse smoking and smokeless tobacco like oral snuff

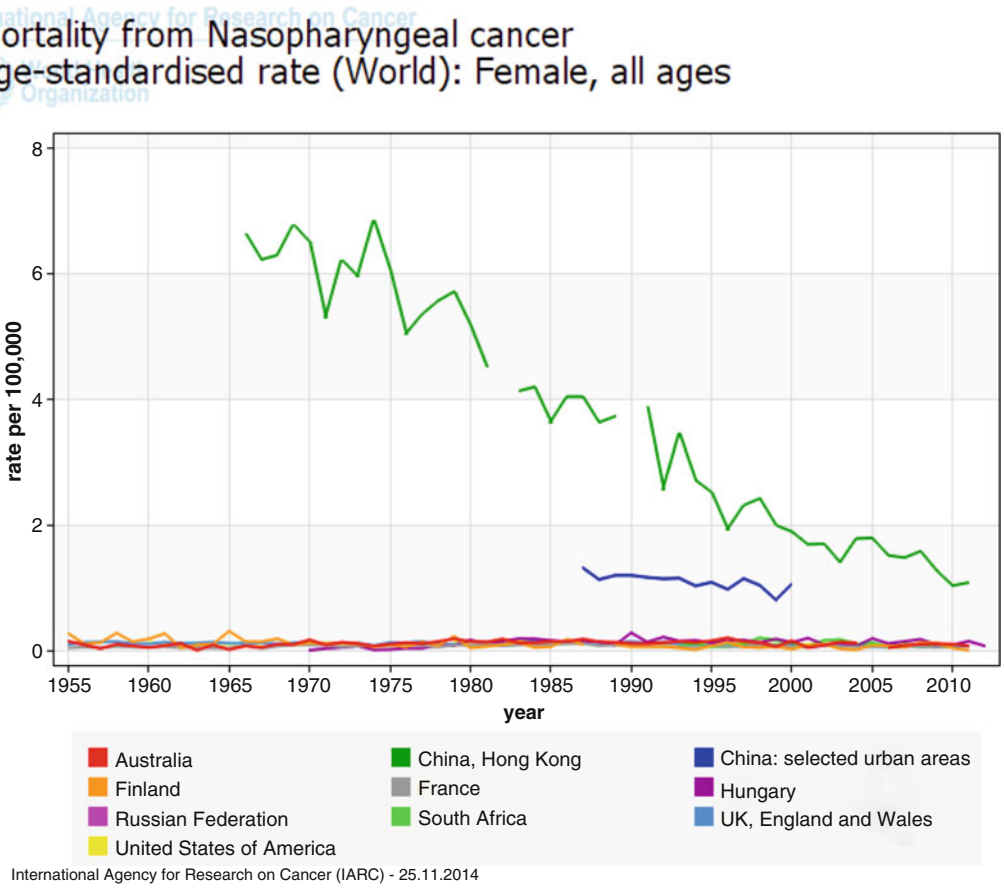


Fig. 1.23 Mortality from nasopharyngeal cancer female. From a lower initial base, Hong Kong women share this success story

or in moist pouches. Tobacco smoke contains more than 70 carcinogenic combustion products. In particular, NNK, NNN and polycyclic aromatic hydrocarbons (PAHs) have been causally linked to UADT cancer. The activity of carcinogens is generally exerted through DNA adducts [97, 98]. Tobacco smoking and quid chewing both cause oxidative stress to tissues, i.e. the sustained presence of reactive oxygen species (ROS), which initiate free radical reactions. ROS can damage proteins, lipids, carbohydrates and DNA. Minor DNA damage can result in mutations which can be part of the causal chain for malignant transformation, whilst sustained DNA damage can result in further perturbations of cell cycle control [99].

As a form of smoking, bidis, a traditional form of raw tobacco hand-wrapped in a temburni leaf and common throughout South Asia, are particularly toxic. A strong interaction was found between alcohol consumption and bidi smoking (OR = 19.6, 95 % CI = 4.6–83.5) in a recent Indian study [100].

In addition to an extensive literature on the carcinogenicity of tobacco smoke in cell and animal models, numerous case–control and cohort studies affirm its key role in man and the super-multiplicative synergism with alcohol drinking [101]. Both smoked and smokeless tobaccos have considerable adverse effects on the upper aerodigestive tract, apart from cancer and OPMD. The severity and extent of periodontal disease are increased by as much as a relative risk of 7 in smokers, depending on the definition of disease, and smoking contributes to poor wound healing, implant failure and increased dental caries, though the evidence for the latter is weak [102].

The International Head and Neck Cancer Epidemiology Consortium has conducted a comprehensive meta-analysis and has concluded that cessation of smoking for 1–4 years reduces the risk of a H&N cancer (OR 0.70 compared to current smoking) but that it takes 20 years to reach the risk of a never smoker [103]. The same is true when oral cancer alone is considered [102]. It is essential to stop smoking after treatment for a head and neck cancer, as continued smoking increases the risk of a second tobacco-related cancer by a factor of at least four [104].

The WHO Framework Convention on Tobacco Control has supported many countries in reducing smoking, though there remain non-signatories and progress is uneven [105]. See Table 1.4.

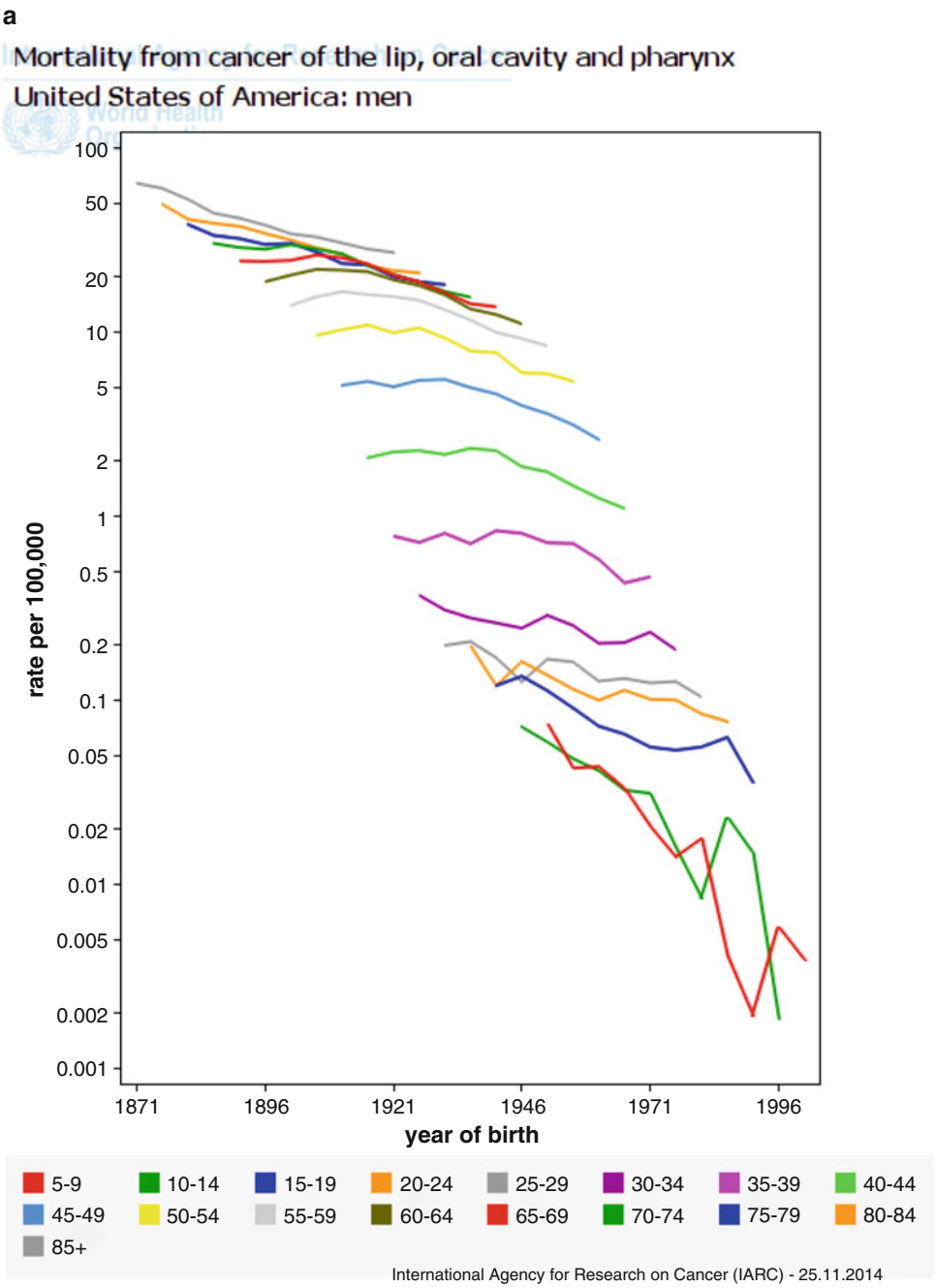


Fig. 1.24 (**a**) Mortality from oral cancer USA male. Trends in mortality rates for cancers of the lip, oral cavity and pharynx combined in American men born between ~1870 and the turn of the twenty-first century. There has been a steady decline at all ages, most marked in the younger cohorts. (**b**) Mortality from oral cancer USA female. Trends in mortality rates for cancers of the lip, oral cavity and pharynx combined in American women born between ~1870 and the turn of the twenty-first century. There has been a steady decline at all ages, most marked in the youngest cohorts. (**c**) Age-specific mortality from oral cancer USA male. This presentation of the age-specific mortality rates for lip, oral cavity and pharyngeal cancers combined for USA males confirms the data above. Although there are declines in all age groups, projections show rising disease burden in the decades ahead because of the ageing of the population

1.19 Alcohol

Unsafe consumption of alcohol, including so-called binge drinking, is a major public health problem worldwide, e.g. contributing between 5000 and 40,000 deaths in the UK annually [108]. The possible beneficial effects of moderate alcohol consumption have been widely canvassed, because of the so-called J-shaped relationship between alcohol intake and all-cause mortality, as shown in a number of meta-analyses [109]. The initial upstroke of this J-curve is

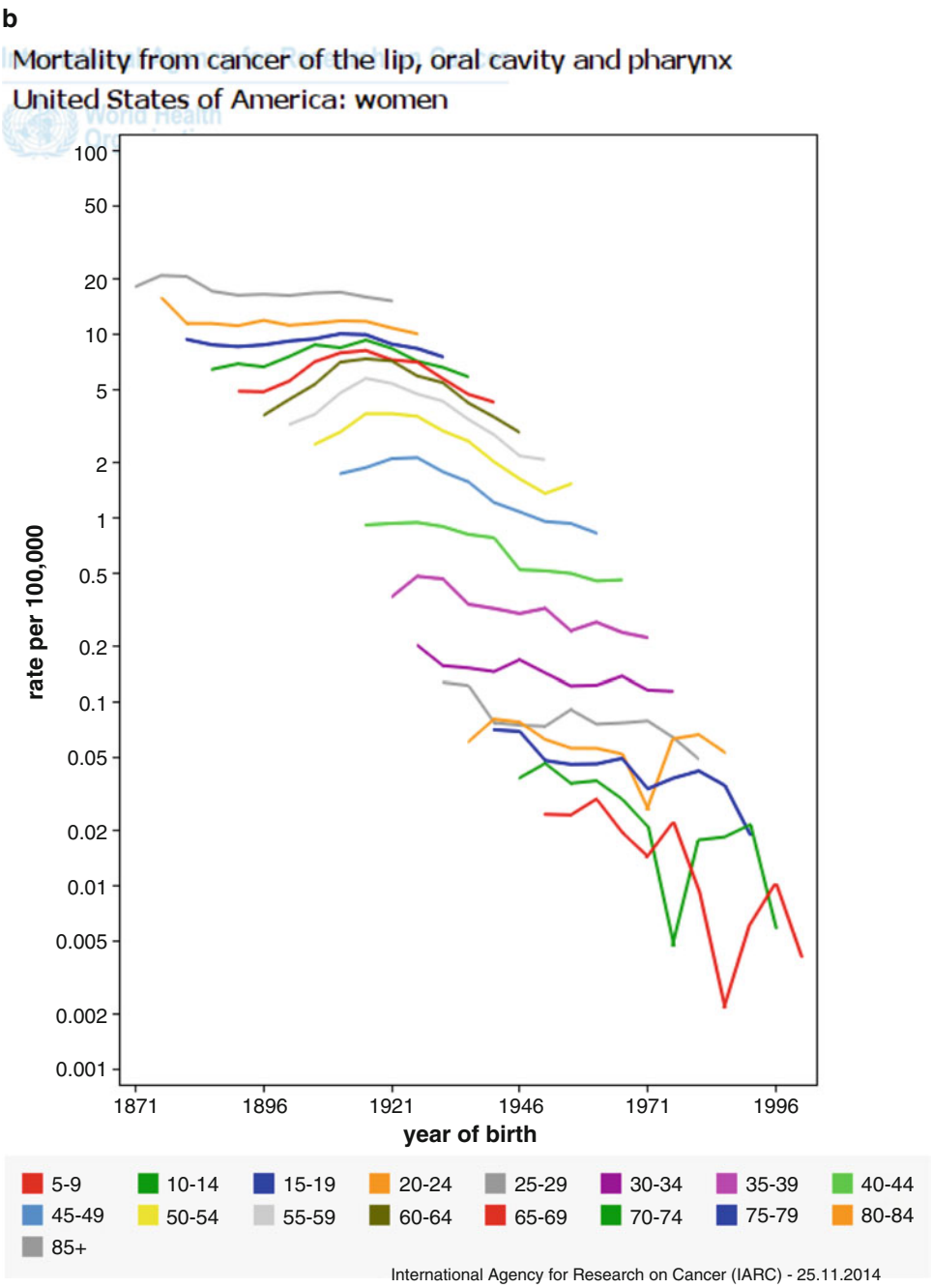


Fig. 1.24 (continued)

thought to be due to the cardioprotective effect of moderate alcohol consumption. In particular, alcohol increases high-density lipoprotein levels, inhibits platelet aggregation and promotes fibrinolysis [110]. On the other hand, it has always been recognised that above an intake of around 10 g of alcohol per day, the detrimental effects of alcohol predominate [109]. The World Health Organisation in Europe is very concerned about the impact on population health and has recently published a comprehensive report on use and abuse of alcohol in member countries and proposes measures to minimise risk [111].

Alcohol is argued to account for about 4 % of cancer deaths overall: predominantly breast cancer in women and upper aerodigestive tract and oesophagus cancer in men [112]. The recent increases in oral cancer reported in younger subjects in the UK were related, at least in part, to growing alcohol use/abuse in that society [44]. The difficulty of accurately quantifying the influence of alcohol in the aetiology of H&N cancer stems from the fact that most people who drink heavily also smoke. It is also difficult to obtain reliable information from individuals on their intake of alcohol. Nevertheless many studies show a dose–response relationship

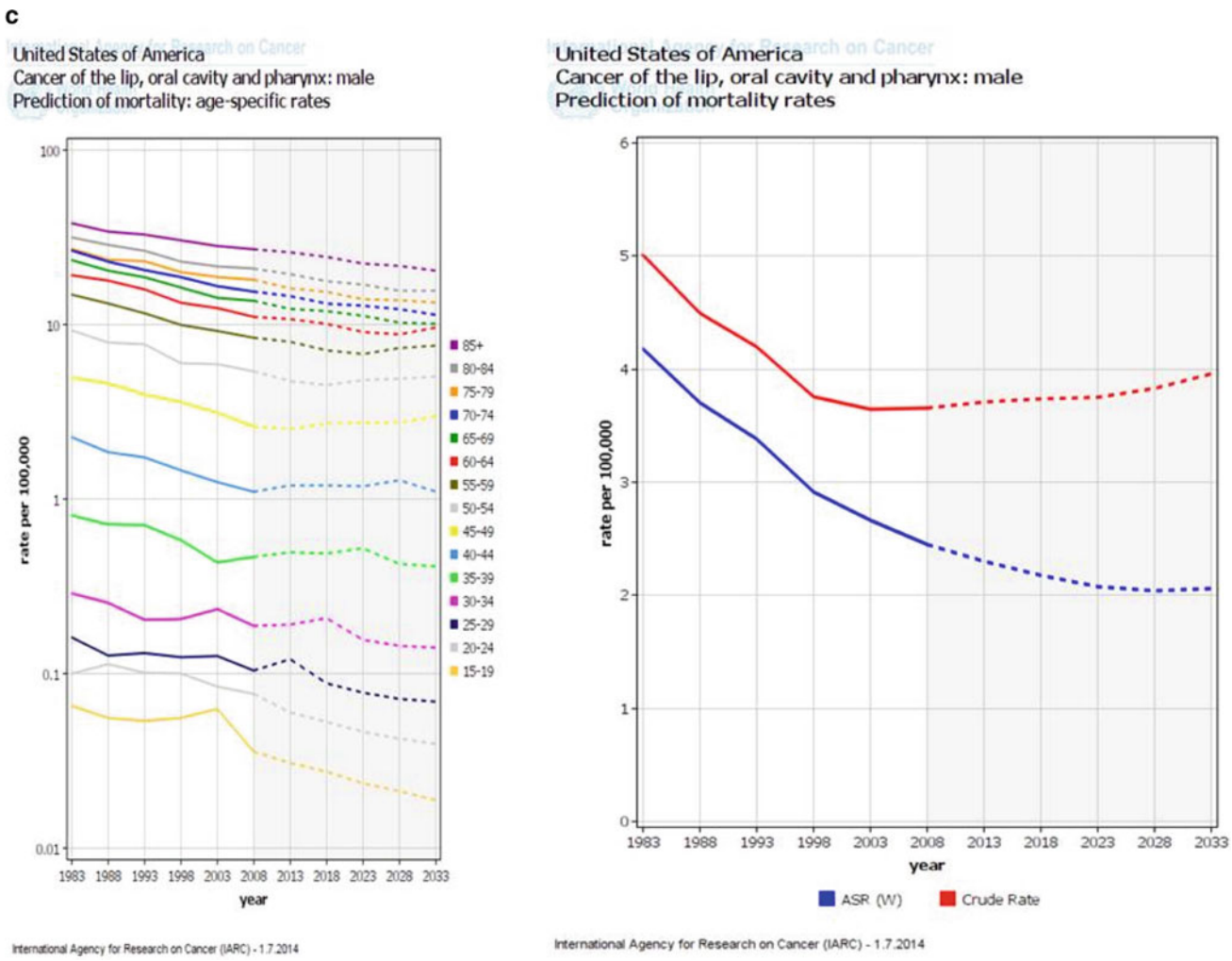


Fig. 1.24 (continued)

between alcohol use and particularly oral and pharyngeal cancer [113], and the survival of HNSCC patients who continue to abuse alcohol is reduced, though not necessarily because of recurrence or second primary neoplasm [114].

The Health Education Council in the UK has historically recommended a weekly of no more than 14 units for women and 21 units for men. Using these criteria, 1 in 4 men and 1 in 10 women in that country are believed to be drinking over this limit, with the number of habitual heavy drinkers estimated at four million [115]. Although the legal age for drinking is 18 years, the average age at which drinking starts has fallen since the early 1970s from around 17 to around 11 years, in boys and girls. The recent emergence of "alcopops" (alcoholic drinks that mimic the taste of nonalcoholic drinks) has resulted in wide uptake among those aged under 18 years.

Internationally, there is a developing view that *any* consumption of alcohol is detrimental, and even the French government now publicly recommends severe constraint or abstinence: the French National Cancer Institute has declared "there is no amount of alcohol, however small, which is good for you" [116]. WHO policy is to minimise alcohol use in all society [117], and the Australian Guidelines to Reduce Health Risks from Drinking Alcohol summarises the science cogently [118]. These state that, for healthy men and women, drinking no more than two standard drinks [viz. 10 g of ethanol] on any day reduces your risk of harm from alcohol-related disease or injury over a lifetime. Drinking no more than four standard drinks on a single occasion reduces the risk of alcohol-related injury arising from that occasion.

Ethanol and water are the main components of most alcoholic beverages, which also contain volatile and nonvolatile flavour compounds. The major alcohol metabolising enzymes are alcohol dehydrogenase, which oxidises ethanol to acetaldehyde, and aldehyde dehydrogenase, that detoxifies acetaldehyde to acetate. Acetaldehyde is responsible for the oral carcinogenic effect of ethanol, owing to its multiple mutagenic effects on DNA. Acetaldehyde can be produced by oral microorganisms through the metabolism of ethanol. To account for the different sources of acetaldehyde production, some studies have examined the interplay between alcohol

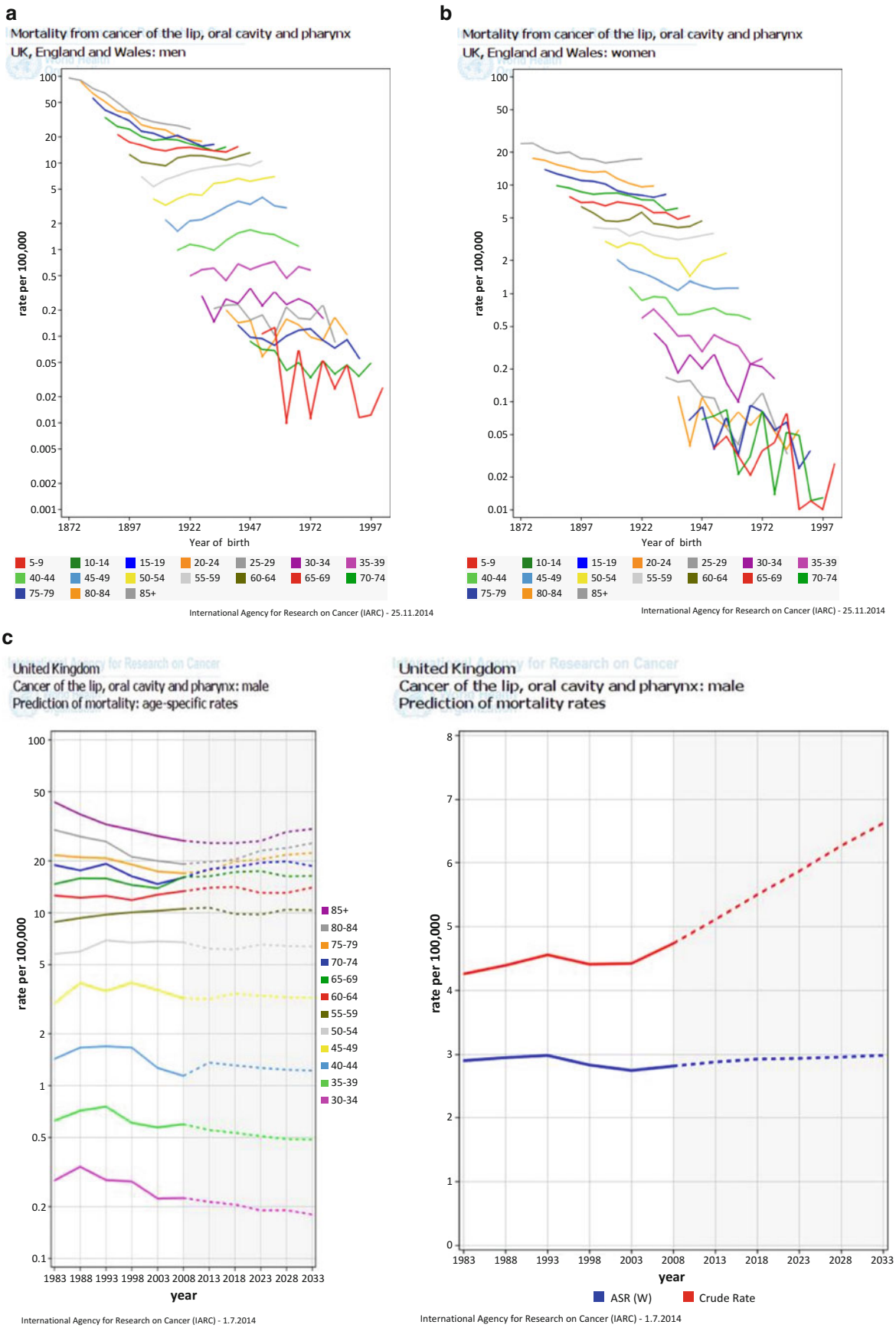


Fig. 1.25 (**a**) Mortality from oral cancer—UK males. (**b**) Mortality from oral cancer—UK females. (**c**) Age-specific mortality from oral cancer—UK males. (**a**–**c**) Birth cohort curves of the mortality rates for lip, oral cavity and pharyngeal cancers for males (**a**) and females (**b**) in England and Wales. The projected rises in numbers in the years ahead, due to ageing of the population, are alarming (**c**)

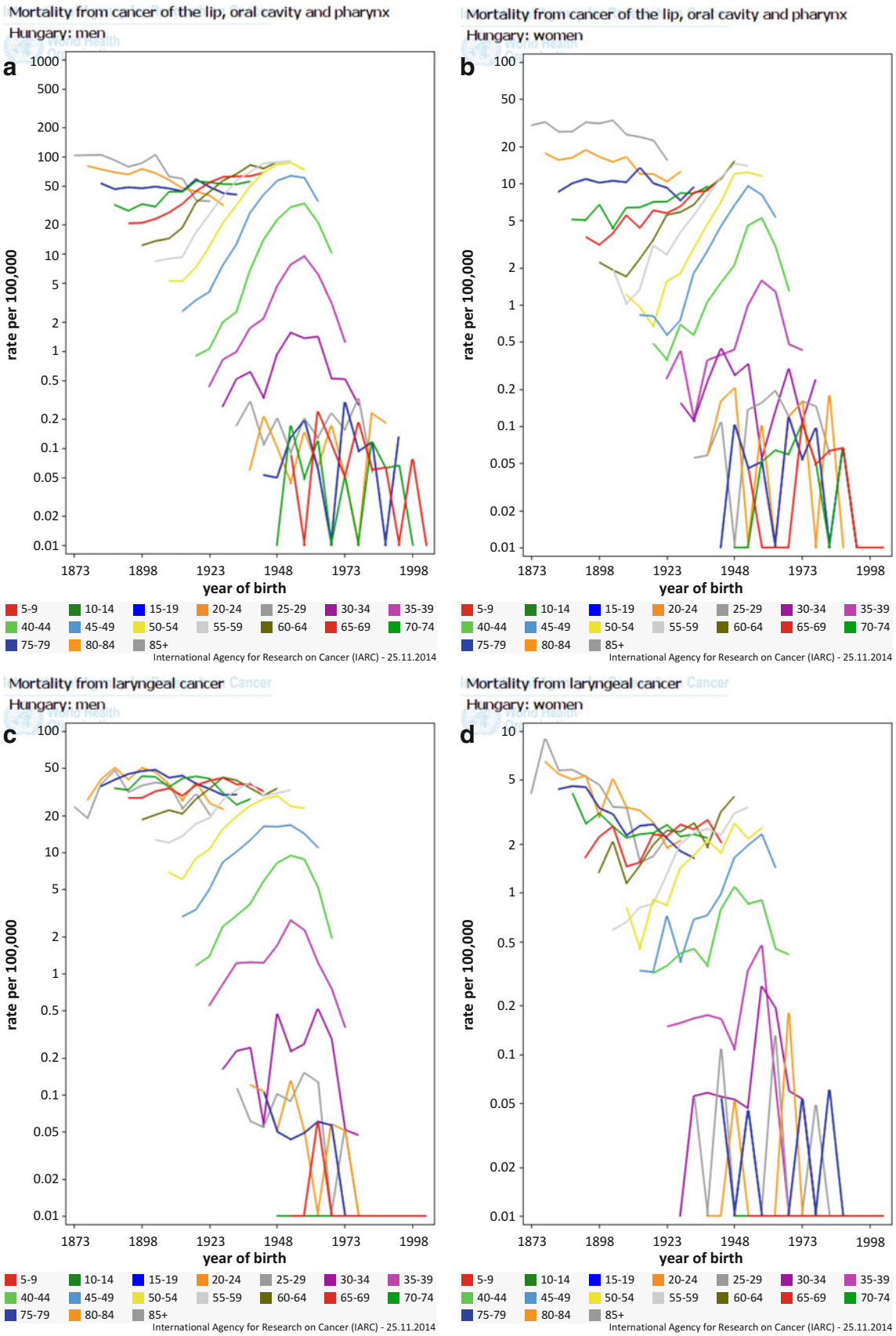


Fig. 1.26 (**a**) Mortality rates for lip, oral cavity and pharyngeal cancers for males in Hungary. (**b**) Mortality rates for lip, oral cavity and pharyngeal cancers for females in Hungary. (**c**) Mortality rates for laryngeal cancers for males in Hungary. (**d**) Mortality rates for laryngeal cancers for females in Hungary. Birth cohort curves of the mortality rates for lip, oral cavity and pharyngeal cancers for males (**a**) and females (**b**) and for laryngeal cancer (**c**, **d**) in Hungary. The challenge for Hungary, apparent in other curves, is confirmed here. Males born in the first half of the twentieth century had rising rates or death from oral and pharyngeal cancer. Those born after 1950 are at less at risk

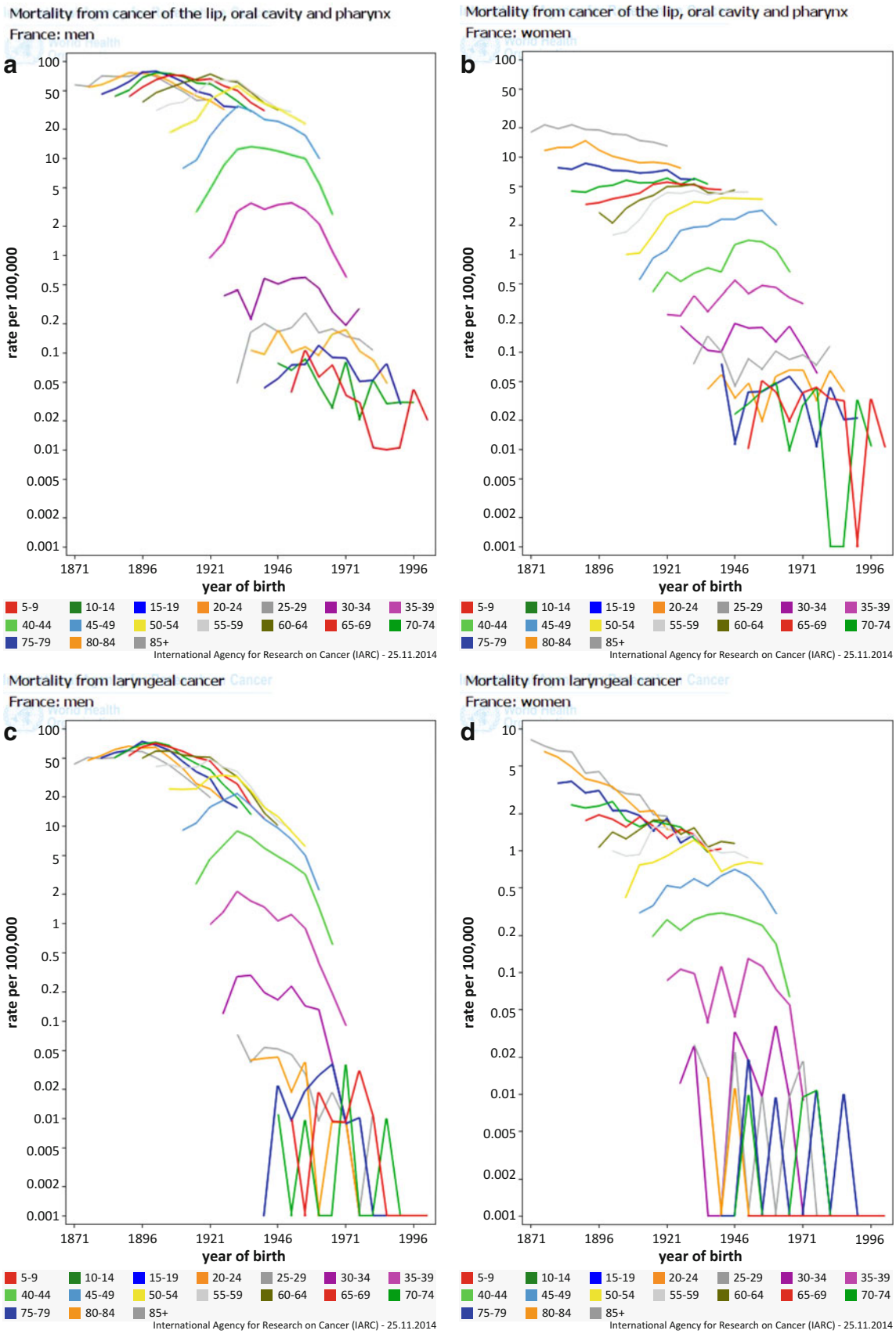


Fig. 1.27 (**a**) Mortality rates for lip, oral cavity and pharyngeal cancers for males in France. (**b**) Mortality rates for lip, oral cavity and pharyngeal cancers for females in France. (**c**) Mortality rates for laryngeal cancers for males in France. (**d**) Mortality rates for laryngeal cancers for females in France. Birth cohort curves of the mortality rates for lip, oral cavity and pharyngeal cancers for males (**a**) and females (**b**) and for laryngeal cancer (**c**, **d**) in France. Birth cohort curves are instructive. For males born in the nineteenth century and the first few decades of the twentieth century, death rates from oral and pharyngeal cancer were extremely high. Those born from around 1940 and later are generating the national average downward trends seen above

Table 1.3 Mortality trends (annual percentage change) for oral and pharyngeal cancer in the USA between 2002 and 2011, by race and sex

	All races			Whites			Blacks		
	Total	Males	Females	Total	Males	Females	Total	Males	Females
All ages	−1.0*	−0.9*	−1.5*	−0.6*	−0.4*	−1.3*	−3.4*	−3.7*	−2.7*

Based on data from [20]
*Annual percentage change in rate is statistically significantly different from zero ($P<0.05$)

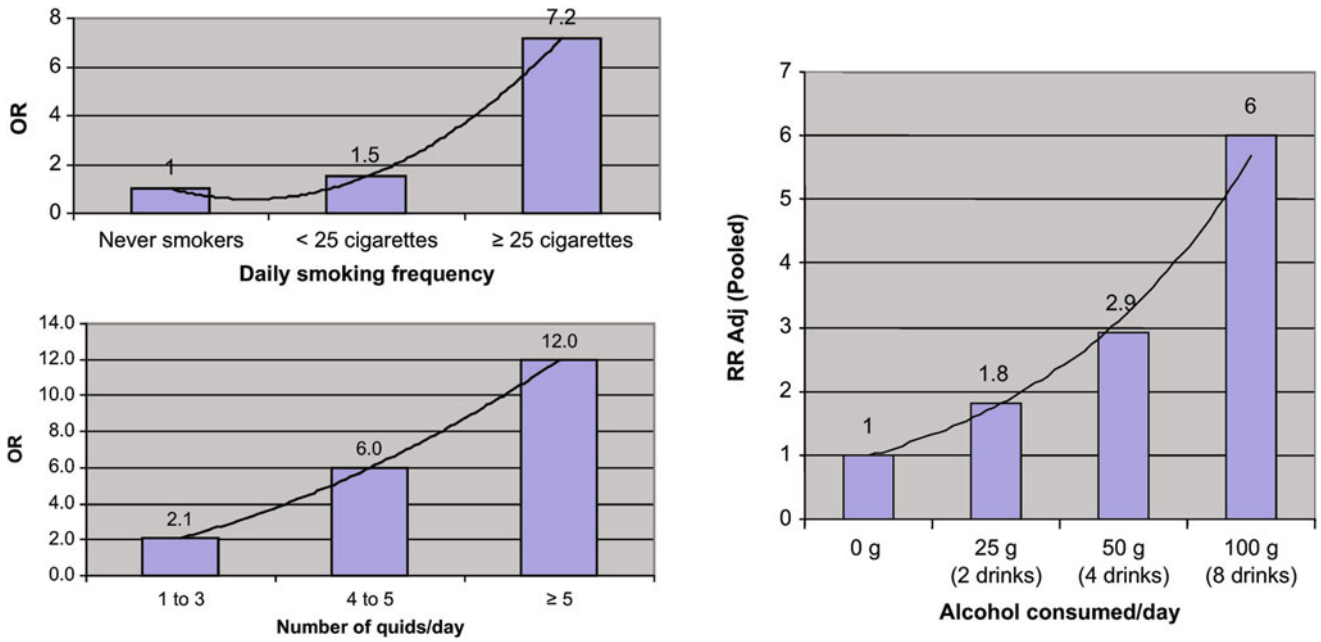


Fig. 1.28 The dose–response relationship between the major risk factors for oral and pharyngeal cancers. [Adapted from Johnson NW, Warnakulasuriya S, Gupta PC, Dimba E, Chindia M, Otoh EC, Sankaranarayanan R, Califano J, Kowalski L. Global Oral Health Inequalities in Incidence and Outcomes for Oral Cancer: Causes and Solutions. Advances in Dental Research 2011; 23(2): 237–246. With permission from Sage Publications]

consumption, oral hygiene (as a proxy measure for the growth of microorganisms) and alcohol metabolising genes (ADH 1B and ALDH 2) [119]. Specific alcoholic beverages have been shown to contain specific impurities or contaminants which can be carcinogenic. *N*-nitrosodimethylamine is present in some beer and whisky and has been associated with an increased risk of oral cancer. Polycyclic aromatic hydrocarbons, some of which are considered to be carcinogenic, are found in many brands of whisky [120].

Alcohol also acts in the following ways to promote oncogenesis [120]. Ethanol:

- Damages the phospholipids of cell membranes and increases permeability. It has been shown to enhance the penetration of tobacco-specific carcinogens across the oral mucosa [121].
- Impairs DNA repair mechanisms.
- Perhaps catalyses the activation of tobacco carcinogens.
- Alcohol is highly calorific. It lessens the protective effect of beneficial foods such as fruits and vegetables by depressing hunger.
- Is hepatotoxic, thus reducing the effectiveness of those enzyme systems central to detoxification of carcinogens, especially the glutathione-S-transferases and cytochrome-p450 systems.

A case–control study in Uruguay conducted between 1992 and 1996 is worthy of note [122]. Histologically confirmed cases ($n=471$) of squamous cell carcinoma of the oral cavity and pharynx in males admitted to four major hospitals in Montevideo were matched with the same number of other patients admitted for a variety of nonsmoking- and nondrinking-related conditions as controls. Alcohol consumption was assessed by interview and the number of grams of ethanol consumed per day calculated. Ever-drinking was associated with a 4.5-fold increased risk of oral plus pharyngeal cancer compared to nondrinkers, though no clear

Table 1.4 Interventions and their effectiveness in reducing tobacco consumption

Intervention	Effectiveness
Large, regular increases in excise taxes that reduce affordability	50 % higher prices reduce consumption by approximately 20 % (10 % quit, 10 % reduce the amount smoked). This is always controversial because smoking prevalence is higher in lower socioeconomic groups in most countries
Mass media counter advertising, warning labels and plain packaging and epidemiological studies (such as deaths from smoking on death records)	Difficult to quantify but does increase cessation rates. Australia was the first country to introduce plain packaging and successfully defended a legal challenge from big tobacco companies: other countries are planning legislation; cost-effective studies are awaited Antitobacco advertisements in mass media, placed by governments and health promotion agencies, have long been common in many countries: it is pleasing to see the growth of newspaper, radio and television warning about areca products becoming common in India and Sri Lanka
Complete bans on tobacco advertising, promotion and sponsorship	Reduces consumption by approximately 15 % in low- and middle-income countries
Complete ban on smoking in public places, including all workplaces	Reduces consumption by 3–14 %. Enforcement is critical: the experience of Hong Kong in sending a cadre of antismoking officials into public places has proven effective
Cessation support for smokers, brief medical advice, pharmacotherapy	At 6 months, brief medical advice doubles the quit rates (from 2–5 % unaided to 4–8 %); medications triple the quit rates (to 8–12 %). Dentists/dental practices can achieve comparable results [106]
Antismuggling technologies: local language labels, improved tax administration, increased customs and international efforts to target smuggling	10 % higher spending on antismuggling efforts reduces smuggling by 5 % and consumption by 2 %

Based on data from [107]

dose–response relationship was observed. Consumption of hard liquor was associated with a 3.6-fold increased risk, whereas pure wine drinking showed only a 2.1-fold increased risk. When risks were analysed by subsites, the highest odds ratios were observed for oral cavity cancer.

Another case–control study conducted in Italy and Switzerland between 1992 and 1997 included 749 cases of oropharyngeal cancer and 1772 hospital controls. Alcohol consumption was measured by the number of drinks consumed per day: one drink corresponding to ~125 ml of wine, 330 ml of beer or 30 ml of spirits (i.e. about 12 g of ethanol). Compared to light drinkers (1–2 drinks per day), the adjusted OR for 3–4 drinks was 2.1 (95 % CI, 1.5–2.9) and 21.1 (95 % CI 14–31.8) for more than 12 drinks per day. Wine drinkers who consumed more than 12 drinks per day were at a 16.1-fold risk compared to the abstainers. Consumption of more than three beers per day resulted in a 2.3-fold risk compared to the non-beer drinkers. In contrast to the Uruguayan study, there was only a 1.9-fold risk for consumption of spirits as compared to non-spirit drinkers [123].

A substantial longitudinal cohort study conducted in the Netherlands [124], commencing with over 120,000 participants in 1986, followed subjects for more than 17 years, at which time 395 HNC and 4288 subjects without HNC were available. For any H&N cancer, the multivariable adjusted incidence rate ratio (RR) was 2.74 (95 % confidence interval (CI) 1.85–4.06) for those drinking ≥30 g ethanol/day compared with abstainers. Importantly this study demonstrated risk by anatomical subsites: RRs were 6.39 for the oral cavity, 3.52 for oro- plus hypopharynx and 1.54 for laryngeal cancer. Compared with never cigarette smokers, current smokers had a RR of 4.49 (95 % CI, 3.11–6.48) for HNC overall: 2.11 for the oral cavity, 8.53 for the oro- plus hypopharynx and 8.07 for larynx. A significant, positive, multiplicative interaction between alcohol consumption and cigarette smoking was found for HNC overall.

A recent meta-analysis computes increased risk of UADT second primary cancers (RR, 2.97; 95 % CI, 1.96–4.50) associated with the drinking of alcohol, with dose–response effect: an increase in the alcohol intake of 10 g/day, which resulted in a modest but significantly increased RR of 1.09 (95 % CI, 1.04–1.14) for UADT second primary cancers [125]. Somewhat controversially, in a meta-analysis of published studies in which it is possible to isolate users of alcohol who have never smoked tobacco or used betel quid, alcohol appears to be protective [126].

There are many confounders in population studies. Most people drink a variety of beverages, and accurate control for tobacco, diet, socioeconomic status and other variables is challenging. Nevertheless, it seems reasonable to conclude that, unfortunately, the benefits of cessation of alcohol on reduction of risk of HNSCC are not evident for at least 20 years [103].

1.20 Mouthwashes

There has been considerable interest in the possible risks of H&N cancer associated with use of alcohol-containing mouthwashes recently, leading some manufacturers to use "alcohol-free" as a marketing tool. Epidemiological findings have not been consistent, and control for other major risk factors, including smoking, is not always easy to ascertain from the published work [127]. Some reviews have argued that daily mouthwash use may be an independent cause of cancers of the head, neck and oesophagus [128, 129]. It is well established that ethanol increases the permeability of lining mucosa, allowing carcinogens to penetrate more freely. Acetaldehyde, the proximal metabolite of ethanol, can accumulate in the mouth from bacterial action, and as explained above this is an established carcinogen. However four case–control studies have shown non-significant, lower or similar oral cancer risks among self-reported mouthwash users compared to nonusers [130, 131]. The most recent meta-analysis has not demonstrated excess risk for oral cancer from alcohol-containing mouthwashes [132–134]. There is, however, a plausible biological basis for risk associated with alcohol-containing mouthwashes, especially in smokers, and it is always prudent to remember that absence of evidence is not evidence for absence.

1.21 Combined Effects of Habits

Whilst the super-multiplicative effects of smoking and drinking have been understood since the classical studies of Blot et al. in the 1980s [135], the true extent of such synergisms of habits, which are bound to vary by ethnicity, has been difficult to assess. A meta-analysis by Petti et al. of studies from SE Asia puts pooled ORs for smoking, drinking, chewing and smoking–drinking–chewing, respectively, at 3.6, 2.2, 7.9 and 40.1, all of which are statistically significant. Among habitués of all three habits, the individual effects accounted for 6.7 % (smoking), 3.1 % (drinking) and 17.7 % (chewing) of the risk, with the interaction effect accounting for the remaining 72.6 %. Some 44,200 oral cancer cases in Southeast Asia annually occur among smoking–drinking–chewing-exposed subjects, and 40,400 of these are exclusively associated with the interaction effect [136]. This has clear implications for public health policies of the type put into effect by Amarasinghe and colleagues in Sri Lanka from the year 2010. We used a simple algorithm by which a cumulative score involving these three habits is used to identify high-risk individuals in population screening studies [137].

In the West, reduced smoking rates and a rise in the proportion of HPV-associated HNSCC have resulted in a much lower rate of second primary neoplasms in treated patients, for example, in France [138, 139] and Canada. This is also reflected in less frequent synchronous primary cancers [140].

1.22 Diet and Nutrition in the Aetiology of Head and Neck Cancer

Dietary factors are estimated to account for approximately 30 % of all cancers in Western countries [141]. This proportion is currently thought to be about 20 % in developing countries and is projected to increase in the future [142]. Poor diet is a significant risk factor for all H&N cancers [143–149] and appears to be second only to tobacco as a cause of oral cancers worldwide [3]. A case–control study of laryngeal cancer in Italy and Switzerland revealed that a diet not only rich but also varied in fruit and vegetables confers decreased risk of laryngeal cancer [146]: low consumption of fruits and vegetables and high consumption of meat with high tobacco and alcohol led to 10- to over 20-fold excess risk of cancer of the oral cavity and pharynx [150], and the classical Mediterranean diet is strongly protective [151]. In the extensive NIH database in the USA, abdominal adiposity is directly associated with increased risk [152].

Evidence comes from case–control and cohort studies, from animal and from in vitro experiments. Protective and unhealthy foods are well understood and form the basis of health education messages in most countries. The micronutrients which confer these benefits are also well understood. Vitamin A and related carotenoids (in particular beta-carotene), vitamins C and E and selenium appear to be particularly protective against most epithelial cancers [153–155], and much of the effect is attributable to their antioxidant activities. Antioxidants act by reducing free radical reactions that can cause DNA mutations and changes in lipid peroxidation of cellular membranes [156]. Other protective roles of micronutrients are modulation of carcinogen metabolism, maintenance of appropriate cell differentiation, inhibition of cell proliferation and oncogene expression, maintenance of immune function and inhibition of formation of endogenous carcinogens [99].

A recent meta-analysis on oral cancer, based on 15 case–control studies and one cohort study, was able to utilise diet data from nearly 5000 subjects. This estimated that each portion of fruit or vegetables consumed per day reduced the risk of oral cancer by around 50 % [157]. These effects are also demonstrable with OPMD. In a population-based case–control study in Japan, where there were 48 cases of oral leukoplakia and 192 control subjects, serum levels of lycopene and beta-carotene were significantly lower in those with leukoplakia: logistic regression showed that high levels of beta-carotene were related to low risk of oral leukoplakia (OR = 0.16) [158]. Our study of OPMD in Sri Lanka initially

showed a protective effect of diets rich in β-carotene-containing fruits and vegetables, but this is swamped by the adverse effects of betel quid, smoking and alcohol [159].

Intervention studies are also encouraging in this respect. In a major double-blind placebo-controlled trial in Kerala [160], up to one-third of subjects showed regression of their oral leukoplakias after 12-month supplementation with oral beta-carotene. Extensive studies from the MD Anderson Cancer Center in the USA are progressively identifying the most effective combinations of antioxidants in the regression of OPMD and the prevention of recurrences and second primary neoplasms in H&N cancer, although it has to be recognised that these agents do not always prevent the progression of an OPMD to overt cancer [161]. Folate emerges as a strong protective dietary factor in the extensive meta-analyses from the International Head and Neck Cancer Epidemiology Consortium (INHANCE) [162].

There is current interest in the protective effects of tea, especially green tea, which contains high levels of polyphenols [163, 164]. These are powerful antioxidants able to counteract both initiation and promotion of carcinogenesis [156].

Nutrition care is very important in the management of patients with HNSCC [165].

1.23 Genetic Predisposition

There is considerable evidence for a minor component of inherited, genetic predisposition in UADT cancers, related to polymorphisms in carcinogen metabolising enzyme systems [166]. A recent extensive meta-analysis [89] pooled individual-level data across 12 case–control studies including 8967 HNC cases and 13,627 controls. After adjusting for potential confounding factors, a family history of H&N cancer in first-degree relatives increased the risk (OR = 1.7, 95 % confidence interval, CI, 1.2–2.3). The risk was higher when the affected relative was a sibling (OR = 2.2, 95 % CI 1.6–3.1) rather than a parent (OR = 1.5, 95 % CI 1.1–1.8) and for more distal H&N sites (hypopharynx and larynx). The OR rose to 7.2 (95 % CI 5.5–9.5) among subjects with family history, who were alcohol and tobacco users. No association was observed for family history of non-tobacco-related neoplasms and the risk of HNC (OR = 1.0, 95 % CI 0.9–1.1). This is confirmed in a recent study from north India, where GSTM1 and GSTT1 null genotype frequencies were significantly higher in patients (adjusted odds ratio (OR) = 2.18; $P < 0.001$ and OR = 1.61; $P = 0.031$, respectively) and in first-degree relatives of patients with HNSCC compared with controls ($P = 0.004$ and $P = 0.041$, respectively): tobacco chewing and GSTM1 null genotype interaction was identified as the strongest gene–environment model to predict HNSCC [167].

Rare cancer syndromes can involve the H&N: Cowden syndrome, caused by mutations in the tumour suppressor gene PTEN, and dyskeratosis congenita, in which oral white lesions in young people have a risk of malignant transformation [168].

1.24 Microorganisms

Microorganisms have been implicated in the aetiology of oral leukoplakia for more than a century, beginning with the classic dorsal leukoplakia of syphilitic glossitis. Today tertiary syphilis is rare, but the fungus, *Candida albicans*, a common oral commensal, is frequently found invading the upper epithelium in histological sections of leukoplakia, more so in the mouth than the pharynx or larynx [169], and this involvement is associated with a higher risk of malignant transformation [170]. The terms "candidal leukoplakia" and "hyperplastic candidiasis" have been used to describe such lesions. Oral cancer patients harboured higher numbers of *Candida* species of different genotypic strain than matched controls, but it cannot be concluded whether this is a cause of effect [171].

Studies of the role of bacteria in the aetiology of UADT cancers are relatively recent. Endogenous production of acetaldehyde and reduction of nitrate to nitrites by oral flora are higher in drinkers with poor oral hygiene [123]. Understanding the role of the oral flora is certainly important in the management of the distressing mucositis associated with much cancer therapy [172]. Since the Nobel Prize in Physiology or Medicine was awarded to Barry J. Marshall and J. Robin Warren in 2005 for the discovery of the causal association of *Helicobacter Pylori* and gastritis, peptic ulcer and gastric cancer and the now widespread availability of next-generation sequencing, studies of the whole microbiome—mycome, bacteriome and virome—associated with H&N cancer are emerging [173]. To repeat, association does not prove cause and effect. Nevertheless such studies can be hypothesis generating. As with the conversion of ethanol to acetaldehyde by bacterial enzymes, mentioned above, microorganisms may promote carcinogenesis or progression of the neoplasm by, inter alia, induction of pro-inflammatory cytokines and other inflammatory mediators. In studying the cancer-associated microbiome, care is necessary in choice of control individuals and sites and in avoidance of contamination between subjects and samples.

It is now clear that high-risk HPV genotypes, particularly HPV 16 and 18, are important cofactors, especially in cancers of the tonsil and elsewhere in the oropharynx (OPC) [174–176], but a significant association with oral cancer, albeit less frequently [177], along with traditional risk factors, is shown in a growing number of studies from many parts of the world, e.g. in China [178].

The rise in OPC, particularly in younger males, is mostly attributable to HPV which is sexually transmitted [179]. Whilst cases where sexual partners appear to share a cancer of the uterine cervix and an oropharyngeal cancer in the male are described, it appears that virus passed from an OPC patient to [usually his] partner in the oropharynx is rapidly cleared: carriage rates in oral rinses in such partners are no different from the population carriage rate as a whole—at least in the USA [180, 181]. However, self-inoculation in women from genitals to mouth is demonstrable [182].

The risk of a second primary neoplasm in patients treated for HPV-related HNSCC is substantially less than for tobacco- and alcohol-related cancers, in an analysis of data from the USA [183].

Vaccination of young women—and increasingly young men—against the main oncogenic types of HPV is now widespread in many countries. This is already having an impact on the incidence of cervical dysplasia and cervical intra-epithelial carcinoma. The probable effect on oropharyngeal cancer incidence will take some time to become fully apparent.

Interest in human herpesviruses and HNSCC has waxed and waned over the years. Epstein–Barr virus is clearly causally related to nasopharyngeal carcinoma and an association with oral cancer, particular in betel quid chewers, recently described in northern Thailand [184].

The current state of knowledge regarding HPVs, EBV and HNSCC is dealt with in Chap. 8 of this volume.

1.25 Dental Factors

Apart from poor oral hygiene, trauma from sharp teeth or ill-fitting appliances may play a role. Such trauma may focus the site at which malignant transformation occurs in the context of a field of molecular change and continuing presence of local carcinogens. The number of missing teeth and the wearing of metal dentures [OR 5.5] were associated with oral cancer independent of other risk factors in a much quoted study from Beijing published in 1990 [185]. Several more recent studies have reported associations of this sort [186, 187]. There is an association between poor periodontal status and oral cancer, with a significant odds ratio of 3.53, according to a recent meta-analysis [188], and of 2.63 in another [189], but it must be remembered that association does not equate with cause and effect [190].

1.26 Air Pollution

Part of the urban/rural difference in the incidence of head and neck cancer has been related to atmospheric pollution. For example, mean sulphur dioxide and smoke concentrations in the atmosphere are positively correlated with squamous cancer of the larynx and, to a lesser extent, the pharynx in data collected some time ago from the West Midland Region of England 1950–1990 [191].

Indoor air pollution resulting from the use of solid fuel such as wood, crop residue, animal dung and coal for cooking and heating is a significant health problem in many developing countries where a greater proportion of people use such fuels, frequently in poorly ventilated areas. Many studies have identified indoor air pollution as a risk factor for H&N cancer [56, 192, 193], and a recent monograph by the International Agency for Research on Cancer has identified indoor air pollution from coal usage as a known human carcinogen whilst that from other biomass (primarily wood) as a probable human carcinogen [194]. Studies carried out in China and Brazil have reported exposure to wood smoke as a risk factor for oral cancer [195], nasopharyngeal cancer [196] and cancer of the upper aerodigestive tract [197].

1.27 Solar Radiation

Prolonged exposure to sunlight represents an important risk factor for the development of squamous cell carcinoma of the lip in people with fair complexions and those with outdoor occupations. Usually the lower lip is involved because it receives considerably more direct sunlight than the upper lip [198]. Evidence comes from many countries, including those at latitudes with clean air through which ultraviolet light penetrates easily, such as Finland [199] or Sweden [200], and from countries closer to the equator with regular long hours of sunshine such as rural Greece where lip cancer can account for 60 % of oral cancers [201] and in India, for example, in fishermen [5]—though some protection may exist in darker-skinned races or individuals. In Finland, the increased risk for lip cancer is confounded by smoking and social class, whereas that for oral cavity and pharynx is not; at these latter sites, alcohol was a much stronger confounder than tobacco [202]. A study from California shows that risk for women is strongly related to lifetime solar radiation exposure, but lipstick and other sunscreens are protective [203]. Although the observation goes back over a decade, there is recent concern that modern cosmetic lip glosses may enhance UV damage to the lips, including increased risk of cancer [203].

Falls in the incidence of lip cancer have been interpreted as due to reduced occupational exposure to sunlight and to reduced pipe and cigar smoking [204, 205].

1.28 Global Scenario of OPMD and Laryngeal Leukoplakia

The term oral potentially malignant disorders was recommended by an international working group convened by the WHO Collaborating Centre for Oral Cancer and Precancer in London in 2005 [206]. It conveys that not all disorders

Table 1.5 Summary of the prevalence of OPMD reported in the literature

Ref No.	Country (year)	Sampling method	M/F ratio	Age group	Disease entity	Definition used	Prevalence (%)
[53]	Sri Lanka (2008)	MSSC	0.6/1.0	≥30	OPMD	WHO 1994	11.3 Weighted for gender and geographical location
[209]	Taiwan (2005)	Random	0.9/1.0	≥15	OPMD Leukoplakia Erythroplakia Lichen planus OSF	Not given	12.7 7.4 1.9 2.9 1.6
[211]	USA (2003)	MSSC	0.9/1.0	≥20	Leukoplakia	Kramer 1978 Kramer 1980	0.5–0.3
[212]	Sri Lanka (2003)	Multistage stratified cluster(MSSC)	–	35–44 years and 65–74 years	OPMD Leukoplakia/ erythroplakia OSF	WHO 1994	4.1 2.6 0.4
[213]	Spain (2002)	Stratified, random	0.8/1.0	≥30	Leukoplakia	WHO 1978 Axell, T et al. 1984	1.6
[214]	Germany (2000)	Stratified, random	1.0/1.0 0.7/1.0	35–44 years 65–74 years	Leukoplakia Leukoplakia	Axell 1976 Zain 1995 WHO-ICD-DA	1.6 1.0
[215]	Japan (2000)	All invited	0.4/1.0	m>40, f>20	Leukoplakia Lichen planus	WHO 1980	0.19 0.21
[216]	Malaysia (1997)	Stratified, random	0.7/1.0	≥25	Leukoplakia Erythroplakia OSF Lichen planus	WHO 1978 Axell, T et al. 1984	0.96 0.01 0.06 0.38
[217]	Netherlands (1996)	Waiting room	0.9/1.0	13–93 years	Leukoplakia	Axell 1984 Axell 1996 Schepman 1995	0.6
[218]	Hungary (1991)	Random	0.7/1.0	All age groups	Leukoplakia Lichen planus	Axell 1984	1.3 0.1
[219]	Japan (1991)	Factory workers	0.5/1.0	18–63 years	Leukoplakia	Axell 1984	2.5
[220]	Sweden (1987)	Stratified, random	Not found	≥15	Lichen planus	Axell 1976	1.9
[221]	Sweden (1987)	All-invited residents	0.9/1.0	≥15	Leukoplakia	Axell 1976	3.6

described under this umbrella will transform to invasive cancer—at least not within the lifespan of the affected individual. Leukoplakia, erythroplakia, oral submucous fibrosis, lichen planus, palatal lesions in reverse smokers, actinic keratosis, discoid lupus erythematosus, dyskeratosis congenita and epidermolysis bullosa are described under the broad definition of OPMD [206, 207].

1.28.1 Global Prevalence of OPMD

Estimates of the global prevalence of OPMD range from 1 % to 5 % [208], although much higher prevalences are reported from Southeast Asia, usually with a male preponderance, e.g. in Sri Lanka (11.3 %) [53], Taiwan (12.7 %) [209] and Pacific countries like Papua New Guinea (11.7 %) [210]. Wide geographical variations across countries and regions are mainly due to differences in socio-demographic characteristics, the type and pattern of tobacco use and clinical definitions of disease (see Table 1.5). In Western countries the overall prevalence is low, and a decreasing trend over time is observed.

Petti [222] conducted a meta-analysis of 23 primary studies on oral leukoplakia, from international data published between 1986 and 2002. The point prevalence estimates were 1.49 % (95 % CI 1.42–1.56 %) and 2.6 % (random effect, 95 % CI 1.72–2.74 %). Leukoplakia was significantly more prevalent among males (prevalence ratio 3.22), but no difference was found between geographical areas and between younger and older adults. Using these data, they calculated that the crude annual oral cancer incidence rate attributable to leukoplakia would be between 6.2 and 29.1 per 100,000, thus suggesting that the global number of oral cancer cases is probably under-reported.

1.28.2 Age and Gender Distribution of OPMD

This varies considerably, mainly dependent on lifestyle and thus on ethnicity and geographical location. In the developed world, leukoplakia is usually found between the fourth and seventh decades of life and in the developing world some 5–10 years earlier [223]. Females are less commonly affected, largely reflecting greater use of relevant habits by men.

1.28.3 Malignant Transformation of OPMD

Risk of malignant transformation varies from site to site within the mouth, from population to population and from study to study [224–226]. A classic study conducted in the 1970s with follow-up over 7 years of over 30,000 Indian villagers showed transformation rates from 10 to 24 per 100,000 per year [225]. Another classic study from the early 1980s, a hospital-based study in Californian patients with oral leukoplakia, with a mean follow-up period of 7.2 years, revealed a malignant transformation rate of 17.5 % [226]. Rates for hospital-based studies are, unsurprisingly, consistently higher than community-based studies because of sampling bias.

Petti [222] has estimated a mean global prevalence of 2.6 % for leukoplakia and a mean global transformation rate of 1.36 % per year (95 % CI 0.69–2.03). Extrapolating from these figures suggests that considerably more OSCC should have been reported in recent times, a possible reason being under-reporting of cases of oral cancer in the developing world. More recently a careful study of 1357 patients with an OPMD from the South of England revealed that 2.6 % of cases transformed to invasive cancer for a total person follow-up time of 12,273 years (mean 9.04 years): the severity of epithelial dysplasia was a significant predictor for malignant transformation [227], especially if aneuploid [228]. Similar findings come from a study of leukoplakia in Shanghai [229]. A study from a dysplasia clinic in the north of England confirms the lateral tongue as a high-risk site and that nonsmokers were 7.1 times more likely to undergo malignant transformation compared to heavy smokers [230].

Controversy continues as to whether or not oral lichen planus [OLP] should be considered an OPMD. Published studies give rates of transformation from 0 to 3.5 %, over varying time periods. A recent comprehensive systematic review evaluated 7806 patients with OLP, among which a mere 85 [1.09 %] developed SCC in an average follow-up time of 51.4 months. Average age at onset of SCC was 60.8 years, with a slight female preponderance. The most common subsite of malignant transformation was the tongue [231]. Size is also a critical determinant [232].

1.28.4 Epidemiology of Laryngeal Leukoplakia

Epithelial precursor lesions of the larynx, clinically defined as leukoplakia and chronic laryngitis, are mostly seen in adults and affect men more often than women. This gender disparity is more pronounced after the sixth decade of life [233]. Epidemiological studies of laryngeal precursor lesions are scarce, and the incidence differs worldwide and depends upon the amount, manner and types of exposure to relevant carcinogens. A comprehensive literature review and analysis of the situation in Slovenia [234], covering a region with approximately 800,000 inhabitants or 40 % of the population, report that 1268 patients were clinically diagnosed with laryngeal leukoplakia and chronic laryngitis during the period from 1979 to 2004. Among these 12⁄1089 (1.1 %) patients with hyperplasia or mild dysplasia progressed to cancer compared with 17⁄179 (9.5 %) of those with mild/severe dysplasia.

1.28.5 Aetiology of Laryngeal Leukoplakia

Laryngeal leukoplakic lesions are strongly associated with tobacco smoking and alcohol use, especially in combination [235–237]. Other risk factors are industrial pollution, specific occupational exposures, nutritional deficiency and hormonal disturbance [238–240]. A recent meta-analysis has shown a weak association between HPV-16 and laryngeal cancer [241]. Several authors have recently devoted much attention to the potential role of gastro-oesophageal reflux disease, but the results are not conclusive [235, 242].

1.29 Salivary Gland Neoplasms

1.29.1 Epidemiology

Neoplasms arising in the salivary glands are relatively uncommon, yet they represent a wide variety of both benign and malignant histologic subtypes. The reported annual incidence, when all salivary gland tumours are considered, varies widely between countries and regions [243].

According to Globocan 2012, the world's highest incidence of salivary neoplasms was reported from the Northern Territory indigenous community of Australia (though the number of cases in this thinly populated area was too small—only three cases—to place credence on this value) and the second highest from USA Hawaii Filipino. Within Japan, the highest rates are reported from the region of Nagasaki, regarded as long-term effects of the atomic bomb explosion in 1945. The estimated annual incidence in the US is 1.5

Table 1.6 Incidence of salivary neoplasms: cases per 100,000 pa, standardised ASR(W)

Population	ASRW male	ASRW female
Australia—Northern territory	0.5	0.9
Croatia	0.9	0.6
Poland, Cracow	0.8	0.9
USA, District of Colombia white	0.9	0.6
USA, Black SEER(9 Registries)	0.7	0.9
USA, White SEER(9 Registries)	1.1	0.7
UK, Oxford region	0.7	0.4
Canada	0.9	0.7
China, Hong Kong	0.8	0.6
India, Chennai	0.5	0.4
Japan, Nagasaki	0.9	0.3
France, Herault	0.9	0.7
Norway	0.5	0.6
Spain, Granada	0.8	0.4
Switzerland, Geneva	0.4	0.5

Based on data from [3]

cases per 100,000 population pa; here they constitute only about 6 % of all head and neck neoplasms [244]; see Table 1.6.

1.29.2 Site, Age and Sex Distribution

Nearly 80 % of these neoplasms arise in parotid glands and 15 % in submandibular glands, with the remainder distributed across the sublingual and minor salivary glands of the oral and oropharyngeal mucosae [245]. In most series, benign neoplasms are the majority, representing 54–79 % of cases described. Pleomorphic adenoma is by far the most common, accounting for about 50 % of all salivary gland neoplasms. Warthin's tumour is second in frequency among benign neoplasms and, in most large studies, mucoepidermoid carcinoma is the most common malignancy [243].

The average ages of patients with benign or malignant tumours are 46 and 47 years, respectively, with peak incidence of most of the specific types in the sixth and seventh decades. However, the highest incidence of pleomorphic adenomas, mucoepidermoid carcinomas and acinic cell carcinomas is significantly younger—in the third and fourth decades. Salivary neoplasms are rare in young people, and in patients under 17 years of age, a neoplasm of a major gland is as likely to be mesenchymal as epithelial in origin [246–249] (Fig. 1.29).

1.29.3 Aetiology of Salivary Gland Neoplasms

The aetiology of salivary gland neoplasms is still poorly understood. Further, especially with neoplasms which have mixed cellularity, notably pleomorphic adenomas and carcinomas arising therein, which show epithelial, myoepithelial and mesenchymal characteristics, controversy remains as to whether there is a single or more than one type of cancer stem cell [243].

Viruses Studies have shown a strong association between Epstein–Barr virus (EBV) and lymphoepithelial carcinomas [250, 251], with geographical variations, as this shows a preponderance for Asian patients [252] and Greenlandic Inuits [253]. Salivary tissue is an established reservoir for EBV, but a clear oncogenic role for EBV or for cytomegalovirus (CMV) has not been demonstrated in other salivary gland carcinomas or in benign parotid neoplasms [251]. SV40 sequences have been postulated in human pleomorphic adenomas [254], but there is no convincing association between human salivary gland neoplasms of epithelial origin and other viruses, including polyomavirus and papillomavirus. EBV is important in lymphoid neoplasms of salivary glands, as at other sites of lymphomata.

Radiation There is convincing evidence implicating exposure to ionising radiation and the development of salivary gland neoplasms. Long-term follow-up studies of the

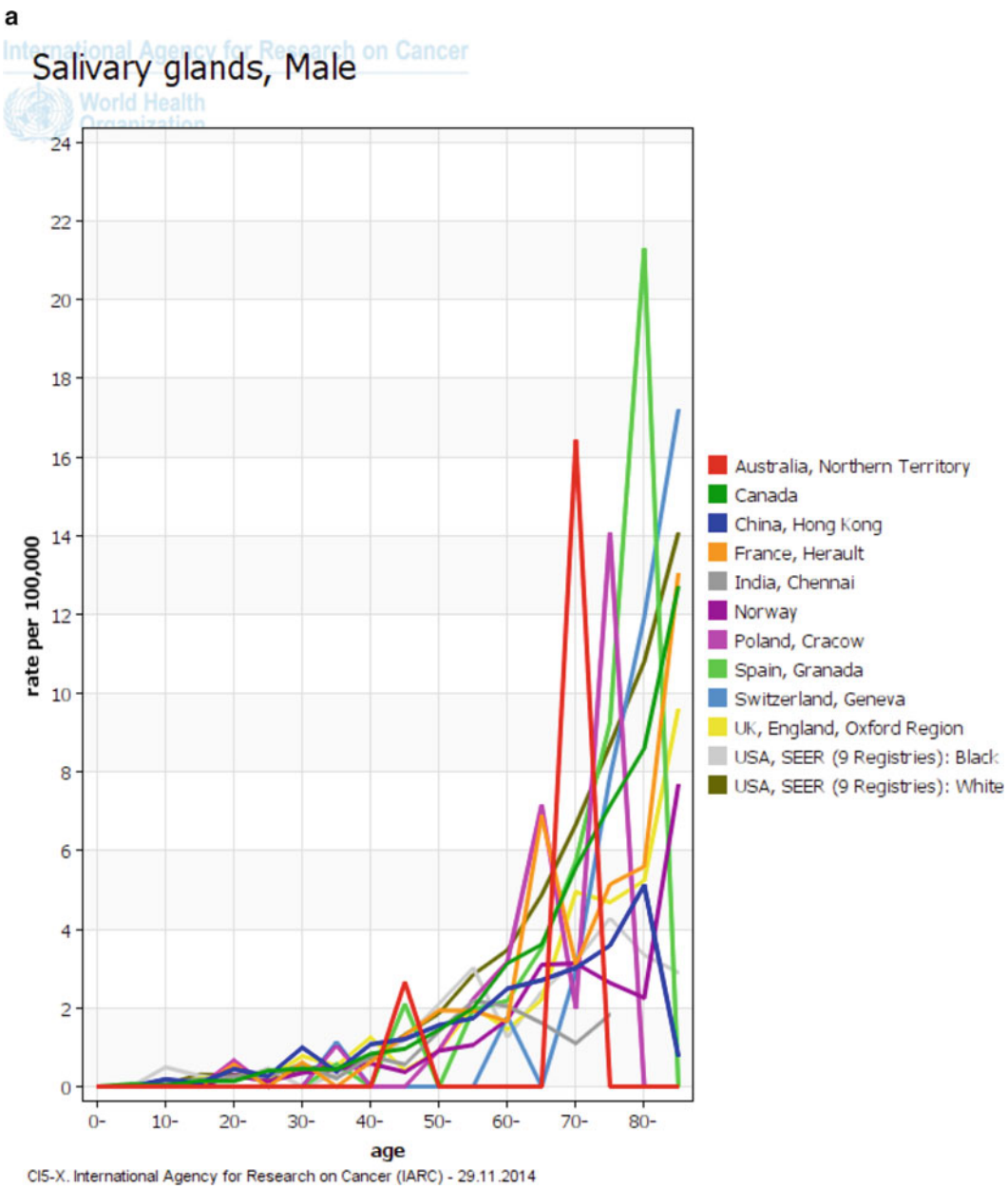


Fig. 1.29 (**a**) Salivary glands in males. (**b**) Salivary glands in females. The incidence of salivary gland neoplasms rises steadily with age, but cases are found in all age groups. Data from selected countries are given in Fig. 1.26 (**a**, males; **b**, females). Note that the scales are, as usual with such data presentations, logarithmic. There is a clear male preponderance

survivors of the atomic bomb explosions in Hiroshima and Nagasaki show an increased relative risk of 3.5 for benign and 11 for malignant salivary neoplasms [255, 256]. The risk was directly related to the level of exposure to ionising radiation. There was a high frequency of both mucoepidermoid carcinoma and Warthin's tumours in these patients [257]. Therapeutic radiation, especially in the head and neck region, has been linked to significantly increased risk [258, 259]. Iodine 131, used in the treatment of thyroid disease, is thought to produce neoplasms, as the isotope is also concentrated in salivary glands [260].

Several studies have suggested that exposure to routine dental radiographs may be associated with an increased risk of salivary neoplasms, though the evidence is inconclusive [261, 262]. Exposure to ultraviolet radiation has also been implicated [263–265], though this seems biologically improbable. There appears to be no excess risk in those exposed to radon [266] or the microwaves of cellular telephones [267, 268].

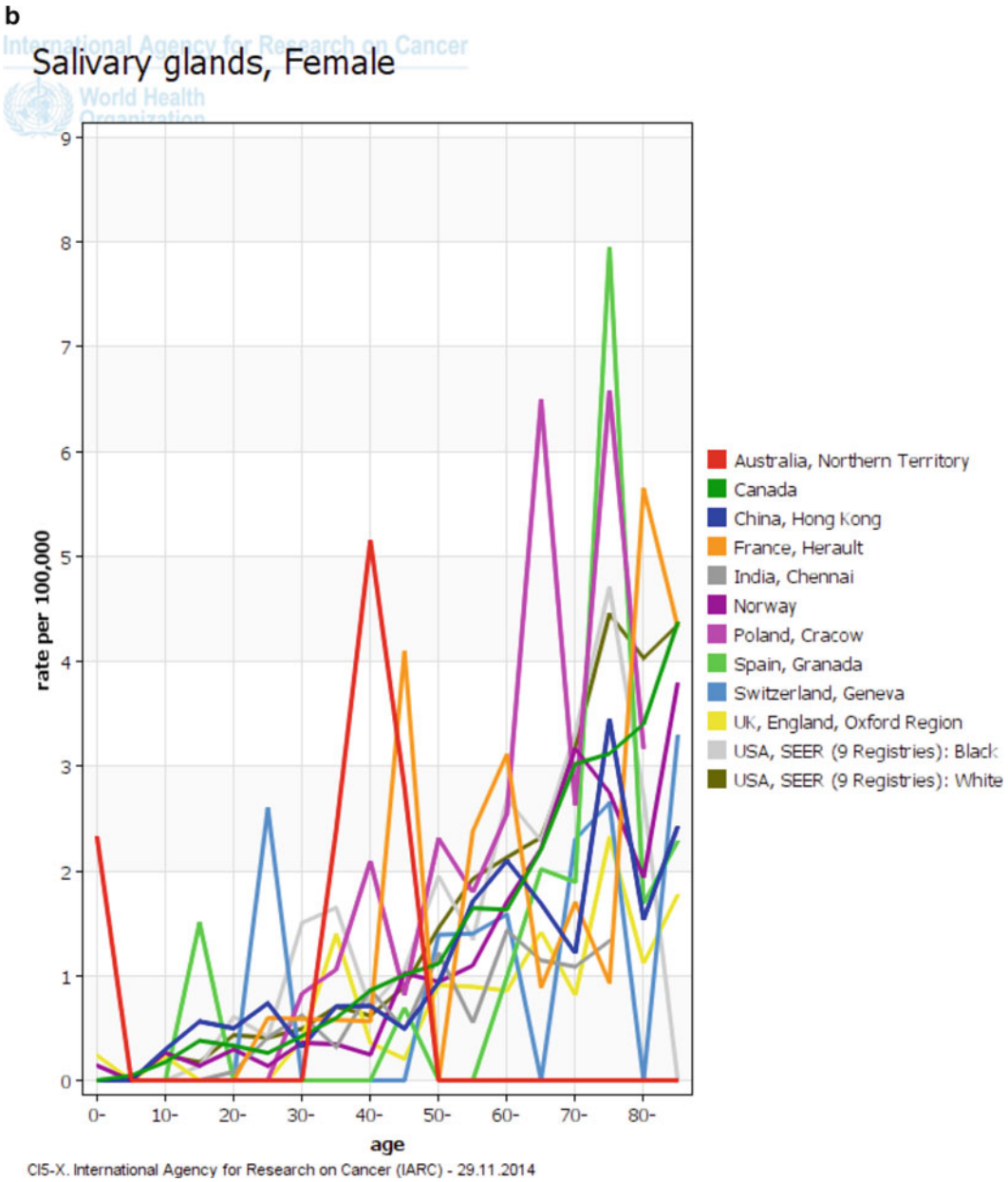


Fig. 1.29 (continued)

Occupation There is a literature relating salivary gland neoplasms to occupation. Suggested risks include rubber manufacturing [269], exposure to metal in the plumbing industry [270] and nickel compounds [269], woodworking in the automobile industry [271] and employment in hairdressing and beauty shops [272, 273]. An increased risk of salivary gland cancers was reported in people living in certain Quebec counties where asbestos was mined, and this risk was inversely proportional to distance from the mines [274].

Lifestyle and Nutrition Tobacco and alcohol, which are highly associated with head and neck squamous cell carcinoma, have not been shown to play a major role in the development of salivary malignancies [275]. However, tobacco smoking has been associated with the development of Warthin's tumour. Exposure to silica dust and kerosene as a cooking fluid increased the risk of salivary neoplasms in a Chinese population [276], and an increased risk of parotid neoplasms was associated with exposure to nickel, chromium, asbestos and cement dust [277]. An elevated level of risk has been described in those with a high cholesterol intake [278].

Hormonal Influences Oestrogen activity or upregulation of oestrogen receptors has been described in pleomorphic ade-

Table 1.7 World standardised incidence rate per 100,000 per annum for Melanoma and for Kaposi sarcoma

	Melanoma skin (C43)		Kaposi sarcoma (C46)	
Country	Male	Female	Male	Female
World	3.3	2.8	0.8	0.4
More developed	10.2	9.3	0.3	0.1
Less developed	0.8	0.7	0.9	0.5
Africa	1.0	1.1	5.5	2.9
Eastern Africa	0.8	1.3	15.1	7.6
Middle Africa	1.4	2.0	1.2	0.4
Northern Africa	0.3	0.4	0.3	0.1
Southern Africa	5.0	3.7	7.6	4.7
Western Africa	0.6	0.6	0.9	0.6
Caribbean	0.8	0.7	0.5	0.1
Central America	1.9	1.3	0.1	0.0
South America	2.9	2.2	0.6	0.1
Northern America	16.1	12.2	0.5	0.1
Asia	0.5	0.4	0.0	0.0
Eastern Asia	0.6	0.5	0.0	0.0
Southeastern Asia	0.5	0.3	0.0	0.0
South Central Asia	0.3	0.2	0.0	0.0
Western Asia	1.8	1.6	0.5	0.2
Europe	8.6	8.9	0.3	0.1
Eastern Europe	4.5	4.6	0.1	0.0
Northern Europe	14.0	15.4	0.3	0.1
Southern Europe	8.1	8.3	0.7	0.2
Western Europe	11.5	12.8	0.2	0.0
Australia	40.5	30.0	0.3	0.0
New Zealand	39.2	33.1	0.2	0.0
Melanesia	3.4	3.8	0.1	0.0
Micronesia	4.0	2.1	0.0	0.0
Polynesia	4.0	2.7	0.0	0.0

Based on data from [2]

nomas in some studies [279] but were absent in another [280]. Progesterone and androgen receptors are present in some salivary neoplasms [279, 281], and binding of hormones to these may influence tumour progression.

1.30 Other Important Cancers of the Head and Neck: Malignant Melanoma and Kaposi Sarcoma (Table 1.7)

Malignant melanoma is recorded by cancer registries separately from mucosal and other cancers. These data represent all skin sites, but the management of melanoma often falls into the hands of head and neck clinicians, so the data are of interest here. DNA damage from ultraviolet light, especially acute sunburn and especially early in life, is the major risk factor. This explains the high incidence rates in Australia, New Zealand, Northern Europe (especially Scandinavia) and among white South Africans: for head and neck melanoma, the risks associated with ultraviolet light are most marked at low latitudes and high altitudes [282]. Melanoma of UADT mucosae is a serious, usually fatal, disease: global epidemiological data will be "buried" in the graphs and tables above. Such data as are available have been reviewed by van der Waal et al. [283].

Kaposi sarcoma (all sites) is an AIDS-defining lesion and is thus most common where HIV disease is most rampant: it is a major problem in sub-Saharan Africa and in many countries of which Kaposi sarcoma (KS) is the most frequently diagnosed cancer [284]. In our series of 710 head and neck cancers in Northern Nigeria, KS was the most common HIV-associated malignancy [285]. KS is seen less commonly in the current era of highly active antiretroviral therapy in populations where such therapy is widely available. Many of the zero numbers in these tables reflect absence of data—or situations where KS is not separately registered.

The aetiology of KS was described in 1994 and is now clearly established as infection with human herpesvirus type

Table 1.8 World standardised mortality rate per 100,000 for malignant melanoma and Kaposi sarcoma, according to the Globocan 2012

	Melanoma skin (C43)		Kaposi sarcoma (C46)	
Country	Male	Female	Male	Female
World	0.9	0.6	0.5	0.3
More developed	2.0	1.2	0.0	0.0
Less developed	0.4	0.3	0.6	0.3
Africa	0.5	0.4	4.9	2.2
Eastern Africa	0.6	0.4	14.2	6.2
Middle Africa	1.0	1.5	1.0	0.4
Northern Africa	0.2	0.2	0.2	0.1
Southern Africa	1.6	0.8	4.3	2.8
Western Africa	0.5	0.5	0.9	0.5
Caribbean	0.3	0.2	0.1	0.0
Central America	0.6	0.4	0.0	0.0
South America	1.0	0.6	0.1	0.0
Northern America	2.6	1.2	0.0	0.0
Asia	0.3	0.2	0.0	0.0
Eastern Asia	0.4	0.3	0.0	0.0
Southeastern Asia	0.3	0.2	0.0	0.0
South Central Asia	0.2	0.1	0.0	0.0
Western Asia	0.6	0.5	0.2	0.1
Europe	2.0	1.3	0.0	0.0
Eastern Europe	2.0	1.4	0.0	0.0
Northern Europe	2.5	1.6	0.0	0.0
Southern Europe	1.6	1.0	0.0	0.0
Western Europe	2.0	1.3	0.0	0.0
Australia	5.8	2.3	0.0	0.0
New Zealand	6.9	2.8	0.0	0.0
Melanesia	2.1	2.3	0.0	0.0
Micronesia	1.0	0.0	0.0	0.0
Polynesia	1.0	0.7	0.0	0.0

Based on data from [2]

8 (HHV-8, also known as Kaposi sarcoma herpesvirus (KSHV)). It is a multifocal malignancy of lymphatic endothelial cells. Endemic KS in HIV-negative subjects still exists, especially in the Mediterranean where it has long been regarded as having an ethnic predilection for certain Jewish groups. There is a puzzle with HIV-/AIDS-related KS, however: the head and neck, especially the mouth, are a common site for KS in HIV-positive subjects; the oropharynx is the primary reservoir, and saliva/oral fluids are the major vehicle of transmission [286]. Transmission occurs via oral–genital contact and is more common in men who have sex with men. In India, which is currently the single nation of the world with the highest number of HIV infections, KS is almost never seen. Whether this is because of different social practices, differences in the strain(s) of KS circulating in that country—with different pathogenicity—or differences in host response remain unknown [287] (Table 1.8).

The death to registration ratio (D/R) for melanoma can be readily calculated here. For ANZ this ranges from 0.09 to 0.18, whereas in Northern Europe the average approaches double this, viz. 0.16 for women and 0.26 for men. Women do better all over the world, possibly because they seek treatment earlier. Note that these outcomes are substantially better than for oral cancer. In Australia and in New Zealand, there are highly effective public education campaigns regarding protection against sun damage and many screening and treatment facilities. In spite of this, the comparatively poor outcomes perhaps reflect a degree of complacency towards very common sun-induced lesions, many of which are benign.

1.31 Primary Neoplasms of the Jaws and Facial Bones

Whilst to a large extent these lesions constitute the "bread and butter" for many oral/maxillofacial pathologists and surgeons, such lesions are comparatively rare: they do not represent anything like the major public health problem of

epithelial tumours of the head and neck. They are not, therefore, a major thrust of this volume, but have excellent coverage in other modern textbooks including those referred to in the Introduction to the present chapter.

It is not appropriate here to indulge in the favourite pastime of oral pathologists to debate the classification of such lesions, uniformity of which would be essential to the comparability of international epidemiological data [288]. Furthermore, it is extremely difficult to mine international and national databases for detailed histological typing so that the incidence and mortality associated with bone and odontogenic tumours might be reliably quantified. Recourse has to be made to case series and, whilst these are valuable, significant regional differences in epidemiology and in risk factors are hard to quantify. A concise summary of the situation with odontogenic tumours is in the WHO "Blue Book" of 2005 [243].

Difficulties also arise because some databases/case series include benign neoplasms—and with odontogenic lesions, there are frequently grey areas regarding the behaviour of a particular diagnostic category or individual lesion. Strictly speaking, cancer registries should only record malignancy. Hamartomatous and benign lesions are very much more common than malignant odontogenic tumours [289]: differences emerge between case series based on dental/oral/maxillofacial departments who are more likely to include the former, whereas cases handled in broader general hospitals or cancer hospitals will select for malignancies.

Ameloblastoma is clearly the most common malignant odontogenic tumour worldwide. An extensive series of 1642 "odontogenic tumours" from Sichuan University [290] found that 97 % of cases were classified as benign: ameloblastoma was the most common malignancy, followed by odontogenic keratocystic tumour. In a series of 1088 cases from Northern California [291], 76 % were (benign) odontomas: ameloblastomas comprised 12 %—a surprisingly high figure perhaps reflecting the specialised nature of this laboratory. This paper also tabulates data from case series all over the world describing the frequencies of the various types of odontogenic "tumour".

There has long been an impression that odontogenic tumours are more common in Africa—perhaps because so many advanced lesions come late to diagnosis. A thoughtful analysis of the literature up to the early 1990s is given by Smith, 1992 [292]. In a more recent series, of 308 odontogenic tumours in Lagos, Southern Nigeria, 97 % of the tumours were benign and only 3.4 % malignant: ameloblastoma with predilection for the mandible was the most frequent [293].

Among primary malignant bone tumours [294], most case series around the world contain very small numbers of patients, but indicate various types of osteo[genic] sarcoma to be most common. Osteosarcomas of all sites account for 40–60 % of primary malignant bone tumours, and ~10 % of these occur in the head and neck, mostly in the jaws. These tend to be diagnosed ~2 decades later than their long bone counterparts, which have a peak incidence between 10 and 14 years of age. Head and neck osteosarcomas metastasise less frequently than those in long bones and have a better 5-year survival rate, reported between 27 % and 84 %. The experience of one USA centre has recently been described [295], with a helpful review of the literature. Out of 2830 biopsies of oral and jaw lesions diagnosed in 1983–2003, in Lagos, 59 (2.08 %) were primary malignant bone tumours, osteosarcoma again being most frequent (28.8 %). Interestingly the mean age at presentation (27 ± 14 years) was lower than reports from other parts of the world.

Biological markers with some value in differential diagnosis and treatment planning are reviewed by Premalatha et al. [296]. Such an approach, hopefully leading to personalised therapy based on key molecular aberrations [297], such as the oncogenic BRAF V600E mutation in a high proportion of ameloblastoma samples, still has a weak evidence base, but this is growing [298].

1.32 Cancer Metastatic to the Head and Neck

Tumours metastatic to the H&N from distant sites are comparatively rare, representing about 1 % of oral neoplasms. Most lesions are found in patients between the fifth and seventh decades of life. They affect the jaws more commonly than soft tissues in a ratio of 2:1 [299]. The most common primary malignancies metastatic to the jaws are the breast (20 %), lung (13 %), kidney (8 %), adrenal (8 %), bone (7 %), colorectal (6 %), prostate (5 %) and liver (5 %).

A review of cases revealed that 54 % of the 218 metastatic tumours to oral soft tissues were located on the attached gingiva, followed by 22 % in the tongue: a role for inflammation in the attraction of metastatic cells to the gingiva has been suggested [300].

1.33 The Future of Head and Cancer Epidemiology

As with many aspects of life, global inequalities are increasing in the incidence rates of head and neck cancers, in the provision and quality of prevention and screening programmes and in access to and quality of patient care [1]. The drivers of these inequalities are sociopolitical: war, poverty, pestilence, climate change, lack of food and water security [301]. The problems do not derive primarily from ignorance

of causes and mechanisms of disease but from ineffective or absent implementation of the right policies and from lack of resources to implement them. As scientists and clinicians devoted to head and neck oncology, we all have a moral responsibility to contribute to these wider social and political challenges. The knowledge to apply world's best practice is within the pages of this book. The leadership of many local and national bodies is acknowledged: these activities need to be in dialogue and synergy with global leadership through agencies such as the World Health Organisation, the International Agency for Research on Cancer, the UICC/International Union Against Cancer, the International Federation of Head and Neck Oncologic Societies, the International Academy of Oral Oncology and others. The International Association for Dental Research launched an initiative in 2010 seeking to reduce global inequalities in oral cancer (and in other orofacial diseases and disorders), and this has led to a Global Oral Health Inequalities Research Network [302].

It is a truism that however sophisticated and effective our diagnostic and treatment armamentarium becomes, head and neck cancer rates around the world will never be reduced by such interventions—though of course hundreds of thousands of lives may be saved or improved. The emphasis must be on primary and on secondary prevention, on the implementation of policies which work to these ends and on their continued evaluation and improvement.

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Head and Neck Cancer Prevention

2

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Abstract

Head and neck cancer (HNC) represents a broad spectrum of diseases that involves the nasal and oropharyngeal cavities, the paranasal sinuses, the major and minor salivary glands, the larynx, and the lymphatic tissues of the neck. The worldwide yearly incidence exceeds over half a million cases. Tobacco (smoking and smokeless) and alcohol use are the principal risk factors; however, a substantial and increasing proportion of head and neck tumors cannot be attributed to these. Recent evidence has shown that the incidence of oropharyngeal cancer among women and younger patients continues to grow, and it is not related to alcohol or tobacco use but to human papillomavirus infection. Substantial advances in treatment regimens made over the last two decades have not improved the 5-year mortality rate that remains around 60 %. Prevention represents the best opportunity to improve oncologic results, and it consists of three levels of intervention: primary prevention (considered the best) aims to avoid exposure to established risk factors; secondary prevention consists of early diagnosis; and tertiary prevention involves active management of patients already treated for HNC. In this chapter, we review the natural history of oral cavity and laryngeal cancer as well as the known mechanisms of carcinogenesis. Precancer and risk markers for cancer are discussed as they relate to prevention in all its forms (primary, secondary, and tertiary). Chemoprevention is the use of natural or synthetic chemicals to reverse, suppress, or prevent the conversion of a premalignant lesion to a true neoplasm. It spans all three forms of prevention, and it can aim at both local and locoregional disease control. All of the major important chemoprevention clinical trials reported on in the scientific literature are presented and discussed critically, and their impact on clinical practice is presented. Attention is given to new directions in the field and how HNC prevention may progress through the search for new, sensitive, and specific biomarkers as well as an improved understanding of the biomolecular mechanisms of tumor invasion, metastasis, and the newly acquired data from the Human Genome Project. Improvement in HNC prevention requires a multidisciplinary approach to face complex processes and multiple factors that may act concurrently in the etiology of disease. Future challenges remain in the correct interpretation of new

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findings and their wise and scientific application. Only then will we be able to impact the field of HNC, transforming prevention into the only form of cure.

Keywords
Prevention • Early diagnosis • Chemoprevention • Precancerous lesions • Risk factors • HPV • Biomarkers • Molecular medicine • Multidisciplinary approach

Take-Home Messages

- Tobacco (smoking and smokeless) and alcohol use are the principal risk factors of head and neck cancers. Recent evidence has shown that an increasing proportion of head and neck tumors, mainly oropharyngeal cancers among women and younger patients, is related to HPV infection. These cancers are generally considered preventable.
- Primary prevention is considered the best form of prevention; it aims at removing and avoiding exposure to established risk factors. Secondary prevention consists of early diagnosis, and tertiary involves management of patients already treated for a cancer.
- Educational activities increase awareness of head and neck cancer and its signs and symptoms among the general public and healthcare professionals. Efforts to promote healthy lifestyle practices mainly in primary schools and in young people should be supported.
- Chemoprevention is defined as the use of agents to halt or reverse the carcinogenetic processes. Up to now no tangible indications for chemoprevention have emerged from the published studies. Natural compounds have recently gained particular interest, but they should only be tested within clinical trials.
- Recent results from basic research seem to underline that cancers not correlated with a known risk factor develop in a random fashion. Translational research will allow us to understand the disease in order to design effective preventive strategies.

2.1 Introduction

Head and neck cancer (HNC) represents a broad spectrum of diseases that involves the nasal and oropharyngeal cavities, the paranasal sinuses, the major and minor salivary glands, the larynx, and the lymphatic tissues of the neck. The worldwide yearly incidence exceeds over half a million cases [1]. Tobacco (smoking and smokeless) and alcohol use are the principal risk factors; however, a substantial and increasing proportion of head and neck tumors cannot be attributed to these. Recent evidence has shown that the incidence of oropharyngeal cancer among women and younger patients continues to grow, and it is not related to alcohol or tobacco use but to HPV infection [1–6].

Substantial advances in treatment regimens made over the last two decades have slightly changed the 5-year mortality rate that remains around 60 % [7–11]. The diagnosis of HNC is often dramatically delayed in spite of easy access for evaluation and screening [12–14]. Late diagnosis results in complex, aggressive, and often mutilating treatment with a high morbidity and significant functional compromise. Local disease control (e.g., minimizing metastases and managing recurrence) and development of a second primary tumor remain two of the most significant challenges [15, 16]. In fact, second primary tumors are the major cause of morbidity and mortality among patients cured for head and neck squamous cell carcinomas (HNSCC).

Prevention of HNC could offer the best opportunity to improve oncologic results, and it consists of three levels of intervention. Primary prevention aims at avoiding exposure to established risk factors. Approximately 80 % of head and neck cancers are tobacco and alcohol related [1, 2]; this percentage is not so easy to reduce because of the addiction induced by their daily use and the powerful impact of advertising by the tobacco and liquor industry particularly on the younger population. The increased incidence of HPV-related cancers has been linked to a change in the sexual patterns in the overall population: lower age at time of first intercourse and higher number of sexual partners [3–6].

Secondary prevention consists of early diagnosis. Early detection programs usually entail regular clinical evaluation of asymptomatic at-risk patients; consistent and reliable instrumental or serologic tools are currently unavailable. Even though screening is not equally successful for all HNCs, the premise is that early diagnosis could improve morbidity and mortality outcomes. Improved screening increases the overall number of diagnoses; however, in order to be truly effective, it must be associated with increased disease-free survival, a decreased mortality rate, and improvement in the effectiveness of treatments. If this is not possible and the patient's quality of life does not improve, the cost-benefit ratio may be too high to be justified [17]. A promising approach could be the identification and characterization of circulating tumor cells (CTC) in the peripheral blood. This approach seems to be able to detect early recurrences in patients treated for a HNSCC [18].

Tertiary prevention involves management of patients already treated for HNC. The interventions range from educational programs to smoking cessation for those patients who

continue to smoke even with the diagnosis of a malignancy and include early diagnosis of recurrences and/or second primary tumors [19].

2.2 Natural History of Head and Neck Cancers

2.2.1 Head and Neck Carcinogenesis

The development of head and neck cancers is generally related to field cancerization and multistep carcinogenesis. Field cancerization is a morphological concept arising from Slaughter's observation that in all resected oral tumors, the macroscopically benign epithelium beyond the periphery of the primary tumor was microscopically abnormal [20]. Exposure of an epithelial field to repeated carcinogenic insults results in development of genetic damage to normal-appearing mucosa. The entire field is susceptible to multifocal development of squamous intraepithelial neoplasia (SIN) and cancer [20–22]. A distinct but related concept is "the field of tissue injury," which includes the molecular changes occurring throughout the tissue exposed to a carcinogen [23]. The field of injury reflects the host's response to and damage from the carcinogen; this may or may not be a precursor to premalignant lesions and frank malignancy. Field cancerization and the field of injury have both been implicated in many malignancies and potentially hold the keys for preventing and curing epithelial cancers and for understanding in vivo epithelial carcinogenesis. Target treatments to reduce cancer risk involve the whole field.

On a molecular level cancer is considered a disease of genetic, progressive, multistep mutation [24–30]; however, carcinogenesis may take multiple paths and may be multifocal. This progression is heralded in tissues by the appearance of associated specific molecular and genotypic damage resulting in phenotypic changes that progress from normal histology to early dysplasia, continuing on to severe dysplasia, superficial cancers, and finally invasive disease [24, 25]. It has been estimated that 4–6 genetic events are required to progress from severe dysplasia to cancer and that one head and neck cancer could require up to 10–20 years to develop. The degenerative advance of cancer, however, is not always linear or sequentially additive: progression can occur away from clinically visible lesions, strongly suggesting that genetic aberrations may not always result in locally apparent disease and accumulation of mutations. Lesions that appear morphologically similar often harbor different molecular fingerprints, suggesting that a given phenotypic change can arise from diverse pathways. This absence of a direct, predictable, and consistent correlation between clinical and histological features of suspect lesions is well documented [24–30]. Recent microarray investigations of chromosomal aberration patterns of HPV-negative oral and oropharyngeal squamous cell carcinomas showed subclasses of cancer with unique genetic and clinical fingerprints. This observation, if confirmed in larger studies, could have important diagnostic and therapeutic implication in clinical practice [31].

2.3 Precancerous Lesions

Epidemiological, experimental and clinical observations teach us that cancer may be preceded by a morphological tissue modification, a precancerous lesion, clinically manifest as a white (leukoplakia), a red (erythroplakia) or a red-white lesion (erythroleukoplakia). According to a recent report by Shiga K et al., the location of the primary lesion in the head and neck may be dependent upon the mechanism of carcinogenesis: the alteration of tumor suppressor genes gives rise to tumors in the pharynx and larynx, while loss of function resulting from methylation of the promoter regions is related to carcinogenesis in the oral cavity. This may be true also for precancerous lesions [27, 30, 32].

2.3.1 Oral Cavity

2.3.1.1 Leukoplakias and Related Lesions

White lesions in the oral cavity were thought to be precancerous as early as 1870 by Paget, who described them as ichthyosis, smoker's patch, and leukokeratosis [33]. Schwimmer was the first to use the term *leukoplakia* in 1877 [34]. In 1936 McCarthy described the microscopic features of oral leukoplakias, grading them as 1–4, where grade 4 referred to lesions showing microscopic evidence of significant dysplasia or early malignant changes [35].

Leukoplakia is a clinical term used to describe a range of white oral lesions; it implies a diagnosis of exclusion of common conditions with similar appearance and harbors intrinsic potential malignancy [36–39]. Microscopically these lesions are characterized by simple orthokeratosis, parakeratosis with epithelial hyperplasia and minimal inflammation, hyperkeratosis, or varying degrees of dysplasia. The latter occurs in up to 16 % of leukoplakias [36]. Leukoplakias and erythroplakias (less frequent than leukoplakias in the general population) may undergo malignant transformations with or without clinical evidence of such change. Only 5–36 % of white lesions can transform into malignancy within 20 years, the annual transformation rate of oral leukoplakia is unlikely to exceed 1 %, and there is no proven correlation between transformation and the degree of dysplasia [40–43]. In spite of the progresses in molecular biology, there is not yet a single reliable marker predictive of malignant transformation [38, 39, 41]. Clinically early stages may be mistaken for reactive lesions that appear either as

painless, nonhealing, indurated ulcerations or hypertrophic lesions. Differential diagnosis is based on the analysis of the risk factors, the natural history, the progression, and, most importantly, the clinical features of the lesion. A definitive diagnosis however can only be obtained after histological confirmation. Only then can the appropriate therapy be selected. The clinical conundrum for lesions without features of malignancy remains whether the initial biopsy is representative of the entire lesion, especially when they present with nonhomogeneous features [40–44]. Microscopic foci of malignant tissue may be present and can only be detected histologically. Unexpected carcinomas in resection specimen have been reported for oral lesions removed after the initial incisional biopsy had not shown the presence of malignant tissue [40–45].The lack of correlation between the histopathologic examination of initial biopsies and the examination of definitive surgical specimens may strongly influence the decision-making process when assessing and managing suspicious lesions [25, 26, 41, 44, 46].

2.3.1.2 Conventional Treatment of Leukoplakias and Related Lesions

In consideration of the reported malignant transformation rate of 5–36 % [40–43], the therapeutic goal for oral leukoplakias is secondary prevention. Treatment modalities include lifestyle modification and elimination of risk factors such as tobacco and alcohol intake, medical therapy with retinoids or antimycotics, surgical excision, cryosurgery, laser evaporation or excision, and most recently photodynamic therapy (PDT). Surgical excision is widely accepted to be the most effective form of treatment [38–46]. A useful initial approach in the management of oral leukoplakias should be the removal of etiologic factors in conjunction with simultaneous anti-inflammatory and antimycotic therapy. If clinical improvement or resolution is not obtained within a few weeks, surgical excision of persistent oral leukoplakias, preferably laser resection, seems to be the most rational next step [47]. Cryotherapy has been used in the treatment of oral precancerous lesions such as oral leukoplakia (OL) and oral verrucous hyperplasia (OVH). Cryotherapy is an in situ treatment modality that destroys pathologic tissues through disruption of the cellular membrane, cellular dehydration, enzyme and protein damage, cellular lysis, thermal shock injury, vascular damage, and immune-mediated cytotoxicity. It has frequently been used with good results to treat thin or relatively thick, plaque-like lesions such as OL, although long-term results are not yet available. Careful patient selection makes it a simple, safe, easy, conservative, and acceptable treatment modality [48, 49]. Photodynamic therapy or hematoporphyrin therapy (HPD) has been used as an alternative treatment for potentially malignant and premalignant oral lesions. This treatment modality is based on a tissue loading process with a light sensitive dye that has greater uptake in malignant or premalignant lesions (higher metabolic activity). Exposure of the tissues to a specific light source gives rise to a photochemical reaction with the oxygenated milieu within and surrounding the target area, ultimately leading to cell (tumor) necrosis. Long-term results were similar to those obtained in patients treated with laser resection [50]. The limits of these alternative treatment modalities are related with the impossibility of obtaining a specimen, because they destroy the tissue, and all information is obtained through a pretreatment biopsy. Results of prospective [51] and retrospective studies [38–47] describing rates of malignant transformation in patients treated with surgical or laser excision of oral leukoplakias are hardly comparable because of differences in diagnostic and inclusion criteria, follow-up time intervals, patient characteristics, and surgical techniques employed. The inconclusive data leaves unproven the hypothesis that surgical removal of potentially malignant oral lesions (regardless of the removal modality) can prevent the onset of oral cancer [28, 39, 40, 43, 52, 53] and form the basis for pilot chemoprevention studies.

2.3.2 Larynx

2.3.2.1 Leukoplakias and Related Lesions

Analogies exist between laryngeal and oral precancerous lesions: the presence of dysplasia has clinical relevance for both, but in laryngeal lesions, a better correlation seems to exist between the grade of dysplasia and the clinical evolution of the lesion [24, 25, 54–58]. The natural history of untreated laryngeal dysplasia is well described for mild and moderate dysplasia. A recent meta-analysis showed that the overall malignant transformation rate was 14 %, and the mean time to malignant transformation was 5.8 years. The malignant transformation rate was higher with increased severity of dysplasia: 30.4 % in severe dysplasia/carcinoma in situ vs. 10.6 % in mild/moderate ($p < 0.0002$) [54].

2.3.2.2 Conventional Treatment of Leukoplakias and Related Lesions

As for the oral cavity, the management of premalignant lesions of the larynx is controversial. The best opportunity for cure must not be missed because of inadequate treatment, and therapy must be oncologically radical with maximal functional preservation. The available data on the treatment of laryngeal premalignancy mostly address severe dysplasia/carcinoma in situ [55–60]. A “wait-and-see” approach cannot be employed in these patients as some studies have indicated an unacceptably high rate of progression to invasive carcinoma. Intervention is recommended for all cases of severe dysplasia and/or carcinoma in situ [58]. Despite substantial recent advances, there is significant morbidity asso-

ciated with nonsurgical therapy sometimes used to treat these conditions [60], while laser surgery seems to be the best treatment modality to fulfill the requirements of oncologic radicality and organ as well as functional preservation [55, 56, 59].

2.3.3 Precancer and Risk Markers for Cancer

A biological marker (biomarker) is a parameter that can be objectively measured and evaluated as an indicator of normal biological and pathogenic processes, gauging the response to therapeutic (most often pharmacological) interventions [61]. A small subset of biomarkers that demonstrate a strong correlation with the desired clinical endpoint can serve as its substitute. These surrogate endpoints are expected to be reasonably likely to predict clinical benefit or harm (or lack thereof) based on epidemiologic, therapeutic, physiopathologic, or other scientific evidence.

The search for reliable biomarkers has an important impact on the evaluation of chemoprevention studies that goes beyond the potential changes to clinical practice. The evaluation of a marker linked to carcinogenesis requires the study of its expression in tumors. This marker (overexpressed, mutated, or masked) is analyzed in precancerous lesions or in normal tissue to assess its presence as an indicator of a biologic process associated with progression of a neoplasia [62]. In head and neck cancer chemoprevention trials, the search for reliable biomarkers focuses on identification of indicators of malignant transformation in clinically suspect lesions, those linked to second primary tumors, and/or identification of individuals at greatest risk for development of neoplasias [62]. Squamous intraepithelial neoplasia (SIN) is defined as a noninvasive lesion with genetic abnormalities resulting in loss of cellular control functions with some phenotypic characteristics of invasive cancer [37, 63]. Preventive measures focus on evaluation and removal of its risk factors and surgical resection [50, 53, 55]. Epithelial tissues display SIN as moderate to severe dysplasia whose grade is determined by the degree of cellular abnormality above the epithelial basement membrane [36–40, 63]. Accuracy in grading is dependent on the quality of the tissue sample, the biopsy site, and the experience of the pathologist. Several studies have shown great inter- and intra-examiner variability in the assessment of presence, absence, and grade of oral epithelial dysplasia [37, 39, 63]. SIN is believed to represent (with appropriate sampling) the total field of abnormal epithelium and to provide identifiable lesions that can be targeted to evaluate the efficacy of new therapeutic interventions [29]. However, only a small portion of these lesions progress to cancer, and they are not always indicative of malignant transformations [40, 42]. A striking discordance between the genetic status and the clinical and histologic features has been reported, particularly as it relates to treatment response [64]. Molecular studies also suggest that dysplasia may not be considered a reliable biomarker for cancer because high-risk modifications can be found in non-dysplastic lesions [53, 62].

Shrinkage of oral premalignant lesions has often been selected as the primary endpoint of many chemoprevention studies. This strategy seems to be suboptimal, given the high spontaneous regression rates and the fact that only a minority of premalignant lesions will transform into cancer. The removal of the etiologic factors correlates highly with regression of oral premalignant lesions; however, tobacco and alcohol cessation are not sufficiently weighed in the interpretation of the results of studies focusing on lesion regression as a study endpoint. These conclusions are further supported by the marginal correlation between leukoplakia response to chemopreventive agents and oral cancer risk seen in the largest and longest-term clinical trial using retinoids in patients with oral premalignant lesions [65]. Clinical or histological responses of oral premalignant lesions to chemoprevention agents would only be clinically meaningful endpoints if they were surrogate markers of invasive cancer. Prentice et al. have discussed the properties of an ideal surrogate endpoint [66]: it must correlate with the true endpoint, it must be modulated by the intervention, and it must fully capture the net effect of the intervention on the true endpoint. Clinical and histological responses of oral premalignant lesions have not been demonstrated to entirely fulfill these criteria. Perhaps in the future, modulation of molecular markers may serve as an early readout of oral cancer risk in patients with premalignant lesions. However, in the absence of a valid surrogate, we suggest that invasive oral cancer be used as a main endpoint and reported in all late-stage oral cancer chemoprevention trials. Selection of invasive oral cancer as the main endpoint in this setting is, however, not without its challenges. In an unselected patient population, invasive cancer takes time to develop and is relatively infrequent, even in patients with an oral premalignant lesion. As a result, size and length of clinical trials using oral cancer as an endpoint need to be extended, with rising costs limiting the number of agents that can be evaluated in each trial. Strategies to overcome these limitations include the selection of high-risk cohorts in which the frequency of the endpoint allows the use of a small sample size and an expedited reading of the efficacy of each agent tested. [67].

There currently isn't a body of evidence strong enough to advocate the use of biomarkers as prognostic indicators for HNC in clinical practice [62]. Molecular markers for cancer risk remain experimental and have been included prospectively in the design of the new-generation oral cancer chemoprevention trials [67, 68]. They have been developed in patients with oral premalignant lesions, and their presence

may serve as selection criteria for participation in these trials. Examples of such markers include chromosomal allelic imbalances, polysomy, p53, overexpression of podoplanin, p63 or epidermal growth factor receptor (EGFR), increased EGFR gene copy number, cyclin D1 polymorphisms, specific gene expression profiles [68], and specific DNA methylation profiles [69]. Research in the field continues particularly with gene expression and salivary proteomics studies [70, 71], and recently published reports identify podoplanin [72, 73], the genotype CD1 AA and AG [58], and PPAR gamma [74] as promising new markers.

2.4 Chemoprevention

Chemoprevention is defined as the use of natural, synthetic, or biologic compounds to either halt, reverse, or prevent the initial phases of carcinogenesis and the progression of neoplastic cells to cancer [61, 68]. It includes all the interventions that employ agents aimed at preventing the development of cancer: its goal is to intervene at the early stage of carcinogenesis, possibly even before it begins, by preventing the changes that eventually give rise to the invasive cancer [74]. Premalignant lesions of the oral cavity represent an ideal model to study chemoprevention. Ready access allows easy monitoring and serial biopsies resulting in greater possibility of early intervention and faster data analysis [75, 76]. Only few studies have been conducted on laryngeal precancer because of limitations related to difficulty in access and monitoring [58, 77–79]. Patients targeted by chemopreventive interventions do not have a diagnosis of cancer, and a few basic concepts have guided chemoprevention studies: the compounds used for prevention should be relatively inexpensive, nontoxic, and administered orally [61, 74, 80].

A new approach to the selection of suitable and promising chemopreventive drugs [81] represents the most significant change and debate in the field. Historically study agents are chosen on the basis of epidemiologic and preclinical studies and are developed specifically for a disease; this is true for compounds derived from natural sources [82–84]. A change from this prevention only approach has been recently attempted in studies that are simultaneously trying to develop preventive as well as therapeutic agents [85, 86]. Beyond new drug discovery, there is an increasing trend to investigate new applications and indications for use of already existing agents; several of these have now been well studied and characterized. Celecoxib was initially developed for arthritis and is now being investigated as a prevention agent most notably in colon, lung, and bladder cancer as well as other sites. Metformin, a mainstay in the treatment of type II diabetes mellitus, is now under investigation in preclinical models of carcinogenesis (colon, breast, and lung) and in clinical prevention trials for breast, uterus, colon, and prostate cancer. Finasteride and dutasteride were initially developed for benign prostatic hypertrophy and are now employed in the prevention of prostate cancer [87–90]. Pioglitazone, another oral hypoglycemic agent, is currently being investigated as a reversal agent for oral leukoplakias [80]. The biggest problem, however, with these approaches is that full evaluation of cancer prevention efficacy is extremely time consuming and often requires several years.

Reverse migration is the third approach recently put forth by Gold [81] for lung cancer, and it has the potential to streamline the development process of new preventive treatment modalities. It involves translating agents, targets, study designs, and treatment concepts developed for advanced cancer to prevention. Molecular targets in advanced cancer can be studied upstream, and preventive agents can be identified among existing treatment modalities. The most striking example of an ad hoc reverse migration is found in breast cancer. Tamoxifen was initially used for metastatic disease, then as adjuvant therapy, and finally as a preventive agent.

2.4.1 Chemopreventive Agents

Head and neck squamous cell carcinomas can be divided in two subsets: tobacco- and alcohol related and virus related. Recent molecular studies have shown that nuclear factor kappa B (NF-kB) and the signaling pathways that control its activity are significant regulators of development and progression of these tumors. Their role in virus-related cancer is not yet well defined, while it is well known in tobacco- and alcohol-related cancers: NF-kB cytokines promote tumor growth and metastases, and serum levels correlate with response to treatment. This pathway is a logical target for chemoprevention, and several NF-kB inhibitors have been tested [80].

2.4.1.1 Vitamins

Retinoids, β-carotene, and α-tocopherol are the main agents employed in chemoprevention studies of oral leukoplakias. More than 30 years have elapsed since the initial clinical studies of natural vitamin A in the management of oral leukoplakia, and several single-arm studies have been reported [91–94].

Vitamin A and Retinoids

Retinoids are precursors, derivatives, and analogues of vitamin A. Naturally occurring β-carotene and vitamin A were the first drugs studied and employed in chemoprevention interventions and trials. Among the synthetic retinoids tested, fenretinide seems to be the more interesting drug because of its effectiveness and its low toxicity compared to other retinoids such as isotretinoin and 13-cis retinoid acid employed both in secondary and tertiary chemoprevention [74, 80, 95].

Vitamin E

Vitamin E is composed of several classes of compounds. Alpha-tocopherol is the most active and best studied. Vitamin E complexes have been used alone or in combination with retinoids since the early 1990s, and several of these trials have reported positive results [74, 80]. Recent randomized trials, however, suggest that vitamin E supplementation could be harmful [96, 97]: increased mortality rates were observed in the intervention arm, and supplementation is no longer considered a viable preventive strategy.

2.4.1.2 Natural Compounds

High levels of naturally occurring antioxidants are considered effective chemopreventive agents [80]. Berry extracts, in particular blackberry, seem to be effective in preventing esophageal and colon cancer in rats; isoflavones, contained in soybeans, are currently being studied in chemoprevention trials for several cancers (breast, pancreas, lung, prostate); and resveratrol, present in grape skins, seems to be effective in prevention of oral cavity tumors when applied topically.

Green Tea

The polyphenols obtained from green tea leaf extract have been shown to be effective inhibitors of head and neck tumor growth and apoptosis enhancers. They seem to act synergistically with erlotinib through a p53-dependent NF-kB inhibitory mechanism [80, 84, 98]. Several clinical trials are ongoing, and green tea seems to be effective in reversing oral leukoplakias [84].

Curcumin

Curcumin is the principal component of the popular Indian spice *turmeric*, a member of the ginger family derived from the plant *Curcuma longa*. It is bright yellow in color, and it has been used as a dietary supplement for thousands of years. Curcumin incorporates several functional groups, and many preclinical studies suggest curcumin may be useful for the prevention and treatment of cancers as an inhibitor of the NF-kB pathway [80, 99]. Curcumin is being used in several clinical studies for chemoprevention of head and neck cancers, particularly in HPV-negative carcinomas [100, 101].

2.4.1.3 Antidiabetic Drugs

Recently some hypoglycemic drugs have shown an association with decreased risk of lung and head and neck cancers. Their efficacy appears to result from inhibition of NF-kB transcription that has been shown to block angiogenesis and tumor growth [80, 102, 103]. Several clinical trials are testing the effectiveness of metformin and pioglitazone in reversing oral leukoplakias and preventing their malignant transformation [80, 89, 104, 105].

2.4.1.4 EGFR (Epidermal Growth Factor Receptor) Inhibitors

EGFR amplification is detected in over 90 % of head and neck tumors, and its overexpression is associated with malignant transformation and poor prognosis. In head and neck carcinomas, epidermal growth factor (EGF) induces the activation of NK-kB reporter genes [99] by phosphorylation of EGFR. Several promising EGFR inhibitors are being tested, particularly gefitinib and erlotinib [80, 106].

Cox Inhibitors

Most studies tested anti-inflammatory drugs, including COX inhibitors and aspirin, because of the strong link between nonsteroidal anti-inflammatory drugs (NSAIDs) and the reduction of cancer incidence demonstrated in human epidemiological studies. The NSAID family inhibits the cyclooxygenase (COX) family of enzymes. COX-2 has been shown to be upregulated as much as 150-fold in HNSCC and 50-fold in the normal-appearing tissue of patients with HNSCC compared to normal subjects [107]. However, the results of the first multicentric studies using these agents are similar to those obtained with the retinoids [108–110]. Heath et al. [108] found that administration of 200 mg of celecoxib twice daily for 48 weeks does not appear to prevent progression of Barrett's dysplasia to cancer. In a Hospital-based case-control study (529 pts with HNSCC vs. 529 controls), Jayaprakash et al. concluded that aspirin use reduces the risk of HNC (25 %; OR 0.75) [110]. This effect is more pronounced in women and in individuals with low to moderate exposure to cigarette smoke or alcohol consumption. Heavy smokers and alcohol drinkers did not benefit from the protective effect of aspirin [111].

2.4.1.5 PI3K-mTOR Inhibitors

PI3K-mTOR has been shown to promote NF-kB activation and drugs such as rapamycin, and its analogues seem to inhibit carcinogenesis of both HPV-related and nonrelated cancers. These findings indicate that mTOR inhibitors could represent a promising target for chemoprevention studies [74, 80, 112].

2.4.2 Chemopreventive Interventions

Prevention can target different groups of patients. Primary chemoprevention focuses on non-cancer individuals at a high risk of cancer, for example, current or former smokers. Secondary chemoprevention focuses on patients with precancerous lesions, and tertiary chemoprevention focuses on patients with a history of cancer and at risk of recurrent or second primary tumors (SPT) [81].

2.4.2.1 Primary Chemoprevention: Intervention in High-Risk Populations

This form of chemoprevention consists of dietary supplementation with vitamins, retinoids, and micronutrients in high-risk populations. Several preventive studies have been conducted all over the world (China, Scandinavian countries, USA) [113, 114]. These trials included thousands of patients at risk for developing a cancer of the upper aerodigestive tract, as a result of dietary micronutrient and vitamin A deficiency or of heavy alcohol and tobacco use. Intervention generally lasted several years, and the results in terms of reduced mortality or reduced incidence of cancer were evaluated for at least 5 years after the end of the interventions. Table *2.1* shows the results of these trials [113–121]. Retinoid and micronutrient supplementation showed a protective effect in populations with low tissue levels of retinoids, but it was dangerous in individuals with normal retinoid levels, causing a higher incidence of cardiovascular disease and lung cancer. Two studies were stopped because of these results [115–120]. A relationship between lung cancer and serum levels of some carotenoids seems to show some gender predilection favoring males, with no apparent association observed among women [122]. These results and a critical review of the literature allow us to conclude that there is no evidence to support antioxidant supplementation for primary or secondary prevention, while vitamin A, beta-carotene, and vitamin E may increase mortality [123–125]. Future randomized trials could evaluate the potential effects of vitamin C and selenium for primary and secondary prevention with close monitoring for potential harmful effects. Antioxidant supplements need to be considered medicinal products and should undergo adequate and exhaustive evaluation before reaching the market [126] since these nutritional supplements are widely used among patients with cancer who perceive them to be anticancer and anti-toxicity agents. Their unregulated and haphazard use may actually be more detrimental than beneficial to these patients. Nutritional supplementation tailored to an individual's background, diet, genetics, tumor histology, and treatments may yield benefits in subsets of patients. Supplementation advice needs to be individualized

Table 2.1 Primary chemoprevention (high risk populations) randomized trials

Author	Design	Length of the study (years)	Patients included	End point	Results	Remarks
Blot WJ [113]	Diet supplementation (A) Retinol + zinc (B) Riboflavin + niacin (C) Vit C + molybdenum (D) Beta-carotene + Vit E + selenium	Diet = 5 Fu = 2	29,584 At risk for esophageal and gastric cancer	Decrease of mortality	Significant decrease in Group D, after 1–2 years	No decrease in the other arms
Li JY [114]	Diet supplementation (A) 12 minerals + 14 Vit (B) Placebo	6	3,318 With esophageal dysplasia	Decrease of cancer mortality and incidence	No short-term effect	Lower cancer mortality (RR=0.96) and cerebrovascular diseases (RR=0.62) in intervention group. Not significant
ABTC Study Group [115] Albanese D [116] Virtamo J [117]	Diet supplementation (A) Alpha-tocopherol (B) Beta-carotene (C) Both (D) Placebo	5–8 (median 6.1)	29,153 Finnish 50–69 years old Smokers ≥5 sig/day	Decrease of lung cancer incidence	Group (A): fewer prostate cancer, more strokes Group (B): higher incidence of lung cancer and stroke	Beneficial and adverse effects disappeared during fu
Omenn GS [118, 119] Goodman GE [120]	Diet supplementation (A) Beta-carotene + vit A (B) Placebo	4 planned (stopped after 3.1)	18,314 Smokers, ex smokers, workers exposed to asbestos	Decrease of lung cancer incidence	Stopped: higher incidence of lung cancer (RR = 1.28); deaths for lung cancer (RR = 1.46) and cardiovascular disease (RR = 1.26) in Group (A)	The adverse effect persisted after stopping supplementation (2004)
Lin J [121]	Diet supplementation (A) Vit C (B) Vit E (C) Beta-carotene (D) Placebo	9.4 (average)	7,627 Women cancer-free before randomization	Decrease of incidence and death from cancer	No benefit	Double-blinded trial

Fu follow-up, *Vit* vitamin

and must come from a credible source, and it is best communicated by a physician [95].

2.4.2.2 Secondary Prevention: Treatment of Precancerous Lesions

This form of chemoprevention includes treatment of precancerous lesions (leukoplakias) with agents acting to reverse morphological precursors of malignancy and to assess their efficacy.

Table 2.2 shows the design and the results of the published randomized trials [75, 127–129]. These studies demonstrate response rates that vary from 44 % to 83 % but also revealed the dermatologic and liver toxicity of natural vitamin A. The effectiveness of these interventions is limited to the duration of the drug intake: a few weeks to months after stopping the drug, the leukoplakias recur. Topical application of a natural or synthetic retinoid also achieved a temporary complete remission in more than 50 % of patients, but the severe local side effects and the necessity to apply the drug locally limited this form of treatment, and it is no longer used [94]. Several authors conducted chemoprevention trials for laryngeal precancerous lesions [77, 78, 130]. The clinical and histologic efficacy of the chemopreventive agents was less than in oral lesions, while similarities were noted in the overall response profile (variability of response rate, side effects). Among these studies particular attention should be given to the Almadori trial [130]: a chemoprevention study with folates in patients with oral and laryngeal leukoplakias based on the observation that serum folate levels are significantly lower in patients with cancerous and precancerous lesions than in at risk and control patients.

While currently no effective form of secondary chemoprevention is available, its main role and goal remain to evaluate and test new agents that are effective and have a low side effect profile.

2.4.2.3 Tertiary Chemoprevention: Prevention of Second Primary Tumors

This form of chemoprevention consists of interventions on patients cured for head and neck cancer using a chemopreventive agent or a combination of agents in order to reduce the risk of second primaries. Patients treated for head and neck cancer have a constant and continuing risk of developing a second primary that varies from 2.7 % to 4 % yearly in the aerodigestive tract as well as in other sites [15, 16, 21, 131]. Recently Coyte A et al. in a retrospective population-based study of the West of Scotland cancer registry found that relative risk of second primaries may be smaller than previous reported because patients treated for a head and neck cancer

Table 2.2 Secondary chemoprevention randomized trials (treatment of precancerous lesions)

Author	Design	Length of the study (months)	Patients included	End point	Result	Remarks
Stich HF [127]	(A) Beta-carotene (B) Beta-carotene + Vit A (C) Placebo	6	130 Tobacco/betel chewers	RC of LKP	Reduction: (A) 15 % (B) 27 % (C) 3 %	Nobody changed the risk habits
Stich HF [128]	(A) Vit A (B) Placebo	6	54 Tobacco/betel chewers	–RC of LKP –Prevention of new LKP	(A) RC = 54 % New LKP = 0 % (B) RC = 3 % New LKP = 21 %	Nobody changed the risk habits
Hong WK [75]	(A) 13-cis-RA (B) Placebo	Interv = 3 Fu = 6	Interv = 24 Placebo = 20	– RC of LKP – Reversion of dysplasia	(A) RC LKP = 67 % $p = 0.0002$ (A) Reversion dysplasia = 54 % $p = 0.01$	Two severe toxicities Relapse of LKP by 3 months after stop of intervention
Lippman SM [129]	Phase I = 13-cis-RA High dose Phase II = (a) 13-cis-RA Low dose (b) Beta-carotene	Phase I = 3 Phase II = (a) 9 (b) 12	Phase I = 70 Phase II = (a) 33 (b) 26	Remission of LKP	Phase I Remission LKP = 55 % Pro = 10 % Phase II (a) Pro = 8 % Tis = 1 Pts (b) Pro = 55 % Tis = 1 Pts SCC = 5 Pts	Severe toxicity in Phase I

Vit Vitamin, *LKP* leukoplakia, *Interv* intervention, *Fu* follow-up, *Pro* progression, *is* in situ, *SCC* squamous cell carcinoma

may benefit from increased surveillance and advice to avoid known risk factors [15]. Adjuvant chemoprevention might modulate epithelial cell biology to halt the progression of carcinogenesis [17, 132].

The development of synthetic vitamin A analogues (all-trans-retinoic acid, 13-cis-retinoic acid, etretinate, fenretinide) with potentially greater therapeutic indexes allowed the rapid expansion of chemoprevention trials [75, 129, 133]. Design and results of the published randomized trials are reported in Table 2.3 [76, 96, 97, 133–138]: in most of these treatment regimens, synthetic retinoids are taken alone or in association with beta-carotene. The reported protective effects are conflicting: in some studies retinoids seem to significantly reduce occurrence of second primaries [76, 133, 134]; in others no protective effect was shown [96, 97, 135, 136]. The toxicity of etretinate is very high, and many patients enrolled in the French study [135] discontinued treatment because of the side effects. The toxicity of high-dose isotretinoin was observed in all of the studies, and its severity required many patients to discontinue therapy [134, 139–141]. On the contrary low-dose isotretinoin was well tolerated and was more effective than β-carotene. Several studies tested the effectiveness of another synthetic retinoid, N-(4-hydroxyphenyl) retinamide (fenretinide or 4-HPR) in preventing the clinical progression of oral leukoplakia via receptor-independent apoptosis and receptor-dependent effects [76, 142, 143]. These studies showed that fenretinide is a well-tolerated drug and able to prevent new occurrences of oral leukoplakias without improved efficacy at higher doses [142, 143]. After interruption of the pharma-

Table 2.3 Tertiary chemoprevention trials (Prevention of second primaries)

Author	Design	Length of the study (years)	Patients included	End point	Results	Remarks
Hong WK [133] Benner SE [134]	(A) 13-cis-RA (B) Placebo	12 Fu = 54.5 (median)	103 Disease-free after therapy for HNSCC	Occurrence of 2nd T	(A) 4 % (B) 24 % $p = 0.005$	13-cis-RA-reduces occurrence of 2nd T, but does not reduce local recurrences and progression of the primary
Bolla M [135]	(A) Etretinate (B) Placebo	12 Fu = 41 (median)	316 Treated for T1/T2 N0/N1 M0 HNSCC	Occurrence of 2nd T	No difference (A) 28 2nd T (B) 29 2nd T	Treatment discontinued in 33 % of patients due to toxicity
Van Zandwijk N [136]	(A) N-acetylcysteine (B) Retinol-palmitate (C) Both (D) Placebo	24 Fu = 49 (median)	2,595 60 % treated for curable HNSCC; 49 % for curable lung cancer	Occurrence of 2nd T and recurrences	No differences in the four groups	25 % of patients continued to smoke after cancer diagnosis
Bairati I [96] Meyer F [97]	(A) Alpha-tocopherol, beta-carotene (B) Placebo	36 Fu = 52 (median)	540 Stage I–II HNSCC during RT	Occurrence of 2nd T and reduction of side effects of RT	Alpha-tocopherol was not related to side effects of RT and cancer recurrence Beta-carotene reduces side effects of RT and decrease local recurrences T	Double-blinded trial
Khuri FR [137]	(A) 13-cis-RA (B) Placebo	36 Fu = 48	1190 Stage I–II HNSCC	Occurrence of 2nd T and OS	No difference	
Perry CF [138]	(A) Isotretinoin high dose (B) Isotretinoin moderate dose	36	151 Cured for a HNSCC	Occurrence of 2nd T: HNSCC, lung and bladder	No difference	
Chiesa F [76]	(A) Fenretinide (B) No intervention	12 Fu = 60	170 After excision of LKP	Recurrence of LKP and occurrence of new LKP and cancer	Protective effect of fenretinide	Protective effect lasted significantly for 7 months after drug interruption

Fu follow-up, *HNSCC* head and neck squamous cell carcinoma, *2nd T* second primary, *RT* radiotherapy, *OS* overall survival, *LKP* leukoplakia

cotherapy however, the protective effect of retinoids decreases over time, and some patients can develop new leukoplakias and squamous cell carcinomas [75, 143]. In the Hong study [75, 134], the difference between the odds ratio of developing a second primary tumor at any site for isotretinoin-treated group diminishes over time, and no statistically significant difference in survival has been observed. In the Chiesa study [76], the protective effect of fenretinide was shown to last significantly for 7 months after the completion of a 1-year intervention.

2.4.3 New Directions in Chemoprevention

As of January 5, 2015, the National Institutes of Health [143] reports two recruiting secondary chemoprevention trials using green tea and erlotinib and vandetanib, respectively. A total of eight active, not recruiting, trials are also underway: two primary chemopreventive studies will evaluate (1) food-based modulation of biomarkers in human tissues at high risk for oral cancer and (2) effect of broccoli sprout extracts on Nrf2 pathway modulation in oral mucosa. Two secondary chemoprevention trials will test respectively celecoxib and sulindac in preventing oral leukoplakia transformation. Four tertiary active but not yet recruiting trials will test effectiveness of a dietary supplementation (alpha-tocopherol and beta-carotene), erlotinib, blackberries, and soy isoflavones in preventing recurrences and second primaries.

Chemoprevention trials are expensive because of the large study population needed and the necessary length of these studies. Cost analysis of the trials includes the sample size, the total number of study subjects and the necessary lengthy follow-up, the number of trial outcomes evaluated, possible delays in the accrual process, and cost-effectiveness of particular retention activities. Based on the negative experiences made with the CARET study, the psychological effects of information relating to possible negative outcomes of the study (involving healthy population) should also be considered [144, 145]. Analyzing the results of a celecoxib plus erlotinib trial Saba (65 Sept) further identified several challenges for the field of chemoprevention [146]. Preventive agents taken by a "premalignant," but otherwise healthy, patient population resulting in significant side effects are not feasible. Toxicity may be acceptable if a drug is effective, but the beneficial effects cannot be transient; they must be durable and sustainable in time. Modulation of tissue biomarkers in a favorable direction is no guarantee of success, and even regression of clinical oral premalignant lesions with histologic reversal of dysplasia does not correlate well with cancer risk reduction [147].

The original promise of HNC chemoprevention will be fulfilled only if putative biomarkers are validated with well-designed and adequately funded long-term studies that allow the creation of accurate molecular risk stratification models and translate into significant changes to clinical practice [17, 98, 132, 142, 148]. Getting the drug right is, of course, one of the main goals, and drug tolerance is critical [146]. The new goal, however, is eradication of premalignant clones rather than temporary suppression of carcinogenesis [147].

2.4.3.1 Search for Additional More Sensitive Markers

Many biomarkers have been studied to improve our knowledge of carcinogenesis, and recently new techniques centered upon gene expression profiling and comparative genomic hybridization with microarray technology have been developed and have allowed reliable detection of predictors of behavior rather than single markers [148–153]. The findings of these studies indicate that these markers identify a subset of patients with poor prognosis, requiring aggressive treatment modalities, including new molecular targeted therapies likely to act as anti-invasion and antimetastatic therapeutic agents [154].

Lee et al. [155] proposed a pharmacogenetic approach that could help in selecting patients for a 13-cRA chemoprevention protocol. They have found germline molecular markers for SPT/recurrence risk in HNSCC patients, identifying a high-risk population with the greatest need for chemoprevention and predicting a favorable response to 13-cRA chemoprevention. The analysis of Lee and colleagues highlights the importance of stratifying global genotyping analyses by treatment. Unstratified analyses on the other hand are limited in their ability to detect markers with predictive effects in treated individuals and prognostic effects in untreated individuals. [156]. Recent findings on the role of mitochondria in the development of oral cancer may provide new research opportunities on the role of metabolism and metabolic activity in carcinogenesis and possibly prevention [157, 158].

2.5 HPV Infection

The human papillomavirus (HPV) is part of a very heterogeneous family of viruses. It represents an important human carcinogen, causing the vast majority of cervical and anogenital tumors and a variable number of cancers in other districts of the human body including the head and neck, mainly the oropharynx [159–166].

2.5.1 Risk Factors for HPV Infection and Oral and Oropharyngeal Squamous Cell Carcinomas

HPV infection is thought to precede the development of an HPV-positive HNSCC. The presence of high-risk HPV infection in oral mucosa and seropositivity increases significantly the risk of developing OSCC [167–171]. Therefore, risk factors for HPV oral infection are likely, by extension, to be risk factors for HPV-positive HNSCC. Patients with HPV-positive tumors appear to be distinct from HPV-negative patients. There is no gender predilection, patients are often nonsmokers and nondrinkers [172, 173] and younger than patients with HPV-negative tumors [174]. The degree to which oral HPV infection may combine with tobacco and/or alcohol use to increase risk of cancer is unclear [175, 176]. In the majority of the studies, OSCC related to HPV infection have a better outcome and a reduced risk of relapse and second tumors as compared with HPV-negative tumors [175, 177–182].

2.5.2 Vaccination as a Form of Prevention

Vaccines designed strictly for prevention of cervical cancer and vulvar genital warts have recently been introduced. The existing vaccines are able to create a robust humoral immune response [183, 184] that is much more effective than the levels of antibodies acquired after a natural infection and persist at least for a 60-month period [184]. Five-year follow-up demonstrates 100 % effectiveness in prevention of persisting infection as well as HPV-16 and HPV-18 CIN 2/3 lesions in young women [183].

HPV-16 is found in the majority of HPV-positive oral cancer [183]. All vaccine trials reported to date have been designed to investigate the ability to generate protection against anogenital HPV infection in women. There is reason to believe that the existing vaccines may be effective against oral HPV infection and prevent vaccine-type HPV-related HNC in both men and women [182–186]. Data also suggests that therapeutic vaccines are effective against low-volume disease and could be used as adjuvant therapy following surgery or radiotherapy to clear microscopic residual disease. Selected HPV-positive OPSCC patients with biomarkers indicating good prognosis might be included in randomized trials with less intensive treatment regimens. HPV vaccination should also be considered for boys, in addition to the current recommendations for immunization of girls [186].

2.6 Conclusions

Improvement in the field of prevention requires a multidisciplinary approach. The development of cancer is a complex process, and multiple factors may be crucial in prevention. A clear geographic variability in cancer risk and burden exists across countries, and specific interventions are required in each region. Primary prevention is considered the best form of prevention. Implementation of a primary prevention program requires knowledge of the specific risk factors (tobacco, alcohol, HPV infection) and the ability to limit exposure and to remove them. Efforts to promote healthy lifestyle practices such as tobacco control and cessation programs, recommendation for dietary modification (including alcohol consumption reduction), and weight control have yielded mixed results without significant reduction in the incidence of new cases of HNSCC [43, 187]. This observation highlights the fact that achieving primary prevention is very difficult and has given greater relevance to secondary prevention. Early detection and diagnosis entails by definition the discovery of pre-neoplastic lesions and early carcinomas. Precancerous lesions and cancer are part of a clinical continuum making it difficult to define where one ends and the other begins. Consequently it becomes difficult to definitively state what represents therapy for one end of the disease spectrum versus the other [154, 188]. Genetic aberrations do not always result in visible lesions, and a large portion of all pre-neoplastic lesions remain clinically silent. Even in recognizing pre-neoplastic alterations, currently there isn't sufficient evidence suggesting that the surgical treatment of precancerous lesions reduces the incidence of cancer [43].

The rapid development of molecular biology, the identification of the fundamental cancer genes and signaling pathways, and the development of new functional diagnostic imaging techniques show renewed promise for early prevention. The stratification of patients in different subgroups based on etiology, genomic classification, and other parameters clearly has important implications. Other than showing promise, however, we have not been able to translate this new knowledge into clinically successful strategies for early detection or chemoprevention of cancer. We are again at the dawn of a new era. Several research groups have identified new signaling pathways that contribute to the etiology of head and neck cancers, and light has been shed on the effect of HPV infection on their genomic landscape. Continued integration of basic research with new treatment options will likely lead to more effective therapeutic strategies [189]. Advances in molecular and cellular pathophysiology hold yet more promise that a deeper understanding of the fundamental disease mechanisms may result in improved prevention and cure. The challenges remain in the correct interpretation of these findings and in their wise and scientific application. The road ahead is very long. Recent results from basic research show that the lifetime risk of cancer is strongly correlated with the total number of divisions of the normal self-renewing cells. These findings seem to underline that the majority of cancers develop in a random fashion [190]. In this context it is also important to understand the epigenetic mechanisms and how they relate to human health and disease [30]. Only then will we be able to impact the

field of head and neck cancer, transforming prevention into the only form of cure and removing the "chemo" from "chemoprevention" [191].

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Cellular and Molecular Pathology of Head and Neck Tumors

3

Adel K. El-Naggar

Abstract

Head and neck pathology encompasses a multitude of organs of diverse histogenesis. Malignancies arising from head and neck sites accordingly are diverse in origins, morphogenesis, and biological behavior. Excluding connective tissue and vascular entities, the main entities that are presented in this chapter include squamous mucosal site, salivary, thyroid and sinonasal, and skull base tumors. The histopathological classification remains the main reference to the diagnosis and, to a large extent, malignancy grading. Advances in immunohistochemical techniques and the development of reagents to cellular intermediate filaments and lineage markers have led to better diagnosis and categorization of undifferentiated entities with overlapping morphologic features. More recently, major strides have been achieved in the molecular genetic characterization and understanding of head and neck tumorigenesis. Although clinically applicable and validated, molecular biomarkers have yet to be realized; it is important to address the recent discoveries and their potential integration with the phenotypic and pathologic features.

This chapter concisely presents the relevant pathomorphologic and molecular features of the tumors of the major head and neck sites for clinical management.

Keywords

Head and neck squamous carcinoma • Molecular genetics • Squamous tumorigenesis • Tumor heterogeneity

3.1 Squamous Mucosal Carcinogenesis

Head and neck squamous carcinoma (HNSC) is the fifth most common cancer worldwide with approximately 500,000 new cases per year. They develop from the squamous mucosal lining of the upper respiratory tract mainly in individuals with a history of abusing risk factors, including cigarette smoking, alcohol abuse, and human papillomavirus. Only 20 % of individuals with these risk factors, however, develop squamous carcinoma [1, 2].

Head and neck mucosal sites are an ideal model of investigating the molecular genetic alterations leading to squamous carcinoma development because of their readily accessible location and association with known risk factors and the presence of defined histopathologic progression stages. In contrast to other major cancer types, HNSC lacks familial inheritance and is difficult to cultivate, and there are no faithful animal models to advance research and development in this field [1].

Squamous tumorigenesis is thought to result from successive accumulation of molecular genetic alterations in the squamous epithelium lining the upper aerodigestive tract [1, 2]. Although the temporal occurrence and the order of these events are largely unknown, some certainly precede the phenotypic changes associated with preinvasive dysplastic lesions. The progression of late-stage dysplasia to invasive carcinoma is a complex one and comprised of both cellular and structural changes as a result of dysregulation of key pathways triggered by the interaction of epithelium and the host stromal elements [3] (Fig. 3.1).

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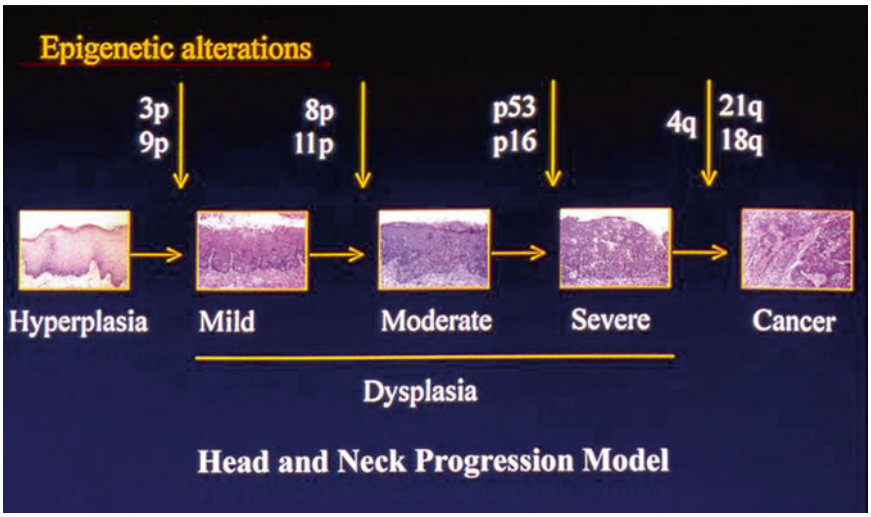

Fig. 3.1 Phenotypic and molecular progression model of head and neck squamous tumorigenesis

3.2 Histopathology

The diagnosis and management of head and neck mucosal lesions are based on the histopathologic assessment of biopsied or excised specimens.

3.2.1 Oral Premalignant Lesions

These lesions are recognized as grossly abnormal mucosa of no definitive etiology and can broadly be classified into leukoplakia (white) and erythroplakia (red). The risk of developing invasive carcinoma from these lesions varies greatly and ranges from 3 to 16 % for leukoplakia and from 30 to 50 % for erythroplakia [2].

3.2.1.1 Leukoplakia

Leukoplakia is defined as a persistent white area of unknown etiology. These lesions may present as either discrete homogenous or delimited nonhomogenous forms. Generally, the nonhomogenous lesions are associated with higher risk than their homogenous counterparts. The majority of leukoplakias develop in tobacco-consuming individuals, and their location and appearance varies according to the geographic location and the manner and nature of the tobacco consumption. A definitive diagnosis is based on the histopathological evaluation of lesional biopsy and serves to rule out mimics, such as lichen planus, and to assess the presence or absence of dysplasia [2]. Histologically, leukoplakia is characterized by epithelial hyperplasia with hyperkeratosis and/or parakeratosis. The development of dysplasia in these lesions is heralded by progressive alteration of the squamous epithelium manifested by changes in basal cell polarity and cellular and nuclear features and is graded as mild, moderate, or severe based on the extent of the dysplastic cellular features.

3.2.1.2 Erythroplakia

Erythroplakia is defined as a grossly red squamous mucosa. They present as either homogenous or nonhomogenous red mucosa with and without leukoplakia association. Erythroplakia represents the end stage of dysplasia histologically and carries the highest risk of progression to invasive squamous carcinoma. Both severe dysplasia and microinvasive carcinoma (>3 mm) are generally treated with complete excision without neck dissection. Lesions with more than 5 mm invasion are eligible for neck dissection [2].

3.2.2 Squamous Carcinoma Variants

Squamous carcinoma manifests multiple, distinct phenotypes with variable site predilections and biological behaviors and includes verrucous, papillary, basaloid, and sarcomatoid phenotypes [4].

3.2.2.1 Verrucous Hyperplasia

Verrucous hyperplasia grossly appears as a white, warty raised growth mainly in the oral cavity. Both verrucous hyperplasia and carcinoma share clinically and pathologically similar and overlapping features. Verrucous hyperplasia shows exophytic growth with minimal inward stromal involvement. A diagnosis can only be achieved by an excisional biopsy where the edges and the full depth of the lesion are represented. The histologic diagnosis, therefore, is generally arbitrary, and the difference is essentially academic since both lesions should be completely excised [5].

3.2.2.2 Verrucous Carcinoma

This is a locally invasive squamous carcinoma with warty gross features and minimal cellular abnormalities. These lesions may frequently present in oral and laryngeal sites and, in their pure form, have minimal metastatic potential.

Verrucous carcinoma typically affects the oral and laryngeal sites, is locally invasive, and, in pure form, rarely metastasizes. Histologically, these tumors are well differentiated and invade with broad pushing borders [4].

3.2.2.3 Conventional Squamous Carcinoma

This is the most common form of presentation and typically graded based on the degree of squamous epithelial alterations and state of keratinization into well-, moderately, and poorly differentiated carcinoma. The pattern of invasion of these lesions may also impact on the extent of invasion, metastasis, and vascular and perineural permeation. Generally, broad, invasive fronts are less ominous than fingerlike invasive fronts [1].

3.2.2.4 Papillary Squamous Carcinoma

Papillary squamous carcinoma is typically laryngeal or nasal in origin and is exophytic in presentation with minimal tissue invasion. An association with HPV infection has been suggested but remains uncertain. Papillary squamous carcinoma typically pursues less aggressive behavior than the other forms of squamous carcinoma, except the verrucous variant [4].

3.2.2.5 Basaloid Squamous Carcinoma

This is a unique high-grade variant of squamous carcinoma with a predilection for hypopharyngeal, tonsillar, and base of tongue sites. They are characterized by uniform, highly malignant basaloid cells with focal squamous differentiation and collagen-like deposition. Recently, an association with high-risk HPV infection has been reported. Morphologically, tumors are characterized by a proliferation of homogenous basaloid cells with necrosis and focal abrupt areas of luteinization. These tumors may be confused with solid adenoid cystic and neuroendocrine carcinomas [4, 6].

3.2.2.6 Sarcomatoid Squamous Carcinoma

Two forms of sarcomatoid squamous carcinoma are recognized: the exophytic form and the ulcerative invasive form. The exophytic ones are usually found in laryngeal and hypopharyngeal sites and may or may not manifest areas of conventional squamous carcinoma. The distinction between this entity and pure sarcoma is based on combined morphologic and immunohistochemical staining for keratin intermediate filaments. Patients with the exophytic form may pursue a relatively better clinical course than the endophytic counterpart [7].

3.3 Viral Associated Squamous Carcinoma Subtypes

3.3.1 Oropharyngeal Carcinoma

Increasing evidence links HPV as an etiologic agent in the development of a subset of HNSC. Current data indicate that the majority of these cases are oropharyngeal, including the tonsils. This is further supported by the high risk of oropharyngeal carcinoma in seropositive HPV-16 and high risk of anogenital cancer patients. The exact prevalence of HPV in HNSC is not accurately known with figures ranging from 5 to >70 %. These variations are related to several factors, including differences in population, tumor sites, method of HPV detection, and histological subtypes. It is clear, however, that HPV-16 is dominantly present in more than 50 % of patients with oropharyngeal SCC. Integration of viral DNA into the nuclear genome is a critical step in the malignant transformation. Subsequent to viral integration, detection of early genes (E2) occurs, and upregulation of E6 and E7 genes is noted. The E6 of the HPV-16 binds to the p53 suppressor genes, consequently, and leads to uncontrolled proliferation of the oropharyngeal squamous mucosa. It has also been shown that the elevated expression of p16 is a surrogate marker in HPV infection. Approximately 10–60 %, dependent on the population and the site of infection of HNSCs, is reported to harbor HPV. Patients with this type of tumor respond better, do not have traditional risk factors, and have better survival. E7 leads to the inactivation of Rb protein and the release of the transcription factor E2F and the upregulation of both p14 and p16 proteins. Evidence for viral integration, especially in tonsillar carcinoma, in tumor cells is critical to the diagnosis. Also, the detection of p16 overexpression as an alternative/complementary to the detection of HPV infection may be helpful. The contribution of viral load to variations in reporting these markers remains to be addressed. In one study, a high viral load of <60 copies/cell was found to correlate positively with survival; however, a later subsequent larger study failed to confirm this finding [6, 8–13].

The traditional risk factors associated with conventional squamous carcinoma may play a secondary, but deleterious, role in this demographic population. Only certain oncogenic subtypes of the papillomavirus, especially HPV-16 and HPV-18, have been identified as etiologic factors in tumorigenesis of HNSC. The E6 and E7 genes of the HPV-16 genes bind to the p53 and Rb suppressor genes, and upregulation of the p16-IK4 inhibitor leads to dysregulation of the cell cycle and tumor development. Interestingly, these tumors are less aggressive and more sensitive to conventional therapy than conventional squamous carcinoma.

3.3.2 Nasopharyngeal Carcinoma

This is a unique form of HNSC that develops in the nasopharyngeal region. They are classified based on their histological appearance into differentiated squamous carcinoma (WHO I) and undifferentiated carcinoma with lymphoid stroma (WHO II or III). The histologic features of type I are similar to well-differentiated squamous carcinoma, while types II and III are highly undifferentiated carcinoma with integral lymphoid components. Nasopharyngeal carcinoma

(NPC) is associated with Epstein–Barr virus infection especially in patients from the Orient and Middle East but less likely in patients from the Western Hemisphere. These tumors are highly sensitive to radiation therapy [14].

3.4 Adverse Pathologic Features of Clinical Relevance

The following histopathologic factors are considered features associated with high risk of recurrence and failure to therapy response:

1. Poor histologic differentiation
2. Fingerlike and single-cell invasive pattern
3. Perineural invasion
4. Close surgical margins (<5 mm)
5. Presence of high-grade dysplasia
6. Extranodal extension of lymph node metastasis [15]

3.5 Molecular Pathology

3.5.1 Cellular Concept

The molecular and biological analysis and understanding of squamous tumorigenesis of the head and neck is largely based on the concept of field characterization conceived by Slaughter et al. in 1953 [16]. This concept assumes that risk factors render the entire aerodigestive mucosal surface susceptible to the squamous carcinoma development. In the small subset of patients with no history of risk factors and/or short temporal exposure to these factors, an inherent genetic susceptibility may play a role [1, 17, 18]. The cellular concept's premise for squamous carcinoma development and progress is that HNSC carcinoma results from molecular and/or biological alterations in the squamous epithelial cells.

3.5.2 DNA-Based Studies

3.5.2.1 LOH Findings

Microsatellites are short tandem repeat DNA sequences scattered throughout the genome. The vast majority of these repeats are polymorphic, inherited differently from each parent among different populations. Using constitutional DNA extracted from fresh or archived specimens as a standard, loss or shift in mobility in tumor microsatellite bands on gel electrophoresis determines the presence or lack of microsatellites of alterations. In general, frequent loss of loci on chromosomes 3p, 9p, and 17p has been detected in premalignant squamous lesions and may constitute any early alterations that may be used in screening of high-risk individuals for early detection of cancer. Other chromosomal alterations, including 4q, 6p, 8p, 11q, 13q, and 18q, are typically more frequent in invasive and advanced squamous carcinomas. Chromosomal gains, in contrast, are infrequent in squamous tumorigenesis and limited to chromosomes 3q26 and 11q13 amplicons and generally are late events [18–22].

3.5.2.2 Specific Gene Findings

p53 Gene p53 is a tumor suppressor gene on chromosome 17p. It is the most frequently mutated gene in HNSC in approximately 50 % of the cases. Tumors from patients with long histories of risk factor exposure are more frequently mutated. Most of the p53 mutations are transversion in type (G:T), but missense mutations can also be found and clustered between exons 5 and 9.

p16 Gene p16 is another tumor suppressor gene on chromosome 9p21. Loss of p16, a potent inhibitor of cell cycle, leads to uncontrolled proliferation. In contrast to p53, mutations of p16 are infrequent events in HNSC. Instead, hypermethylation of the p16 promoter and the first exon is the major mechanism for loss of function [23–25].

FHIT Gene (Fragile Histidine Triad) FHIT, on the short area of chromosome 3p14.2, has also been implicated in HNSC. However, the frequency and the temporal involvement of this gene in squamous tumorigenesis remain undefined [2].

Cyclin D1 Gene Cyclin D1, a critical cell cycle gene within chromosome 11p amplicon, has also been found to be highly amplified in advanced premalignant and invasive lesions. Polymorphism at this gene has been associated with high risk of developing squamous carcinoma [26].

p63 Gene p63 is a member of the p53 gene family and located on chromosome 3q29-29 region. p63 is a vital gene in normal epithelial development and has been implicated in several epithelial tumor developments. p63 has two different promoters resulting in two different protein products, on retaining the transactivation domain (TA p63) and another lacking it (Δ(delta)Np63).

Both isotypes undergo alternative splicing at the carboxy-terminal leading to six isoforms (three each) [α (alpha), β (beta), and *v* (upsilon)]. Studies of this gene and its main isotypes in HNSC indicate an important role in tumorigenesis, especially the ΔN isotypes. Overexpression of this isotype blocks differentiation and metastasis, promotes

proliferation in HNS tumorigenesis, and may be an attractive target for therapeutic intervention in a subset of patients with these tumors [27, 28].

3.5.3 Epigenetic Alterations

Epigenetic alteration is the process of gene silencing by non-DNA alterations and includes cytosine methylation of the CpG islands at the promoter and/or chromatin modulation and histone acetylation. These epigenetic modifications are reversible and may be of future therapeutic value. Cytosine methylation of several tumor suppressor genes in HNSC has been the target of numerous studies. Genes that have been found to be highly methylated in HNSC include p16, MGMT, RARB, E-cadherin, and DAPk [29, 30]. The diagnostic and therapeutic potential of these alterations remain to be achieved.

3.5.4 Genomic Studies

In genomic studies of HNSC using varied platforms, patient populations have recently been conducted. The inherent heterogeneity of these tumors complicates the interpretation and renders a clear conclusion difficult. Although results have shown evidence for segregating different responsive and aggressive behaviors, lymph node metastasis and tumor sites, the complexity of the analysis, and the heterogeneity of tumors and biological behaviors limit the clinical utilization of these platforms [31–34].

3.6 MicroRNAs

MicroRNAs, highly conserved and ubiquitous short (18–22 nt) noncoding RNA sequences, were found to regulate gene expression posttranscriptionally by base pairing with 3′-UTR (untranslated region) of cognate RNA transcript. Dependent on the extent of base pairing with target RNA, miRNA may lead to translational regression of degradation. Because of the partial complementarity between miRNAs and their targets, each miRNA may regulate several genes. A few recent studies of these molecules have recently been published. Several miRNAs, including miR-375 and miR-221, have been found to be significantly altered in HNSC [35, 36]. Another study of squamous carcinoma of the tongue identified 24 upregulated and 13 downregulated miRNAs. Of the most significantly upregulated, miR-184 was identified. Inhibition of the miR-184 cell lines led to decreased proliferation, downregulation of C-Myc, and induction of apoptosis. Further analysis of these molecules is warranted for their potential therapeutic use [37].

3.7 Growth Factors and Signal Transduction Pathways

Understanding the signaling pathways, trafficking, and regulation of fundamental inter- and intracellular tumor/host interactions will lead to understanding the biology of individual tumors and the development of effective targeted therapy in HNSC. Alterations in several growth factor receptor pathways play a critical role in the development and progression of HNSC. Several growth factors affecting signaling pathways in HNSC have been identified. These include the EGFR, Ras, NFkB, TGFβ, and PI3k/AkT/mammalian target of rapamycin (mTOR) pathways.

3.7.1 Epidermal Growth Factor

The epidermal growth factor (EGFR) gene is located on the short arm of chromosome 17 and encodes for a transmembrane tyrosine kinase receptor expressed on several epithelial cells. EGFR activation is a critical early event in the development of squamous carcinoma. EGFR is a glycoprotein receptor with a cysteine-rich ligand-binding domain with short sequence and intracellular tyrosine kinase and carboxy-terminal scaffolding domains. The activation of EGFR family members is either through ligand dependence or independence.

The independent activation is the result of mutation or overexpression-induced homodimerization or heterodimerization with other Grb family members. Ligand-independent activation of EGFR in HNSC has been linked to a transition mutation, EGFR variant III (EGFRvIII). Ligand binding to the EGFR initiates phosphorylation and triggers a signal transduction cascade that results in the activation of downstream molecules and increase in cell proliferation. Overexpression of EGFR has been amply reported in HNSC to be associated with aggressive behavior, poor progression, and response to targeted anti-EGFR therapy [38–40]. Studies of mutations in the hot-spot exons of this gene have yielded negative results. However, increased gene copy numbers have been reported in a subset of these tumors. Currently, immunohistochemical staining with anti-EGFR is the most commonly used method of assessment of this gene. It is unknown, however, whether the activated form (phosphorylated) or the total EGFR level correlates better with the activity and response to therapy in HNSC [41]. The interest and available data on EGFR have led to interest in the development of molecularly targeted small-molecule inhibitors in the treatment of HNSC. New anti-EGFR tyrosine kinase activity has been used in clinical trials as single or multiple agents and modalities with limited success (response rate 10–15 %). The binding by ligands (EGF, TGF2, amphiregulin, and heparin-binding EGF) leads to antiphosphorylation

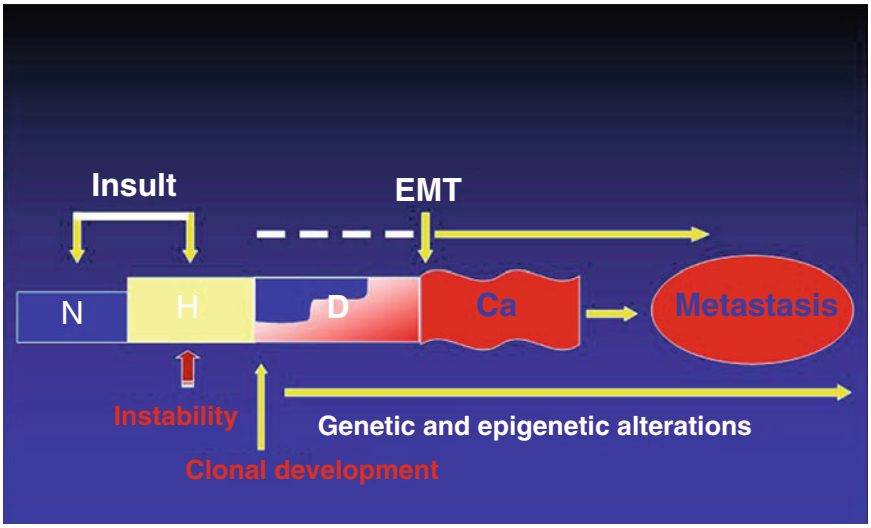

Fig. 3.2 Proposed model of epithelial-to-mesenchymal transition in squamous tumors

of multiple tyrosine residues at the carboxy-terminus, where SRC and other proteins interact with transducer mitogenic signals [39].

3.7.2 VEGF and FGF

Elevated expression of VEGF and FGF and their receptors has been reported to be associated with angiogenesis and aggressive behavior in HNSC. The regulation of this growth factor is primarily through the hypoxia-inducible factor 1α (HIF-1α)-dependent and hypoxia-inducible factor 1α (HIF-1α)-independent processes and involves both PI3k and AkT pathways [42–47].

A humanized VEGF monoclonal antibody (bevacizumab) has recently been tested and shown to inhibit angiogenesis [48, 49].

3.7.3 PI3k/AkT/mTOR Pathway Inhibitors

Activation of these pathways plays an important role in the development and progression of HNSC. Mutation of the PI3k gene leads to cellular transformation of HNSC. Restoration of this pathway may lead to inhibition of PI3k phosphorylation and expression, which is responsible for radioresistance in HNSCC [50]. Also, activation of the AkT pathway may lead to EGFR overexpression and enhance resistance to targeted treatment. The mTOR has been shown to regulate critical cellular processes, including motility, proliferation, survival, and transcription.

mTOR inhibition, however, may lead to negative feedback of the insulin-like growth factor, which may lead to activation of PF3k and AkT and potentially counteracting the mTOR inhibitor [51]. Multiple agents or single agents targeting multiple pathways may be an ideal strategy.

The complexity of the aberrant signaling in HNSCC underlines the difficulties in treating these patients (Fig. 3.2).

3.8 Structural Concept

3.8.1 Mesenchymal-to-Epithelial Transformation

In the last two decades, minimal attention has been paid to the role of epithelial/stromal interactions of invasion, progression, and metastasis in HNSC. Recent investigations in several solid tumor models have shown that invasion and metastasis are associated with alteration in cell-to-cell and cell-to-matrix adhesion, altered epithelial cell polarity, and increased motility. Several studies have shown that this process is initiated in response to extracellular stimuli and factors. Growth factors and their receptors play a central role in the transduction of key events associated with this process. Among the most important of these are the Ras, SRC, PI3k, and MAP kinase pathways. The activation of these pathways has been shown to lead to downregulation of adhesion molecules (e.g., E-cadherin) and elevation of surrogate mesenchymal markers (e.g., vimentin) [3, 52, 53]. This process is highly relevant to squamous carcinoma invasion and metastasis, where E-cadherin is a key adhesion molecule in squamous epithelial cells. E-cadherin is not only important in cell-to-cell and cell-to-basement adhesion but also in mediating cell-to-cell cross talk through Ca-dependent homotypic interactions [38, 54, 55]. Several growth factors, including TGFB, lead to downregulation of E-cadherin and other cellular features associated with EMT. However, the manifestation of EMT in HNSC may vary considerably from tumor to tumor and within a given tumor. Not infrequently, minimal EMT changes are observed in well-differentiated tumors

with broad invasive fronts, while complete mesenchymal transformations are found in the sarcomatoid form of these tumors. In addition to the semiquantitative changes in these molecules, qualitative changes may also occur. This is clearly manifested in the phenotypic distribution of E-cadherin from membranous to cytoplasmic localization.

EMT, therefore, is a dynamic and heterogeneous process that underlies the biology of a squamous carcinoma and that the degree and extent of these changes reflect their aggressive nature.

3.8.2 Biomarker Applications in Head and Neck Tumorigenesis

Early diagnosis in high-risk individuals for HNSC is key to improving treatment and prognosis of this disease. Similarly, predicting the biological behavior, response to nonsurgical therapy, and toxicity is important in stratifying patients for treatment and targeted therapy. Therefore, the identification of sensitive and reproducible markers is critical to the success of these efforts. The application of tissue-based assay requires that they accurately and reproducibly reflect the underlying pathological and biological processes. These processes are dynamically varied in and between individuals. Quantitation of lesional variabilities and confounding nonneoplastic processes is necessary for accurate interpretation and the exclusion of false-positive and false-negative results. Integrating tissue assessment and biomarker results might ultimately be the best model of risk assessment for head and neck cancer patients [2, 24, 56].

3.9 Salivary Gland Tumors

Salivary gland tumors are rare and remarkably heterogeneous neoplasms of an uncertain histogenesis. They constitute only 2–3 % of all head and neck neoplasms, with an overall incidence of approximately 2.5–3 per 100,000 persons per year [57, 58]. Major salivary glands are the most commonly afflicted sites, with 80 % of tumors occurring in the parotid gland, 10–15 % in the submandibular gland, and 5–10 % in the sublingual and minor glands [59]. Most tumors (80 %) of parotid gland origin are benign, whereas those arising in submandibular, sublingual, and minor glands are more often malignant. Primary malignant salivary gland neoplasms compose approximately 5–10 % of all the head and neck carcinomas and 0.3 % of all cancers [57]. Generally, salivary neoplasms present in middle and older age (mean age 56 years), with only 2–3 % occurring in children under 10 years of age, and more commonly in males than in females [57, 60].

3.9.1 Salivary Tumors in Children

The majority of salivary neoplasms in children are nonepithelial and mainly of vascular origin. The most common is mucoepidermoid followed by acinic cell carcinomas forming approximately 60 % of malignant neoplasms in this category. The most common benign epithelial neoplasm in this age group is pleomorphic adenoma (PA). It is worth noting that a rare congenital tumor known as embryoma or sialoblastoma occurs prenatally. Histologically, these tumors represent a neoplastic growth of embryonic, primitive, basaloid epithelial cell of the salivary gland. These lesions are considered of low-grade malignancy. The differential diagnosis is basal cell adenocarcinoma and adenoid cystic carcinoma (ACC) [61–63].

3.9.2 Fine Needle Aspiration in the Evaluation of Salivary Masses

Fine needle aspiration (FNA) may be used in the initial evaluation of a salivary mass. The main indications of this procedure are to exclude lymphoreticular disorder, inflammatory and granulocytic reactive lesions, and metastasis. FNA may not be recommended in the diagnosis of primary salivary gland tumors and cystic lesions. Not uncommonly, FNA may induce neurosis and reactive, inflammatory, and reparative manifestations that may obscure the underlying neoplastic conditions. Occasionally, however, especially in the planning of the extent of the operation, surgeons may utilize this technique to obtain a malignant diagnosis.

Pathologic features of clinical importance:

1. Tumor size
2. Histologic diagnosis
3. Malignancy grade (when applicable)
4. Margin status
5. Perineural involvement

3.10 Histopathology (Table 3.1)

3.10.1 Benign Tumors

3.10.1.1 Pleomorphic Adenomas

PAs are the most common benign salivary tumors that primarily occur in the parotid gland. Clinically, these tumors pursue a benign clinical course with a tendency for local recurrence due to mainly nodular extension. Rarely, some PAs may metastasize while retaining their benign phenotypic features. Histologically they manifest varied cellular components, comprising epithelial and myoepithelial cells in

Table 3.1 Simplified classification of salivary gland tumors

Myoepithelial/epithelial	Epithelial
Benign	
Myoepithelioma	Oncocytoma
Pleomorphic adenoma	Basal cell adenoma
Malignant (carcinoma)	
Myoepithelial	Mucoepidermoid
Epimyoepithelial	Salivary duct
Basaloid salivary	Adenoid cystic, solid
Adenoid cystic	Basaloid salivary
Terminal duct	Acinic cell

variable background of myxoid and/or chondroid stroma [57, 64–66].

Karyotypic analyses have identified recurrent and specific cytogenetic abnormalities, with t(3;8) (p21;q12) reported in more than 40 %, and a small subset manifesting rearrangements of the 12q14-15 region [67]. The latter includes translocation involving 12q14-15 with chromosome 9p12 or different partners and/or inversion of both chromosomes at the same breakpoint. Random clonal abnormalities have also been detected in more than 20 % of PAs [68, 69]. Molecular studies using microsatellite repeat markers reported frequent loss of heterozygosity at the long arm of chromosomes 8 and 12p loci [67, 70]. Two specific genetic markers have been consistently identified in PAs; the PLAG1 on chromosome 3p21 is the most frequent upregulated gene, but its biological significance in the development of pleomorphic adenoma remains uncertain [71].

The second recurrent and specific chromosomal alteration involving 12q14-15 leads to overexpression of the high-mobility group A2 gene (HMGA2). The gene is an architectural factor that regulates transcription through binding to AT-rich DNA. Microarray analysis of PA and PLAG1-transfected cells has identified most of the unregulated genes to be growth factors, such as IGF, BDGF1, CRABP2, SMARCD1, and EFNB1 [72]. Together these findings indicate that the PLAG1 gene contributes to oncogenesis through the induction of growth factors [73].

3.10.2 Warthin's and Oncocytic Tumors

Warthin's tumor (WT) is the second most common benign salivary gland tumor. It arises almost exclusively in intra- or periparotid lymphoid stroma. Histopathologically, the tumor manifests oncotypic epithelial cell proliferation within lymphoid stroma with and without cystic formation. A spectrum of oncocytic tumors ranging from nodular oncocytic hyperplasia, adenoma, and carcinoma has been described and most likely related to Warthin's tumors [74]. Current molecular and cytogenetic studies indicate that the majority of these lesions manifest a normal karyotype [75], while approximately 10 % have cytogenetic abnormalities; the most common cytogenetic alteration identified is the t(11;19) (q21-22;p13) [76, 77]. The same translocation and its fusion gene product *CRTC1/MAML2* were also found in mucoepidermoid carcinoma (MEC). The finding of this abnormality in both tumors, along with their reported simultaneous occurrence, indicates a genetic link between these lesions. Collectively, the data support a clonal origin in a subset of these tumors with a propensity to transformation to MEC or oncocytic carcinoma.

3.10.3 Basal Cell Tumors

Both basal cell adenomas and carcinomas are rare and constitute approximately 2–3 % of all salivary gland tumors. These tumors may not infrequently pose diagnostic difficulties due to their cytomorphologic similarities. They are typically formed of bland basal cell proliferation in nest and/or cord formation with intercellular eosinophilic homogenous material deposition [78]. Because of the infrequency of these tumors, only small numbers have been genetically analyzed; a common cytogenetic alteration in few tumors was trisomy 8, but other sporadic cytogenetic alterations, including t(7;13) translocation, have also been reported [79]. CGH analyses of examples of these tumors showed loss of chromosomes 2, 6, and 7, gains of chromosomes 1 and 8, and amplification of 12q region. Molecular analysis of these tumors has reported frequent loss of heterozygosity at chromosome 16q12-13, a region that houses the cylindromatosis gene (CYLD) [79].

3.10.3.1 Canalicular Adenoma

Canalicular adenoma is characterized by columnar epithelial cells forming anastomosing bilayered cellular formations including nests and is trabecular in a vascular stroma. The lesions are typically well circumscribed and encapsulated [57, 65]. Differential diagnosis of canalicular adenoma from basal cell adenoma and ACC may occasionally be difficult, especially on biopsy specimens. Because of their rarity and benign nature, molecular studies of this entity are very rare.

3.10.4 Myoepithelial Tumor

Myoepithelial tumors are formed almost exclusively of myoepithelial cells, which are rare and are less than 1 % of all salivary gland neoplasms. Some tumors may show focal areas of pleomorphic adenoma. They may manifest a variety of phenotypic forms, including plasmacytoid, spindle, clear, and/or epithelial features. Current molecular genetic data on these lesions are sparse and preclude any definitive findings that contribute to either their development or biology. Cytogenetic analyses of a few examples have reported nonspecific

chromosomal abnormalities and were insufficient for comment on their contribution to these tumors [80, 81]. Upregulation of the WT1 mRNA has been detected in some benign and malignant myoepithelial tumors, but the oncogenic role of this event in their development is unknown [82].

3.10.5 Malignant Tumors

3.10.5.1 Mucoepidermoid Carcinoma

MECs compose approximately 30 % of malignant salivary neoplasms and are most common in children and adolescents. MEC manifests three distinctive phenotypic grades based on the cellularity and architectural features of the tumors. Of all salivary neoplasms, MEC is the only entity in which both cytogenetic and molecular analyses have led to the identification of consistent unique alteration that may constitute an initiating event in the development of a subset of these tumors. Several cytogenetic analyses of MEC have shown translocation t(11;19) (q21;p13) either alone or with other nonspecific alterations [75, 83–85].

Cloning of this translocation has identified a fusion oncogene composed of exon 1 of the *MECT1* (*CRTC1/WAMTP*) gene (Fig. 3.3) on chromosome 19p13 and exons 2–5 of the MAML2 gene on chromosome 11q21 regions [86]. MAML2, a member of the mastermind gene family, encodes a nuclear protein that binds to the CSL transcriptional factor and the intracellular domain of the Notch receptor to activate the Notch target gene. The fusion partner is the *CRTC1 (MECT1)*, a member of the highly conserved CREβ/cAMP coactivator gene family [87, 88]. Studies of this fusion transcript in a series of MEC have reported a correlation between fusion-positive tumors and low tumor grade and better behavior. Fusion-negative MEC may evolve from a different evolutionary pathway and may represent a biologically distinctive category. The results also suggest that tumors lacking the fusion transcript behave more aggressively. The finding of the fusion transcript in both sporadic Warthin's tumor and MEC and concomitant tumors supports an early or etiologic role in the development of a subset of these tumors. Epithelial ductal cells in heterotypic salivary tissue in intra- or periparotid lymphoid stroma acquiring the t(11;19) fusion gene give rise to Warthin's tumor, while the same alteration in the salivary tissue gives rise to MEC in sporadic presentations. The development of MEC in Warthin's tumor may therefore result from metaplastic changes in ductal cells with the fusion transcript [89–92].

3.10.5.2 Salivary Duct Carcinoma and Adenocarcinoma Ex-pleomorphic Adenoma

Salivary duct carcinoma (SDC) and adenocarcinomas present either de novo or in the setting of pleomorphic adenoma and manifest remarkable similarity to mammary duct carcinoma [93, 94]. Cytogenetic studies of some of these tumors have shown that rearrangements of chromosome 8q12, alteration of chromosome 12q13-15 region, and amplification of both the HMG1C and MDM2 genes may be potentially associated with these tumors. Other studies have shown that translocations of chromosome 5(q22-23, q32-33) and t(10;12) (p15;q14-15) resulted in transportations of the entire HMG1C gene to chromosome 10 marker [57, 95–97].

Using microsatellite markers on microdissected benign and matching malignant components of salivary gland carcinoma ex-pleomorphic adenoma (Ca ExPA) have shown alterations at 8q and/or 12q in both components and restricted

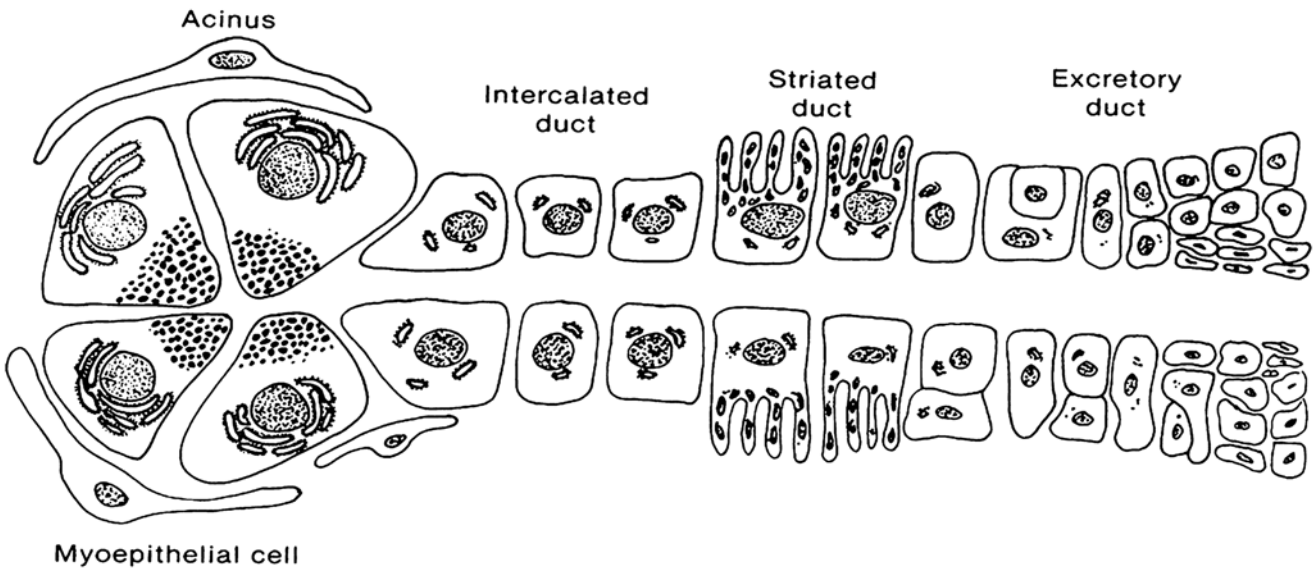

Fig. 3.3 Ductal structure and proposed origin of salivary gland tumors

alterations at chromosome 17p loci in the malignant component [95, 96]. These findings suggest that alterations at 8q and 12q regions represent early events, whereas alteration at 17p is associated or coincident with the malignant transformation. Studies of specific genes and loci have also reported homozygous deletion of the p16 gene on chromosome 9p21 [98, 99] and p53 alterations and loss of heterozygosity at different loci on chromosome [73]. A subset of SDCs, as in mammary ductal carcinomas, express hormonal and growth factor overexpression that may be used in their biological and therapeutic stratification [98]. Overexpression of HER-2, EGFR, and androgen receptors is found in more than one-third of these tumors [100, 101].

3.10.5.3 Adenoid Cystic Carcinoma

ACC is the second most common malignant salivary gland tumor and the most clinically relentless malignancy. ACC is known for its indolent and persistent clinical behavior and propensity for perineural invasion. ACC manifests three phenotypic subtypes, which are nearly always present in the majority of tumors but with variable proportions [102]. These include the tubular, cribriform, and solid morphologic variants. In both the tubular and the cribriform phenotypes, the tumor units consist of myoepithelial and ductal epithelial cells. Cytogenetic studies of these tumors have reported frequent alterations at chromosomes 6p, 9p, and 17p, with the most consistent alteration at the 6q regions (Table 3.2) [99, 103].

Studies of ACC found a high frequency of loss of heterozygosity at 6q23-25, and this correlated with histologic grade and clinical behavior. Studies using microsatellite markers have also reported frequent loss at chromosomes 12q, 6q23-qter, 13q21-33, and 19q regions. These regions house two genes, PLAGL1 and LATS, that were not mutated in any of these tumors. A recent comparative genomic hybridization of ACCs identified a novel gain at chromosome 22q13 region in 30 % of the tumors in addition to the loss of chromosome 6q and gains of chromosomes 16p and 17q regions [104–106]. Microarray analysis of a few examples of these tumors has shown amplification of MDM2, HMG1C, MYC, and other genes located on chromosomes 8q and 12q14 [107–109]. A frequent finding in these tumors is the overexpression of the C-Kit protein. C-Kit (CD117) is a transmembrane tyrosine kinase receptor encoded by the C-Kit gene on chromosome 4. The C-Kit ligand, a stem cell factor (also known as steel factor and mast cell growth factor), induces signal transduction pathways affecting development, cell growth, and migration of different cell functions [110–112]. The role and the cellular distribution of this gene product in the biology and as a target in these tumors remain to be determined.

3.10.5.4 Acinic Cell Carcinomas

Acinic cell carcinoma is a distinctive salivary malignancy that develops almost exclusively in the parotid gland. These tumors arise from acinar cells and manifest granular serous cellular features with variable and overlapping morphologic subtypes [113]. They are generally low-grade indolent carcinomas, occasionally presenting as high-grade carcinomas with high mitotic figures, necrosis, and lymph node metastasis [114]. In addition, several examples of transformation into dedifferentiation or anaplastic carcinomas have been reported. Cytogenetic and molecular studies of these tumors are few and inconclusive. One study cites evidence for a frequent loss of heterozygosity at limited chromosomal regions [115], including 4p15-16, 6p25-qter, and 17p11, suggesting that these regions may contain critical genes related to their development. In another study of multiple samples of an ACC, variable clonal alterations were obtained, suggesting multiclonal origin [116]. Studies of dedifferentiated acinic cell carcinoma have shown an association of such transformation with cyclin D1 upregulation. The lack of confirmatory and validation follow-up studies precludes any speculation on the role of these findings in this entity.

3.10.5.5 Polymorphous Salivary Adenocarcinoma (Terminal Duct Carcinoma)

This entity is characterized by intratumoral growth pattern variabilities and uniformed monotonous cellular composition. The hard palate is the most frequent site, but they may rarely occur in major salivary glands. The tumor constitutes 19.6 % of malignant minor gland tumors. Because of the lack of encapsulations, these tumors typically infiltrate adjacent tissue and are prone to perineural invasions. The recurrence rate for these tumors is approximately 17 %, and regional metastasis occurs in approximately 9 % [117].

3.10.5.6 Epimyoepithelial Carcinoma

This rare entity represents a malignancy of low-grade and indolent course that is composed of dual myoepithelial and ductal tumor cells. Histopathologically, the tumor forms duct and tubular formations of relatively prominent clear myoepithelial cells and inner cuboidal and uniform duct cells.

Table 3.2 Adenoid cystic carcinoma (ACC)

Acinic cell carcinoma	Pleomorphic adenoma	Warthin's	Mucoepidermoid carcinoma
	Adenoid cystic carcinoma	Oncocytoma	Adenocarcinoma
	Monomorphic adenomas		
	Epithelial myoepithelial carcinomas		

3.11 Rare Salivary Gland Neoplasms and Subjects

3.11.1 Squamous Carcinoma

Rarely squamous carcinoma may arise de novo in major salivary glands and if presented not underlined. The exclusion of metastasis from other sites must be proved. Rare carcinomas reported to be of primary origin include small cell and lymphoepithelial carcinoma.

3.11.2 Nonepithelial Neoplasms

Nonepithelial neoplasms form less than 5 % of all salivary gland tumors. They represent lesions arising from salivary gland supporting connective tissue. The most common lesions are angioma, lipoma, neurofibroma, and hemangiopericytoma. The growth and microscopic features of these lesions are identical to those encountered in other sites.

3.11.3 Primary Lymphoma

Lymphomas are very rare and mainly found in the parotid gland. The majority of primary lymphomas are of the MALT type. They may arise in either intraparotid lymph nodes or the parenchyma. The vast majority is of the follicular B-cell derivation with rare instances of T-cell origin.

3.12 Metastasis to Salivary Glands

The most common metastasis to major salivary glands, especially the parotid gland, is squamous carcinoma followed by melanoma of the skin. This is largely due to the lymphatic drainage of the skin of the face. Hematogenous spread to the parotid gland originates primarily from kidney, breast, and lung carcinomas. Metastasis to the submandibular gland is very rare due to the lack of intraglandular lymph nodes. Epithelial neoplasms are rarer and disproportionately malignant [57].

3.12.1 Genomic and Proteomics of Salivary Gland Tumors

Proteomic analysis of solid tumors remains limited and difficult to execute. There is only a single study of ACC xenografts by fluorescent two-dimensional gel, electrophoresis, and matrix-assisted laser-desorption/ionization techniques. This study identified four upregulated and five downregulated proteins. Of these proteins, maspin and stathmin were confirmed to be highly expressed in human ACC. Similar attempts have been made in some salivary gland tumors. The results, however, should be considered preliminary or suspect until verified [72, 93, 118, 119].

3.13 Thyroid and Parathyroid Tumors

3.13.1 Thyroid

Thyroid nodules are one of the most common clinical conditions. The vast majority of these are reactive lesions or benign tumors and only 10 % are malignant. Approximately 14,000 new cases of thyroid carcinomas are diagnosed per year in the USA [120]. The histologic subtypes of thyroid malignancies include papillary, follicular, poorly differentiated, anaplastic, and medullary carcinomas. Broadly, these tumors can be categorized into differentiated (papillary, follicular, and medullary) and undifferentiated (poorly differentiated and anaplastic) carcinomas [121, 122]. The papillary, follicular, poorly differentiated (insular), and majority of anaplastic carcinomas arise from the follicular epithelial cells, while the MTC is derived from parafollicular calcitonin-producing C cells [123–126].

3.13.2 Etiology

The etiology of thyroid malignancies is largely unknown, although exposure to radiation during childhood (papillary) and iodine deficiency (follicular) has been linked to the development of certain carcinoma subtypes. Papillary thyroid carcinoma may affect any age but especially children, young adults, and females. Carcinomas typically present as an enlarged mass with or without ipsilateral nodal involvement [127–130].

Initial radioscintigraphy is helpful in distinguishing between hot (benign) and cold (malignant) nodules [131].

3.13.3 Pathology

3.13.3.1 Cytology

Fine needle aspiration (FNA) is the first line of diagnostic techniques for thyroid tumor diagnosis. In general, an accurate diagnosis of papillary and medullary thyroid carcinoma can be readily made on FNA. The sensitivity and the specificity of FNA in diagnosing follicular lesions, including follicular variant of papillary carcinoma, however, is low. It is estimated that up to 30 % of FNA-based diagnoses of follicular neoplasms are indeterminate [132, 133].

3.13.3.2 Histology

Thyroid neoplasms are generally classified based on their histogenesis from epithelial (follicular cell) and neuroectodermal (C-cell) neoplasms. Epithelial neoplasms are broadly benign follicular adenomas and differentiated neoplasms and poorly differentiated and anaplastic carcinomas.

3.13.3.3 Follicular Adenoma

Adenomas are characterized by a well-circumscribed nodular growth with thin encapsulation. They may present as solitary or multiple nodules at any age and gender. Microscopically, they may manifest microfollicular, trabecular, and macrofollicular forms. The main differential diagnoses for adenomas are follicular hyperplasia (goiter) and follicular carcinoma. Oncocytic changes due to the high content of mitochondria are most likely secondary to respiratory cellular demands. The biological behavior of these neoplasms is similar to those of corresponding follicular tumors [134–136].

3.13.3.4 Differentiated Carcinomas

- *Follicular type*

  Follicular carcinomas comprise approximately 5–10 % of all thyroid malignancies. They generally afflict females in their middle age than males. A high incidence of these tumors is reported in iodine-deficient regions, suggesting a role for continuous TSH stimulation in the genesis of this entity. The diagnosis of this entity is based on the findings of a thick fibrous capsule and the presence of capsular and/or vascular penetration [134]. These tumors can be further classified as minimally invasive or encapsulated, if invasion did not extend beyond the capsule.

  Follicular carcinoma is typically solitary and may present or be preceded by metastasis typical to the bone, lung, and brain [125, 137–139].

  Patients present with a single palpable cold mass with a high propensity for radioactive iodine uptake [140, 141].

- *Papillary type*

  Papillary carcinoma is the most common of all thyroid carcinomas, accounting for more than 70 % of these tumors. They may present at any age with peak incidence between 30 and 40 years of age. Females are far more affected than males, and young patients typically have a better and long protracted course than older patients, especially men. There is strong circumstantial evidence linking Hashimoto's thyroiditis to increased incidence of papillary thyroid carcinoma [142–144].

  Papillary thyroid carcinomas are multifocal in more than 75 % of the cases, and total thyroidectomy is generally the treatment of choice. Papillary thyroid carcinoma may present as a thyroid mass (80 %) or as a lymph node metastasis (20 %). The hallmark of papillary carcinoma is finding papillary structures lined by cuboidal or columnar cells with clear and/or cleaved nuclei. The nuclear features are especially helpful in the diagnosis of the follicular variant of this entity. Not uncommonly present (40 %) is the concentric calcification associated with this tumor (psammoma bodies). Several histopathologic variants of this entity have been described with some being associated with a more aggressive clinical course. However, the lack of prospective studies with long-term follow-up renders the significance of these subtypes tenuous. The clinical aggressiveness of papillary thyroid carcinoma varies depending on the gender, age, and size of the tumor with older males having a more aggressive course as well as patients with large invasive tumors [120, 126].

- *Undifferentiated carcinomas*:

  (a) Poorly differentiated

  This histologic variant represents a tumor that lacks follicular or papillary differentiation and the cellular anaplasia of anaplastic carcinoma. Tumors typically manifest cell nests or cords with monotonous cellular features. The differential diagnosis is mostly with medullary thyroid carcinoma. Tumor cells react positively to antithyroglobulin antibodies and they are negative for calcitonin. Their behavior is considered more aggressive than the fully differentiated tumors [122, 145].

  (b) Anaplastic

  Anaplastic thyroid carcinoma (ATC) is the most clinically aggressive neoplasm and accounts for 4–10 % of all thyroid malignancies. This entity afflicts elderly individuals and is more common in females than males (3:1) [146, 147].

  Clinically, patients present with rapidly progressive local disease. The majority of these tumors arise from preexisting differentiated thyroid carcinoma, most commonly the papillary phenotype. In resected specimens of these tumors, evidence for a differentiated carcinoma can be found. The etiology of ATC is unknown, but previous radiation of thyroid lesions has been linked to the development of these tumors. Histopathologically, these tumors manifest highly malignant tumor cell composition with heterogeneous features and tumor necrosis. The most common pathologic phenotypes are sarcomatous, giant cell, and squamous variants. The differential diagnoses of these tumors include sarcomatoid carcinoma of the upper aerodigestive tract, sarcoma, and melanoma [121, 148–150]. Immunostaining assists in excluding sarcoma and melanoma. The prognosis of these patients is very poor.

- *Medullary carcinoma*

  Medullary thyroid carcinoma arises from the C cell, a neuroectodermally derived cell, and accounts for 3–10 % of thyroid cancer. The tumors present in two forms: sporadic,

the most common, which accounts for 70–80 %, and the familial form, which represents the remaining 20–30 %. The tumors affect both genders equally and patients in middle age.

The familial and the sporadic forms have mutations in the RET gene; the frequency and the type of these mutations vary. Tumors in the sporadic form present with a solitary mass with or without neck enlargement and paraneoplastic syndrome. Tumors in the familial form are generally multifocal and affect the younger age and children [151, 152].

The most common location of these tumors is the lateral aspect of the upper two-thirds of the thyroid lobes, where a high aggregation of C cells can be found. Histopathologically, tumors consist of nests and cords and organized structures composed of small- to medium-sized cells with uniform nuclei. Tumor clusters are encircled by delicate vessels and fibrous tissue. Not uncommonly, deposition of dense homogenous eosinophilic materials representing amyloid deposition is noted. The amyloid nature of these materials can be verified by either Congo red staining or by light microscopic birefringence [52].

Immunostaining for calcitonin and other neuroendocrine markers may be used for confirmation. The most common sites of metastasis for MTC are the regional lymph nodes, lung, liver, and bone. The prognosis of MTC depends on several factors, including age, gender, size, and stage. Generally, the young and females have better outcomes. Patients with MEN-2B have a worse outcome.

The differential diagnosis of these tumors includes metastasis from neuroendocrine carcinoma, renal cell carcinoma, and microfollicular thyroid neoplasm.

- *Sclerosing mucoepidermoid carcinoma*
  This is a rare malignancy of the thyroid gland, typically in association with Hashimoto's thyroiditis. It is characterized by infiltrating sclerotic stroma with infiltrating nests of squamoid cells with occasional mucinous cells. The stroma is characteristically infiltrated by numerous eosinophils.

3.14 Molecular Analysis of Thyroid Neoplasms

3.14.1 Genetics

RAS gene mutations were frequently found not only in thyroid carcinomas but also in adenoma [153]. Point mutations in RAS have been linked to early thyroid tumorigenesis. Whether adenomas with RAS gene mutations represent a biologically malignant lesion remains unknown [154–157]. Rearrangements of the PPARγ/RAX8 translocation have also been reported in follicular carcinoma and adenomas suggesting that it may constitute an early event in their development [158–162].

Several studies have also shown mutation in the RAS gene RET/PTC rearrangements on chromosome 10 and BRAF oncogene mutations in thyroid carcinoma. The frequency and the biological significance of these events are the subject of debate and remain to be determined. The most frequent of these genetic alterations is the BRAF point mutation in Exon 15 at codon 600 [129, 163–166]. This mutation has been reported in up to 70 % of PTC cases.

RET-mutated MTC are characterized by early onset and metastasis to lymph nodes and distant organs [152, 167]. The RET proto-oncogene encodes a receptor tyrosine kinase (RTR) that is widely expressed in neuroendocrine cells. RET point mutation in the intracellular or extracellular kinase domain occurs in medullary thyroid carcinoma [168, 169]. RET gene rearrangements, however, are associated with papillary thyroid carcinoma.

The common underlying denominator in tumor growth is the constitutive activation of the RET kinase [143, 170–172]. The molecular mechanisms that result in RET activation and the pathophysiology vary widely [87].

PTCs with RET gene arrangements are heterogeneous and generally indolent and rarely present with metastasis. In these tumors, chromosomal rearrangements involving the RET gene fuse the 5′ end and a promoter of a gene upstream of the RET kinase domain leading to the expression of a chimeric product, a RET/PTC. RET/PTCs are localized to the cytoplasm since they lack the NH2-terminal sequence and the transmembrane domain of the RET gene. All NH2-terminal fusion partners identified to date contain homodimerization domains that mediate dimerization and activation of the kinase region in RET/PTC oncoproteins [169–171, 173, 174]. Recent studies have also established the anaplastic phenotypic transformation from differentiated thyroid carcinoma through the analysis of RAS and BRAF genes [146, 147, 156, 175–177]. Galectin-3 is an antiapoptotic molecule of the B-galactoside-binding lectin family. Alteration in the expression of galectin-3 has been proposed as a diagnostic marker of thyroid malignancy [131, 133, 178, 179].

3.14.2 Genomics

Gene expression analysis of several thyroid neoplasms has been performed. Upregulation of MET, SGRPINA, FNI, CD44, and DPP4 and downregulation of TFF3 gene have been reported in some of these studies [160, 178, 180–183]. In genomic analysis, although they are allowed for the identification of thyroid neoplasm and the biological categorization within carcinomas, the utilization of these assays in the clinical diagnosis is limited and impractical.

3.15 Parathyroid Lesions

Parathyroid glands are derived from the third and fourth pharyngeal pouches and are recognized by the fifth to the sixth week of gestation. The majority of humans have two pairs of parathyroid glands. Multiples up to 10 (13 %), and as few as 1, have been reported in humans.

Normal glands are encapsulated, small, soft, and tan to red-brown in color. Parathyroid cells are organized in lobules with fat cells and vascular stroma. The degree of fat in normal parathyroid varies but in general is approximately 60 %. Although, literally, a nonneoplastic process, evidence of clonality and evolution to adenoma and carcinoma based on clonality analysis has been documented [184–187].

3.15.1 Parathyroid Hyperplasia

Parathyroid hyperplasia is pathologically characterized by increased parathyroid cells with reduction of fat cells in parathyroid lobules. This may occur in all four glands with a variable degree. Generally, this may signify a systemic etiology such as calcium deficiency, vitamin D alterations, or kidney diseases. Hyperplasia of the parathyroid can also be a manifestation of MEN type I syndrome. Histopathologically, they manifest diffuse or nodular cellular proliferation. The cellular feature varies and may include clear and oncocytic cytoplasm [188].

3.15.2 Parathyroid Adenoma

Parathyroid adenoma is a benign parathyroid gland neoplasm and is the most common cause of hyperparathyroidism accounting for more than 80 % of cases. Parathyroid adenoma affects more females than males in the middle age. These lesions are considered clonal in origin and present as a single well-circumscribed nodule with a peripheral rim of parathyroid tissue [127, 189]. Adenoma is typically homogenous and contains no adipose tissue cells. Although they may arise in any gland, they are more frequently reported in the lower glands [120].

3.15.3 Locally Infiltrative Parathyroid Neoplasm (Atypical Parathyroid Adenoma)

Occasionally, parathyroid neoplasms with cytomorphologic features identical to those of hyperplasia or adenoma and infiltrative growth into surrounding soft tissue with intersecting fibrous bands may be encountered. The lack of high and abnormal mitotic figures, necrosis, and marked cellular pleomorphism precludes a definitive malignant diagnosis. These lesions are typically prone to local recurrence because of the difficulties to completely excise them. These lesions may also be called atypical parathyroid adenoma.

3.15.4 Parathyroid Carcinoma

Parathyroid carcinoma is a rare, highly malignant neoplasm accounting for less than 5 % of patients with hyperparathyroidism. This entity may be hormonally active or inactive [190]. The inactive carcinoma has reportedly been more aggressive. These tumors present as a solid mass that is difficult to excise due to its infiltrative nature. Histopathologically, these tumors are characterized by a proliferation of markedly pleomorphic cells, high and abnormal mitotic figures, broad intersecting fibrous bands, vascular and soft tissue invasion, and necrosis. This is a surgically treated disease, but more than a third of these patients experience metastasis.

3.15.5 Molecular Analysis of Parathyroid Lesions

Alterations in the overexpression of cyclin D and chromosome 11q13 regions have been shown to characterize parathyroid nodular hyperplasia and adenoma. Other clonal and molecular findings support a clonal basis for the development of at least a subset of these lesions. The cyclin D and retinoblastoma glue have frequently been found in parathyroid carcinoma alterations [120, 191–193]. Mutation at the MEN1 gene on chromosome 11q13 region has been reported in up to 50 %. Genome-wide studies have also shown loss of 11q region in addition to other chromosomes [194–196].

Molecular alterations of parathyroid carcinoma are rare and inconclusive, but alterations of the retinoblastoma and the MEN1 genes have been reported. Proteins have reported to be limited to these tumors. Loss of heterozygosity and mutation of the HRPT2 gene, which encodes for the parafibromin, have also been documented in parathyroid carcinoma and are believed to be restricted to malignancy. If validated, they may have a diagnostic and therapeutic implication [197–199]. Somatic mutations as well as germ line mutations of the HPRT2 have been implicated to underlie primary hyperparathyroidism [200].

3.16 Sinonasal and Skull Base Tumors

A wide spectrum of malignant neoplasms arises from the sinonasal and skull base regions. The majority of these tumors are poorly or undifferentiated malignancies and manifest overlapping features resulting in diagnostic challenges

[201, 202]. Excluding tumorlike lesions like hamartomas and teratomas, the most commonly encountered benign neoplasms are Schneiderian papillomas.

3.16.1 Schneiderian Papillomas

Schneiderian papillomas account for 0.4–5.0 % of all sinonasal tumors and are classified based on their growth and histological features into exophytic, inverted, and cylindrical subtypes. The exophytic forms arise predominantly in the nasal septum, but they may also occur in the nasal cavity and the maxillary sinus. They are usually solitary and rarely associated with malignant transformations. Histologically, they manifest a fibrovascular core lined by hyperplastic nonkeratinizing squamous and/or transitional epithelium. The main differential diagnosis is papillary squamous carcinoma. The latter exhibits cellular features of malignancy and stromal invasion. These lesions are prone to recurrence in up to 22–40 % of the cases. Inverted papillomas comprise approximately 45 % of all papillomas and are characterized by inward growth due to invagination of the epithelial components into the stroma. They commonly arise in the nasal cavity and paranasal sinuses and rarely in the septum. These lesions are also known for high recurrence rate and progression into carcinoma [203]. The epithelial lining of the inverted papilloma is commonly nonkeratinizing, stratified, squamous epithelium with vacuolation, intraepithelial microcysts, and acute inflammatory cells. Malignant transformation may present as differentiated or poorly differentiated squamous carcinoma with and without evidence of dysplasia. The presence of keratinization is always associated with carcinoma. The differential diagnosis of inverted papilloma includes other forms of Schneiderian papilloma. Recurrence rate is approximately 45–75 %. Molecular studies of these lesions are rare. However, evidence for monoclonality has been reported, but no specific genetic alterations were linked to progression [203].

3.16.2 Salivary-Type Neoplasms

Salivary tumors arising at these locations are derived from minor glands and manifest identical morphologic features to those arising in major and minor salivary glands. The difference is their encapsulated nature and the associated difficulties in assessing margin status. The most common benign tumor is pleomorphic adenoma and the most common malignancies are adenoid cystic, mucoepidermoid, and acinic cell carcinomas in descending order and adenocarcinoma, not otherwise classified. The differential diagnosis is mainly from metastasis and nonsalivary seromucinous carcinoma [202].

3.16.3 Nonsalivary-Type Adenocarcinoma

These adenocarcinomas are classified into seromucinous type and intestinal type. The seromucinous type most likely arises from the seromucinous gland lining, the respiratory epithelium of the nasal cavity. They are typically well-differentiated adenocarcinoma. The intestinal type is similar to adenocarcinoma of the colorectal sites. These tumors arise from the respiratory epithelium most likely due to intestinal metaplasia as a result of exposure to wood dust or leather chemical processing. These tumors affect middle and elderly individuals with the aforementioned risk factors. The tumors manifest identical phenotypic features to their intestinal counterparts, including mucinous production and signet ring formation. The biological behavior of these tumors is generally aggressive with the majority of patients succumbing to their disease within 3 years. Molecular and phenotypic studies of this entity have shown evidence for shared molecular alterations with colonic adenocarcinoma [204–208].

3.16.4 Squamous Carcinoma

Carcinomas of the sinonasal cavity comprise approximately 3 % of all malignant tumors. The majority (70 %) is squamous in derivation. The vast majority occurs in the maxillary sinus and a small subset occurs in other nasal sites. Several etiologic factors have been linked to the development of these tumors, among which nickel and thorotrast exposure were the most commonly incriminated. These tumors typically affect men in their 50s–60s. Histopathologically, they may present as keratinizing or nonkeratinizing squamous carcinoma [201, 209].

Other forms of squamous carcinomas as verrucous and spindle cell and basaloid squamous carcinomas have been described. The differential diagnoses of these tumors include metastasis, ameloblastomas, and inverted papilloma. The biological behaviors of this entity depend on the site and degree of differentiation with the nasal carcinoma patients fairing better than those with paranasal tumors [202].

3.16.5 Undifferentiated Sinonasal Carcinoma

These tumors are characterized by their lack of differentiation and affect both males and females equally. Histologically, they manifest undifferentiated carcinoma similar to those of type III NPC. These tumors run an aggressive biological course and present in advanced stage. Because of the undifferentiated nature, they may be confused with a wide variety of undifferentiated neoplasms at these sites. These include poorly differentiated squamous carcinoma, NPC, neuroblastoma, melanoma, lymphoma, and small round cell tumors.

Immunohistochemical and molecular markers are important in differentiating these tumors, especially on small pretreatment biopsies [202, 210, 211].

3.16.6 Neuroendocrine Carcinomas

Neuroendocrine carcinomas of the sinonasal region are uncommon relative to the larynx and are classified into typical (well-differentiated) and atypical carcinoid (moderately differentiated) and small and large cell (poorly differentiated) carcinoma. The most common subtype is the poorly differentiated subtype, which typically affects the nasal cavity with extension to the ethmoid and maxillary sinuses. They affect men and women equally with a wide range of age. The diagnosis and differential diagnosis is established by performing keratin and other neuroendocrine markers [212–214].

3.16.6.1 Small Round Cell Tumors and Neuroblastoma

A host of tumors that share a small, rounded, and basal-like tumor cell composition is not uncommonly presented at these sites. These include neuroblastoma, rhabdomyosarcoma, neuroendocrine carcinoma (small cell), and Ewing's/neuroectodermal tumors [215–217]. Although younger age groups are more frequently affected, older ages may also be presented with these tumors. They occur equally in both sexes. There are no known predisposing factors associated with the development of these tumors and most likely familial and genetic factors may underlie their development. The diagnosis of these tumors, especially on initial biopsy, is challenging and is largely aided by ancillary immunohistochemical and molecular markers [201, 217–221].

3.16.6.2 Sinonasal Melanoma

Primary sinonasal melanoma is very rare and accounts for 1 % of all melanomas and 2.4 % of nasal malignancies. The most common sites for this entity are the nasal cavity and the paranasal sinuses, with the most frequent sites being the nasal septum, the lateral nasal wall, and the middle and inferior turbinates. Histologically, cells are small, rounded, and undifferentiated and commonly manifest melanin pigment. These tumors are highly aggressive and prone to recurrence. They are typically presented at middle or older age, but they may present at any age. The differential diagnosis of this tumor includes all small round undifferentiated tumors at these locations (Fig. 3.4) [216, 222–225].

3.16.6.3 Fibrous and Vascular Neoplasms

These tumors are divided into a benign, low-grade category and include fibromatosis, fibroma, myxoma, hemangioma, schwannoma and hemangiopericytoma, and solitary fibrous tumor and low-grade fibrosarcoma. Their diagnosis is based

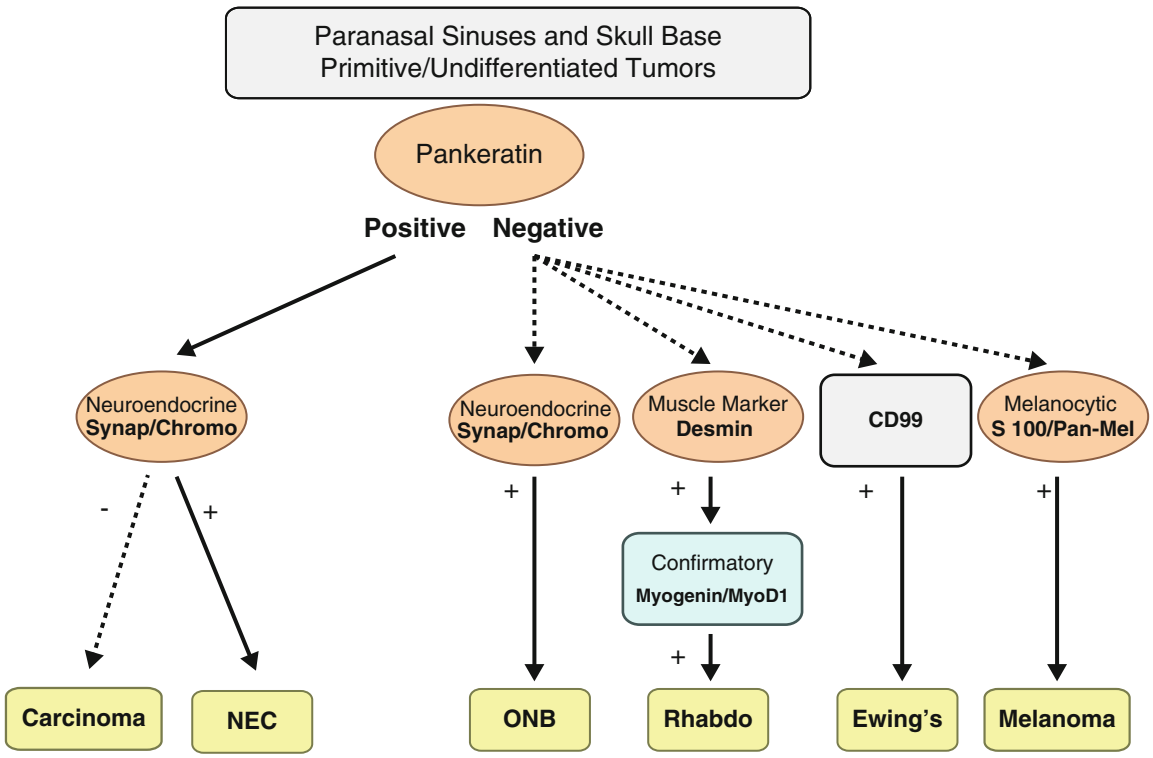

Fig. 3.4 Algorithmic marker applications for sinonasal undifferentiated neoplasms

on the histopathologic features, and their treatment is largely surgical [202].

3.16.6.4 Odontogenic Tumors

Odontogenic lesions may also present in the sinonasal sites especially the maxillary sinus and include calcifying odontogenic and tumor ameloblastoma. The most important differential diagnosis for these tumors is inverted squamous papilloma and squamous carcinoma. These tumors typically occur in young and middle-aged individuals and behave as benign or locally destructive tumors. Ameloblastoma may, however, transform into more malignant ameloblastic carcinoma. Complete excision of these tumors is curative.

3.16.6.5 Teratocarcinosarcoma

Teratocarcinosarcoma is an extremely rare carcinoma that may lead to management difficulties. The histogenesis of this entity remains unsettled, but an origin from stem cell is possible. Histologically, these tumors are characterized by the presence of immature neural elements and malignant epithelial and mesenchymal tumors. The tumor affects mainly men in their middle and old age. These tumors are treated surgically with postoperative radiotherapy [226].

3.16.6.6 Lymphoproliferative Disorders

Non-Hodgkin lymphoma is the most common lymphoproliferative disease in the sinonasal tract. Of the different subtypes that represent this category, the Nk1 T-cell lymphoma is the dominant lymphoma at these sites.

T-cell lymphoma (natural killer) typically afflicts predominantly men in their middle or old age. The disease has been reported to be more common in Asians. The most common presentation is destructive midfacial lesions with obstructive symptoms. The disease is strongly associated with EBV. Histologically, the disease is characterized by polymorphous cell infiltrate, including lymphocytes, plasma cells, histiocytes, and eosinophils with necrosis [227–231].

The differential diagnosis of this entity includes infectious conditions, especially fungal organisms and especially Wegener's granulomatosis. The absence of EBV virus and antineutrophil cytoplasmic antibodies excludes the latter.

3.16.6.7 Molecular and Genetic

Advances in molecular genetic studies of skull base neoplasms are limited to small round cell tumors, including Ewing's, synovial, and rhabdomyosarcomas. A specific translocation generating oncogenic fusion transcripts has been identified in some of these tumors and currently used in their diagnosis and management stratification. In Ewing's sarcoma and peripheral primitive neuroectodermal tumor, the EWS/FLI-1 gene resulting from the t(11;22) (q24;q12) is detected in 80 % of tumors. The fusion gene has also been detected in neuroblastoma and rhabdomyosarcoma [220, 221, 232]. The PAX–FKHR fusion gene has also been used in the diagnosis and to guide treatments in alveolar rhabdomyosarcoma. Future identification of specific translocation will lead to better diagnosis and classification of other tumors.

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Oncogenomics/Proteomics of Head and Neck Cancers

4

Jason I. Kass, Howard S. Moskowitz, and Jennifer R. Grandis

Abstract

Over the past 20 years, we have seen a rapid development in our understanding of the molecular mechanisms of head and neck squamous cell cancer (HNSCC). These discoveries are in large part the result of advances in technology. Here, we first review the major technologies in both oncogenomics and proteomics as they apply to HNSCC and then review the results of seminal studies. These data lay the foundation for the next decade of discovery in HNSCC and are relevant to the clinician and scientist.

Keywords

Oncogene • Proteomics • Sequencing technology • Head and neck cancer • The Cancer Genome Atlas (TCGA) • Tissue microarray (TMA) • RPPA • Mass spectroscopy • MALDI • SELDI • Exome

4.1 Introduction

Head and neck squamous cell carcinoma (HNSCC) is the most common histology of cancers arising from the upper aerodigestive tract, comprising approximately 90 % of all tumors in this region. HNSCC encompasses a variety of anatomic subsites. Despite possessing similar histologic characteristics, the clinical behavior, including metastatic rate and response to therapy, varies between subsites and even within an individual subsite, indicating biologic heterogeneity in the setting of common histology. Current treatment strategies rely on traditional, clinical, radiologic, and histopathologic parameters to determine the stage of disease using the T (tumor), N (node), and M (metastasis) classification system. This system allows for estimation of disease burden, which is presumed to predict clinical outcomes and assist the clinician in making the most appropriate decision for patient management. However, the biologic heterogeneity of HNSCC is reflected by the dysregulation of multiple pathways including cellular differentiation, angiogenesis, and apoptosis. Apparently, identical histologic tumors may have similar phenotypic characteristics but develop through dysregulation of different pathways and can have different clinical courses.

Despite their intrinsic differences, all HNSCCs are treated similarly. Standard therapy for stage I/II tumors is surgical resection and/or radiation therapy. By contrast, treatment for advanced stage III/IV tumor requires the combination of chemotherapy, radiation therapy, and/or surgery. Given this relatively uniform treatment, clinical outcome after curative therapy varies greatly. The advent of new surgical techniques, radiation therapy, and chemotherapy have improved local control and overall quality of life, but survival rates for head and neck cancer have not increased significantly. It is likely that the diversity in outcome reflects intrinsic heterogeneity in the molecular components of individual tumors.

Clinical outcome is not accurately predicted by clinical, radiographic, or histologic characteristics. A limited number

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of histologic features such as perineural, perivascular, or nodal extracapsular spread are associated with increased tumor aggressiveness and may influence management decisions. Unfortunately, currently recognized individual markers associated with tumor development generally lack sensitivity or specificity, and there is currently no single molecular marker that is used for patient management in HNSCC. Human papillomavirus (HPV) has emerged as a viral-mediated driver of oropharyngeal HNSCC. Although patients with HPV-positive HNSCC generally have better survival outcomes compared with individuals with HPV-negative disease, HPV status is not a part of current evidence-based NCCN (National Comprehensive Cancer Network) guidelines. Ongoing clinical trials include both surgical and nonsurgical phase II studies that are determining eligibility based, in part, on HPV (or its surrogate p16) tumor status.

Given the heterogeneity of genetic alterations found in these tumors, a greater understanding of the molecular basis of the biochemical pathways involved in carcinogenesis potentially can facilitate diagnosis, drug discovery, and therapy for affected patients. These molecular changes involve interacting networks that operate at the transcriptional, translational, and posttranslational levels. Traditional approaches have generally not been useful due to the complexity of interactions, the difficulty of finding the proper combinations of genes and proteins to investigate, and the reliance on techniques that examine one or only several genes or proteins at a time.

The application of novel unbiased discovery technologies offers the opportunity for comprehensive and systematic molecular analysis to capture the complex cascade of events underpinning the clinical behavior of tumors. Tumors are believed to harbor molecular signatures that can be identified through the combined application of high-throughput profiling techniques and sophisticated bioinformatics tools for complex data analysis and pattern recognition. The main underlying goal is the identification of new targets that may provide insights into the underlying mechanisms of cancer biology, which in turn can potentially lead to novel approaches to cancer diagnosis, prediction of clinical outcomes, and development of new therapeutic strategies.

4.2 Oncogenomic Technologies

Cancer can be simplistically thought of as the overexpression of oncogenes and/or the silencing of tumor suppressor genes. However, in most cancers, including HNSCC, cancer development and progression is likely due to numerous genetic alterations involving a variety of different pathways. Although common alterations underlie many types of cancer, an individual cancer often develops due to an accumulation of specific mutations in DNA. Since these mutations accumulate randomly, different combinations of mutations exist between different individuals with the same type of cancer. Cytogenetic analysis of cells has evolved from the gross visual analysis of chromosomes to a detailed study of the regions of chromosomal gain, loss, and translocation. Techniques used include comparative genomic hybridization (CGH) where normal and tumor DNA is labeled and hybridized to normal metaphase chromosomes and the fluorescence pattern is then analyzed for increased or decreased intensity, representing copy number differences between genomes. Similarly, fluorescent in situ hybridization (FISH) utilizes labeled sequence specific probes, allowing for the detection of particular genes of interest as well as visualization of copy number per cell.

More localized and specific analysis has been made possible through the advent of high-throughput DNA-sequencing facilities as well as novel approaches to examine genomic variability. Single nucleotide polymorphisms (SNPs) are areas in the genome with an altered DNA sequence that may represent markers for disease predisposition or may be used to genetically identify patients. Microsatellites are tandem nucleotide repeats that are generally located in noncoding areas of the genome. They can have variable length and have been mapped to specific chromosomal regions, allowing for detection of adjacent genes of interest. In addition, microRNAs are a noncoding family of genes involved in posttranscriptional gene regulation that are associated with cell proliferation, cell differentiation, cell death, and carcinogenesis. Each of these can be investigated through the use of array technologies.

Another commonly utilized platform for oncogenomic analysis is DNA microarray technology, which offers the capacity for parallel measurement of relative gene expression levels (Fig. 4.1). These technologies are based on the selective mRNA or cDNA hybridization to DNA probes on the array surface. There are two general categories of microarrays, commercially available microarrays with defined content or microarrays produced with variable and customizable content. Microarray technology involves DNA sequence hybridization onto microscopic surfaces, which can be read by a laser able to detect the signal of minute fluorophores. These studies can incorporate nearly the entire known genome in a single experiment.

Advances in DNA-sequencing technology now allow for large-scale whole-genome sequencing with high fidelity and low cost in a timely fashion. Collectively referred to as next-generation sequencing, these technologies can sequence upward of three billion bases in a single run [1]. There are currently over ten different strategies being applied to whole-genome sequencing. They employ technologies that vary from amplifying DNA fragments inside water droplets immersed in oil to the detection of electric currents created from the chemical reaction during DNA synthesis. One of

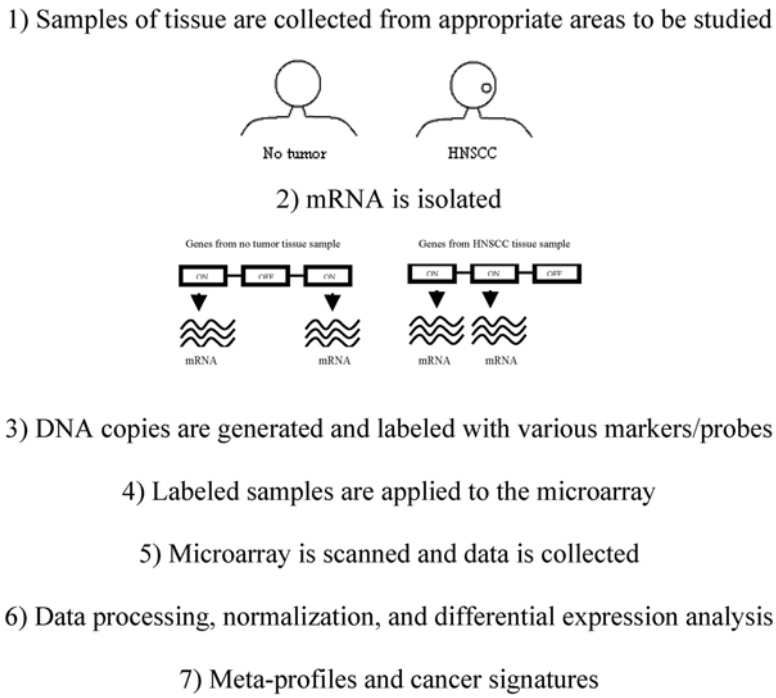

Fig. 4.1 Algorithm for using DNA microarray analysis to identify altered expression levels in HNSCC. After careful selection of patients, tissue samples are collected from study participants and mRNA is isolated. The mRNA represents the expression profile of the isolated cells as only active genes will produce mRNA. Microarray data from various tissues can be compared to generate differential expression patterns reflective of variations in gene expression between subjects. This data can be combined to define cancer signatures reflective of specific steps in tumorigenesis

the fastest strategies includes engineered polymerases with reversible fluorescent nucleotides that can rapidly terminate and restart DNA synthesis. This provides nucleotide readouts of over one million nucleotides/second. Accuracy varies between 98 % and 99.9 % depending on the sequencing strategy. Additionally, by looking at only the coding regions of a genome, the exome, one can rapidly identify all the expressed mutations in an individual tumor.

Each of these technologies generates large amounts of data from a single sample, particularly from tumor lysates or serum. Bioinformatics technologies enable the statistical analysis of the data and generate prediction algorithms to shortcut the experimental process. These data can be examined via unsupervised analysis using data based only on gene expression patterns regardless of the specific characteristics of the tissue being examined. This approach offers the potential to segregate different tumor types and allows identification of tumor subtypes that are not distinguishable by clinical, radiologic, or histologic characteristics. By contrast, supervised approaches select genes with parameters or conditions, and the analysis is dependent on the supervising parameter to discriminate the groups or categories with highest prediction accuracy. A predictive gene list is generated from a training set and the results are then confirmed by cross validation and analysis by an independent cohort of patient samples. Importantly for many cancers, including HNSCC, the molecular data has been collated and organized into a readily available online database that can be accessed by researchers worldwide (Table 4.1). The Cancer Genome Atlas (TCGA) provided by the National Cancer Institute has sequenced 528 head and neck tumors to date and represents a valuable translational research resource [8].

4.3 Proteomic Technologies

Proteome analysis is complementary to DNA microarray and sequencing technologies. Some techniques of proteomic analysis are widely used and clinically applicable such as enzyme-linked immunosorbent assay and immunohistochemistry, while others are used primarily as research tools such as immunoblotting and immunoprecipitation. Most of these techniques are limited to the study of only one or a few proteins at a given time. More comprehensive screening is permitted through 2D gel electrophoresis (2-DE). 2-DE is the method with the highest resolution for separation of protein mixtures and is believed to be superior for pattern analysis of complex samples. However, 2-DE may be difficult to use with certain proteins such as membrane proteins and basic proteins and has limited resolution of proteins in the low molecular weight spectrum. 2-DE separates proteins according to isoelectric points (isoelectric focusing) followed by separation according to molecular mass (SDS-PAGE). Peptide mass fingerprinting permits in-gel digestion of the protein spot of interest with a specific enzyme and resulting peptides are extracted from the gel and molecular weights of these peptides are measured. Alternatively, the peptides can be fragmented in a mass spectrometer yielding partial amino acid sequences from the peptides, which act as sequence tags.

Table 4.1 Publically available HNSCC microarray gene expression datasets

Authors	Tissue samples	Platform
Cohen et al. [2]	10 primary HNSCC	Affymetrix HG-U133 Plus 2
Rickman et al. [3]	186 primary HNSCC	Affymetrix HG-U133 Plus 2
Thurlow et al. [4]	71 primary HNSCC, 14 normal oral epithelium	Affymetrix HG-U133 Plus 2
Chung et al. [5]	40 primary HNSCC from 29 patients	Affymetrix X3P
Chung et al. [6]	55 primary HNSCC, 5 recurrent	Agilent Human 1
Walter et al. [7]	138 tumors from larynx, oral cavity, oropharynx and hypopharynx	Agilent 44 K microarray
TCGA [8]	528 primary HNSCC from 508 patients (as of 11/2014)	>20 platforms (https://tcga-data.nci.nih.gov/tcga/tcgaPlatformDesign.jsp)
Toruner et al. [9]	16 primary oral cavity SCC and 4 adjacent normal tissue from 16 patients	Affymetrix HG-U133A
Ye et al. [10]	26 primary oral cavity SCC and 12 adjacent normal tissues from 26 patients	Affymetrix HG-U133A
Kuriakose et al. [11]	22 primary HNSCC and 22 adjacent normal tissues from 22 patients	Human Genome U95A (Affymetrix)
Sticht et al. [12]	35 primary oral cavity SCC from 35 patients and 6 normal oral tissue from normal controls	Human Oligo Set 4.0 (Operon)
Pyeon et al. [13]	42 primary HNSCC from 42 patients and 14 normal oral tissue from normal controls	Affymetrix HG-U133A

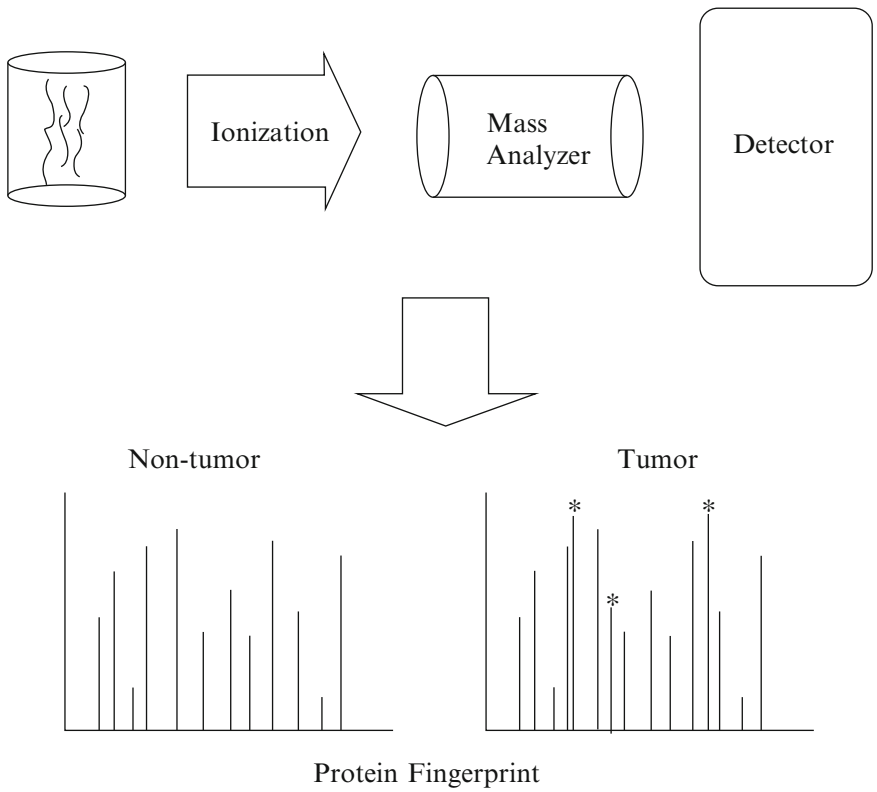

Fig. 4.2 Mass spectrometry approaches to biomarker analysis. Analysis begins with a protein or peptide mixture that is processed to maximize the number of detected differentially expressed proteins. The sample is subsequently ionized by a variety of instruments such as a laser and separated by a mass analyzer (time-of-flight or ion trap) based on mass and charge. The resulting spectra are representative of the ionized proteins within the initial sample. Bioinformatics approaches are then utilized to compare the spectra to identify unique and differing protein components (*asterisk* indicates differentially expressed *m*/*z* species)

Fundamentally important to recent advances in proteomics have been improvements in the speed, accuracy, and sensitivity of mass spectrometry (MS) instruments for the analysis of complex protein mixtures or tissues (Fig. 4.2). MS analyzes proteins or peptides as ions, which can be distinguished based on mass to charge ratio (*m*/*z*). Basic components of the instrument are the ion source that volatilizes and ionizes the proteins, the mass analyzer which separates proteins based on *m*/*z* values, and the detector which detects the sample after separation. The two most commonly used MS approaches are matrix-assisted laser desorption ionization (MALDI) and surface-enhanced laser desorption ionization (SELDI). These high-throughput methodologies have the ability to observe large numbers of protein events. Furthermore, as compared to 2-DE, they permit improved speed, high-throughput capability,

lower amounts of protein sample, effective resolution of low mass proteins, and direct application to assay development. Furthermore, sample loading and processing can be fully automated.

MALDI is commonly used for bioanalysis and employs laser energy to ionize and volatize proteins. A matrix such as a UV-absorbing organic acid is mixed with the sample to absorb laser energy and transfer it to the proteins to generate ions, which are then transferred to the mass analyzer. Ionization is not uniform and depends on relative protein abundance and intrinsic chemical characteristics. MALDI is generally coupled with a time-of-flight (TOF) mass analyzer, which separates proteins based on time to traverse a flight tube and strike a detector. MALDI-TOF-MS is a particle-counting method that relies on molar abundance. It requires minimal sample preparation, can distinguish hundreds to thousands of proteins from a complex mixture, and can detect subtle protein modifications. However, MALDI has a limited mass range and limited sensitivity for low-abundance proteins, and proteins with extremely high concentration can interfere with detection of proteins with similar m/z ratios.

SELDI utilizes a surface to capture and partially purify proteins from a complex sample based on physical and biochemical properties and is dependent on protein conformational stability for reliable detection. A variety of coated surfaces are presently available that bind proteins based on hydrophobicity, anionic or cationic charge, or binding to metals. SELDI also partially purifies the protein sample, making it less complex than the similar unfractionated sample for MALDI. This partial purification may lose critical proteins, but theoretically generates fewer problems with highly abundant proteins. When the process is expanded to many hundreds of samples, population-specific protein expression profiles can be deduced that are characteristic of the assayed group. However, the identified mass spectrum does not enable protein identification and none of the interactions are specific.

Reverse phase protein array (RPPA) is another high-throughput platform for marker screening. RPPA utilizes lysed histopathologically relevant pure cell populations. The lysate is immobilized in an array configuration via a pin-based microarray onto nitrocellulose slides with each spot containing the whole cellular protein contents. Each slide is then probed with an antibody that can be detected by a variety of assays. Protein samples are arrayed in miniature dilution curves to ensure that the analyte of interest remains in the linear range of detection. A subset of HNSCC TCGA samples have been analyzed by RPPA and the proteomic information is publically available.

Tissue microarray (TMA) technology applies advanced array-based approaches to data gathering with standardized medical pathology laboratory practices. A TMA block is loaded with freshly sectioned core biopsies from paraffin-embedded tissues derived from cohorts of cancer patients on a single slide. Automated digital image capture is followed by pathologist scoring of the image. Further evolution in the analysis of stained TMA sections involves automated scoring of staining intensities and features on TMA slides using image analysis software. TMA provides the capability to perform rapid analysis of comprehensive panels of normal and disease specimens. TMA allows visualization of molecular targets in up to thousands of tissue specimens at a time and reveals cellular localization, prevalence, and clinical significance of candidate genes and gene products. However, TMA is limited by the availability of antisera, only provides a semiquantitative estimation of protein levels, and may miss important histologic areas due to the small size of the core biopsies utilized in these arrays.

4.4 Oncogenomics of HNSCC

4.4.1 Genomic Changes Underlying Malignant Transformation

Cancer develops from the accumulation of various genetic alterations. DNA microarrays and whole-exome sequencing have emerged as powerful tools for the parallel measurement of relative gene expression levels in HNSCC (Table 4.1). The usage of DNA microarrays and genome sequencing to generate clinically relevant molecular signatures has grown in its acceptance. Early studies showed the heterogeneous nature of HNSCC tumors at the molecular level. However, direct comparison between studies has often proved difficult due to the variety of gene expression arrays, platforms, and data analysis algorithms used.

HNSCC cell line studies have provided initial insights into the genetic variations that may underlie the cancer phenotype using these preclinical models. Cell lines offer relative homogeneity of samples for investigation but may suffer from artifacts of immortalization and passage in vitro compared with human tumors. One microarray study analyzed 25 HNSCC cell lines and one immortalized human oral keratinocyte cell line and found wide alteration in the gene expression in cell cycle regulation, oncogenesis, cell proliferation, differentiation, and apoptosis [14]. This study revealed two distinctive subtypes of gene expression patterns, but these patterns did not seem to correlate with the clinical staging or differentiation grade of the original tumors. Another study used SNP array-based loss of heterozygosity (LOH) profiling on whole-genome loss of 41 HNSCC cell lines and found several frequent LOH regions [15]. This report identified a region on chromosome 8 that exhibited the most frequent LOH (87.9 %) and found that the mitochondrial tumor suppressor gene 1, a candidate tumor suppressor gene residing in this area, was consistently down-

regulated in expression, suggesting that it may be a tumor suppressor in HNSCC.

Another report utilized genome-wide comparative genomic hybridization and expression microarray analyses to reveal known and novel amplicons that showed concomitant increase of copy number and expression of target genes for both laryngeal SCC cell lines and primary tumors [16]. They found that the overexpression of 739 genes could be attributed to gene copy number alteration in cell lines, of which 325 genes showed the same phenomenon in primary tumors. Subsequently, this group analyzed oral tongue SCC cell lines and found that these cell lines exhibited similar genomic alterations as had been previously found in their laryngeal SCC cell lines despite the differences in clinicopathologic features between these anatomic subsites [17]. A wide variety of genes were found to be altered including deletions of known tumor suppressor genes including *FHIT*, *CSMD1*, and *CDKN2A*.

Other studies have attempted to provide a framework for improving our understanding of the molecular events underpinning various aspects of these tumors. The progression of normal epithelia through premalignancy to HNSCC is a multistep process that has been associated with distinct histologic characteristics at each stage. An early study analyzed invasive SCC lesions from the oropharynx and oral cavity, and using hierarchical clustering analysis, they were able to show that oral SCC was distinguishable from normal oral tissue, but there was heterogeneity among the tumors even of a particular histopathologic grade and stage [18]. This study identified 239 genes that were overexpressed and 75 genes that were downregulated, but could not find statistically significant differences in gene expression between metastatic and nonmetastatic tumors. Later, another group established a transcriptional progression model of HNSCC in the progression from normal mucosa to dysplastic epithelium to invasive HNSCC [14]. Matched samples were analyzed using gene expression arrays, significance analysis of microarrays, hierarchical clustering, and principal components analysis to identify genes with differential expression patterns between the tissue groups. The progression from normal to premalignant was associated with altered expression of 334 genes (108 upregulated and 226 downregulated), while the progression of premalignant to malignant was only associated with altered expression of 18 genes (5 upregulated and 13 downregulated). This transcriptional model suggested that the majority of alterations occurred before the development of invasive cancer.

An alternative strategy was used in another study employing forward and stepwise logistic regression analyses to identify potential biomarkers for the early detection of oral SCC by comparing gene expression of primary oral SCC, oral dysplasia, and clinically normal oral tissue [15]. They identified combinations of genes, which differentiated oral SCC from controls that included laminin-gamma 2 chain, collagen type IV alpha 1 chain, collagen type I alpha 1 chain, and peptidyl arginine deiminase type 1. Another group analyzed 41 HNSCC tumors from various anatomic sites and compared them with normal oral mucosa with gene expression arrays [16]. They used statistical and data-filtering criteria to identify 2890 genes differentially expressed between the two groups and revealed functional gene expression signatures that were highly represented in HNSCC including those involved in inflammatory response, epidermal differentiation, cell adhesion, and extracellular matrix functions. They suggested that the disease signature is an intrinsic feature of a HNSCC and may function as a predictor of early local treatment failure.

Several studies have attempted to build on the growing lists of putative biomarkers by generating gene sets, which may be able to lead to useful predictions regarding the propensity for a given lesion to be or develop into a cancerous lesion. One study matched tumor and normal specimens from the oral cavity and analyzed microarray gene expression data with a supervised learning algorithm [17]. This study generated a 25-gene signature that could classify normal and tumor specimen that was highly accurate on independent validation test sets but failed to predict non-oral tumors. Many of the genes in the predictor set had been previously implicated in oral SCC. The predictor set comprised several epithelial marker genes that had categories of potential interest including extracellular matrix components and cell adhesion molecules. Similarly, a different group attempted to generate a classifier set for oral SCC and leuokoplakias and found differential expression of 118 marker gene candidates by complementary DNA microarray [18]. Further evaluation demonstrated an 11-gene predictor set that could distinguish the two groups with greater than 97 % accuracy.

Most recently, there have been collaborative efforts to sequence the exome of HNSCC tumors. In 2011, two groups reported on genome data from 125 tumors [19, 20]. The whole-exome sequencing of 92 tumors provided a snapshot of the commonly mutated genes and signaling pathways for individual tumors [19]. Not surprisingly, this data validated many of the smaller sequencing efforts in the literature. The most commonly mutated genes were involved in cell death (TP53, PTEN, PIK3CA) and proliferation (CDKN2A, HRAS). This work revealed a previously unknown contribution from genes involved in terminal differentiation of squamous cells (NOTCH1, IRF6, TP63). Additionally, there were clear mechanistic differences between patients whose cancers were driven by tobacco and alcohol exposure as compared to HPV-positive tumors in the oropharynx. HPV-positive oropharyngeal tumors had two- to fourfold fewer mutations, did not have TP53 mutations, and were more likely to have PIK3CA-activating mutations. Interestingly, the impact of HPV on HNSCC outside the oropharynx does carry the same impact on mutation rate [21]. Overall, there were few activating mutations observed in the sequence data,

and the majority of mutations were tumor suppressor genes. The phosphoinositol 3-kinase (PI3K) pathway is one of the few pathways that have activating mutations. Inhibitors of PIK3CA are in phase I and II clinical trials.

4.4.2 Genomic Changes Underlying Metastases

Metastasis is the principal cause of death in patients suffering from cancer, but the underlying molecular mechanisms are poorly understood. It is widely believed that the accumulation of genetic damage leads to the expression of a malignant phenotype that precedes metastasis formation. In order for a tumor to metastasize, it has to gain a number of functions distinct from the primary tumor. These include the ability to adhere to and then traverse the basement membrane, pass through an extracellular matrix, enter and exit the blood stream, and finally invade a new microenvironment to replicate. To do so requires a number of molecular changes distinct from cellular division [22].

Several groups have investigated differences in gene expression between head and neck primary tumors that had or had not metastasized. In one analysis of tumors from the oral cavity and oropharynx, 101 genes demonstrated significant expression differences between the metastatic and nonmetastatic tumors [23]. These genes included a variety of cellular functions putatively associated with cancer behavior, and the gene with the greatest differential expression between the metastatic and nonmetastatic tumors was collagen type 11 alpha 1. A different study used microarray analysis to measure gene expression changes associated with tumor progression in patients with stage III or stage IV untreated oral SCC [24]. They identified 140 genes that consistently increased in expression during progression from normal tissue to invasive tumor to metastatic node as well as 94 genes that decreased in expression in a similar progression, which revealed a distinct pattern of gene expression during the progression from histologically normal tissue to primary carcinoma to nodal metastasis.

In another study, 82 primary tumors located in the oropharynx or oral cavity regions were analyzed using DNA microarray gene expression profiling [25]. This study established a set of 102 predictor genes for determining the presence of lymph node metastases. Many of the predictor genes they found were previously implicated in metastasis. The application of this gene set to a validation group gave an overall predictive accuracy of 86 % as compared with 68 % based solely on clinical diagnosis. A subsequent study implemented this dataset as a reference dataset and an independent gene expression dataset of metastasized and nonmetastasized HNSCC tumors as validation dataset [26]. They utilized supervised gene-based and pathway-based analysis to evaluate differences in gene expression to enhance the understanding of the biological context of the results. The identified gene sets were involved in extracellular matrix remodeling (including matrix metalloproteinases (MMPs) and their regulatory pathways) as well as hypoxia and angiogenesis.

Another group looked at 186 primary tumors and analyzed the samples with respect to whether the development of metastasis was the first recurrent event [3]. They collected transcriptome and array-comparative genomic hybridization data followed by non-supervised hierarchical clustering to distinguish tumors differing in pathological differentiation. They were able to identify associated functional changes and created a four-gene model (*PSMD10*, *HSD17B12*, *FLOT2*, and *KRT17*) which predicted metastatic status with 77 % success in a separate validation group, and the prediction was independent of clinical criteria. Similarly, another study revealed that gene expression patterns in 60 primary and previously untreated HNSCC allowed the tumors to be categorized into four distinct subtypes with statistically different recurrence-free survival [6]. Clinical nodal staging resulted in low prediction accuracy when used as the supervising parameter. However, supervised analyses using pathological staging to predict lymph node metastasis status improved the prediction accuracy of gene expression from the primary tumor, which was further improved by analysis based on anatomic subsites leading to a prediction accuracy of 83 %.

A large-scale gene expression analysis of the hypopharynx, a location associated with particularly aggressive behavior, found 119 genes that were highly differentially expressed between early and late tumors [27]. Furthermore, 164 differentially expressed genes were found that differentiated between relatively non-aggressive and aggressive tumors. Clustering of the associated probe sets defined the two groups of samples and correctly assigned 92 % of the tumors. In a separate study, genome-wide analysis was performed looking for LOH and allelic imbalance (AI) on specimens of tumor stroma and tumor epithelium isolated by laser capture microdissection on 122 patients with HNSCC and a history of smoking [28]. They found nearly twice as many areas of LOH/AI within the stroma as was found in the epithelium, more than 40 areas in total. Furthermore, they found three stroma-specific loci that were significantly associated with tumor size and cervical lymph node metastasis, highlighting the importance of examining stromal and epithelial elements and suggesting that stromal alterations play an important role in HNSCC behavior.

In the last 7–10 years, a new concept has been solidified regarding metastases of squamous cell carcinoma. This reflects recognition of dedifferentiation of squamous cells from an epithelial molecular profile to a more primal mesenchymal phenotype, normally present in embryonic development, but lost in mature tissues. This change in gene

expression has collectively been referred to as "epithelial to mesenchymal transition" (EMT). During EMT, many of the genetic changes documented above occur including a loss of cell attachment via changes in integrins (E-cadherin), activation of matrix metalloproteinases, and activation of genes involved with cell migration. In metastatic HNSCC, these tumors have altered patterns of expression, reflecting these changes with changes in EMT-related genes including *snail* and *twist* [29].

Finally, although head and neck cancer cells may become mesenchymal as they leave their primary site and metastasize, they switch back to an epithelial expression pattern once they arrive in a new distant site. It is currently unknown how this occurs, but recent evidence regarding a chloride ion channel may provide insight regarding this behavior. *TMEM16A (Ano1)*, a calcium-activated chloride channel, is frequently overexpressed in HNSCC and has been shown to behave as an oncogene [30]. When *TMEM16A* is inhibited in stable cell lines, these cells became more motile and were able to metastasize in a mouse model [31]. On the expression level, inhibition of the ion channel correlated with an expression pattern of a mesenchymal phenotype, while overexpression correlated with an epithelial phenotype. Dynamic changes in ion channel function may play a role in how cells transition between these phenotypes.

4.4.3 Genomic Changes Underlying Variable Responses to Treatment

Treatment protocols often involve the use of chemotherapy and/or radiation. Several recent studies have directed their attention toward the identification of genetic alterations that would give prognostic information regarding a given tumor's likelihood of response to various treatment protocols. Cetuximab, the *EGFR* antagonist, was initially developed as a potential radiosensitizer, when it was observed that tumors with high *EGFR* expression were radioresistant.

One study on HNSCC cell lines that exhibited relative radioresistance and radiosensitivity identified 167 genes that were significantly overexpressed in radioresistant cells, 25 of which included cancer-related genes involved in growth, proliferation, apoptosis, and adhesion [32]. Another study used significance analysis of microarrays for gene selection and a multivariate linear regression model for prediction of radiosensitivity [33]. They identified three novel genes whose expression values correlated with radiation sensitivity, and the overexpression of one of these genes, *RbAp48*, in a cancer cell line induced radiosensitization.

The use of tissue microarrays has also been used clinically to find genes that may help predict a response to therapy. Recently, 38 patients who received radiation were analyzed using a cDNA tissue microarray, and five candidate genes were identified (*VEGF*, *BCL-2*, *CLAUDIN-4*, *YAP-1*, and *c-MET*) as predictors for response to therapy. Protein expression of these five genes was then prospectively evaluated in 86 patients who underwent radiation. All five biomarkers were predictive of a poor response to therapy and two (*YAP-1* and *c-MET*) were synergistic [34].

In another study, 92 biopsies were obtained from untreated HNSCC patients prior to treatment with cisplatin-based chemoradiation for advanced HNSCC [35]. This group utilized supervised analyses to predict locoregional control and disease recurrence and found several gene sets that were enriched in recurrences. They utilized a signature established by Chung et al. [6] for HNSCC defining a high-risk group and found it to be predictive for locoregional control and disease-free survival in their dataset. A more targeted analysis utilized a cDNA array consisting of genes associated with angiogenesis and/or metastasis [36]. Seventeen genes were correlated with locoregional failure, of which *MDM2* and *erbB2* were found to be predictors of locoregional failure in their population of patients treated with CRT.

The biomarker *ERCC1*, a DNA repair enzyme, has been a strong biomarker for response to cisplatin. Cisplatin acts as an alkylating agent inducing lethal mutations in cell and preferentially targets dividing cells. Tumors that express high levels of *ERCC1* can repair these DNA mutations and are resistant to cisplatin. Patients whose tumors have low *ERCC1* expression are more susceptible to treatment. The usefulness of *ERCC1* to predict response to cisplatin has been documented prospectively in the treatment of non-small-cell lung cancer [37] as well as a recent randomized phase II clinical trial of HSNCC [38].

Other targeted chemotherapeutics are in development. *TP53*, the most widely mutated gene in HNSCC, leads to loss of apoptosis and oncogenesis, and strategies to restore *TP53* function could be promising in the treatment of HNSCC. Recently, a small molecule 17-(allylamino)-17-demethoxygelanamycin (17AAG) has been shown to restore p53 function and induce increased cell death in HNSCC cell lines [39]. It remains to be seen what effect it can have in animal and human models.

4.4.4 Genomic Changes Found in Surrogate Tissues

An evolving area of investigation involves the use of surrogate tissues in the investigation of HNSCC. Using saliva from patients with primary T1/T2 oral SCC with matched control patients in terms of age, gender, and smoking history, one group used microarrays to profile the human salivary transcriptome [40]. They found 1679 genes that were signifi-

cantly differentially expressed between the groups including seven cancer-related mRNA biomarkers that exhibited at least a 3.5-fold elevation in oral SCC saliva (*IL8*, *IL1B*, *DUSP1*, *HA3*, *OAZ1*, *S100P*, *SAT*). The combination of four of these biomarkers had a discriminatory power of 91 % sensitivity and specificity for oral cancer detection. A subsequent study compared the clinical accuracy of saliva with that of blood by using RNA biomarkers for oral cancer detection [41]. Using four serum mRNA markers, a sensitivity of 91 % and a specificity of 71 % were obtained for distinguishing oral cancer. However, the four salivary mRNA markers had a higher receiver operating characteristic curve value, demonstrating that for oral cancer detection, salivary transcriptome diagnostics may demonstrate a slight advantage as compared with serum.

MicroRNAs (miRNAs) are small noncoding molecules of RNA, often 20 nucleotides in length, that act at the posttranscriptional level to change the expression of key genes and have emerged as a mechanism for transcriptional control of tumors, including HNSCC [42, 43]. As of June 2013, there were over 1600 human miRs documented. Many are specific to squamous epithelium and associated with all aspects of cellular function including cell cycle regulation, apoptosis, cell proliferation, migration, and growth [44]. There are even miRNA expression profiles that are different between HPV-infected and non-infected cells. As with mRNA, miRs can be detected in saliva. A recent study of panel of three miRs, which are differentially expressed in HNSCC, was tested in 112 subjects (56 with HNSCC and 56 normal controls) [45]. These three miRs (miR-9, miR-134, and miR-191) were able to discriminate with good reliability HNSCC from normal controls. These miRs were also validated by TCGA miR data.

In the current era of HPV-associated oropharyngeal HNSCC, both plasma and saliva have been investigated as markers for response to treatment. HPV-16 DNA can be detected in both saliva and plasma samples. The presence of HPV-16 DNA in both saliva and plasma has been noted to be 100 % specific with a 100 % positive predictive value [46]. In this study however it had poor sensitivity (76 %) and very low negative predictive value (42 %). Interestingly, its presence after treatment was 91 % specific in predicting recurrence within 3 years.

4.4.5 Meta-analyses of HNSCC Microarray Studies

A cumulative analysis looked at studies incorporating DNA microarray analysis to examine genetic expression changes associated with the development of HNSCC [47]. Eighty-four genes were identified with common alterations in transcriptional expression across multiple studies. Many of these had been reported to be involved with HNSCC including MMPs, integrins, collagens, fibronectin, tenascin C, and cathepsin L, as well as many genes with less characterized roles in HNSCC. Only one gene, transglutaminase 3, was common to at least three of the reviewed studies. Overall, they found that genes encoding extracellular matrix and integral membrane proteins, cell adhesion molecules, and proteins involved in epidermal development and differentiation were most frequently identified in these studies. Furthermore, their results suggested a global downregulation of genes encoding ribosomal proteins and cholesterol biosynthesis enzymes and an upregulation of MMPs and inflammatory response genes.

Another study looked at 63 HNSCC transcriptomic studies in three categories of comparisons, premalignant vs. normal (Pre), primary tumors vs. normal (TvN), and metastatic or invasive vs. primary tumors (Meta) [48]. They used a systems biology approach via network-based meta-analysis and verified that 82 genes, 1260 genes, and 321 genes in the Pre, TvN, and Meta comparisons, respectively, were found reported at least twice. Overall, 1442 unique genes were reported at least twice in the studies that they analyzed. In terms of the direction of fold changes of the verified genes, the least contradiction was found in the TvN group and the most contradiction was found in the Pre group. Furthermore, they found that few genes overlapped between the Pre and Meta groups, although many genes overlapped between the other pairs of comparisons. Genes that were highly reported in prior studies across all three stages were *ECM1*, *EMP1*, *CXCL10*, and *POSTN*. Subsequently, they constructed knowledge-based networks, which revealed that integrin signaling and antigen presentation pathways were highly enriched in the dataset, and they found that chromosomal regions of 6p21, 19p13, and 19q13 had genomic alterations that were correlated with the nodal status of HNSCC.

There are currently 12 published gene expression datasets of HNSCC publically available with full clinical annotation [49]. Three of them were obtained using the same Affymetrix platform (U133 plus 2.0) and contain nearly 21,000 gene transcripts. These three datasets were recently used to generate a 172-gene profile to risk-stratify patients as either high or low for disease recurrence and then validated against six other datasets. This most recent gene profile compares well to the four other genetic signatures also generated by microarray data (radiosensitivity index, 13-gene SCCA signature, hypoxia metagene, and 42-gene high-risk signature). These genetic signatures are working their way toward a clinical-grade assay for detecting HSNCC and determining the severity of disease.

4.5 HNSCC Proteomics

4.5.1 Tumor Tissue Studies

High-throughput proteomic technologies have been utilized to detect biologically significant differences in protein expression of HNSCC in the same types of samples utilized in gene expression analysis. These studies have used a variety of techniques as outlined earlier in the chapter. One study utilized SELDI-TOF-MS to generate proteomic spectra and used the "Lasso algorithm" to extrapolate proteomic patterns that can best discriminate HNSCC patients from non-cancer controls which identified 65 significant data points to be used for discrimination [50]. Testing of these points yielded moderate sensitivity of 68 % and specificity of 73 % indicating that with further improvement and validation, it may be useful as a screening test for HNSCC in the future. More recently, another study analyzed 113 HNSCC, 73 healthy, 99 tumor-distant, and 18 samples of tumor-adjacent squamous mucosa by SELDI-TOF-MS [51]. They found 48 protein peaks differentially expressed between healthy mucosa and HNSCC. A supervised prediction analysis revealed greater than 90 % classification of healthy mucosa and tumor samples, and 72 % of the tumor-adjacent mucosa samples were predicted as aberrant, providing evidence for the existence of genetically altered fields with inconspicuous histology.

MALDI-TOF has also been successfully used in HNSCC proteomic studies. In one such investigation, MALDI-TOF was coupled with magnetic bead fractionation to analyze an HNSCC cohort consisting of matched pretreatment and 6–12 month posttreatment samples for analysis [52]. A set of approximately 200 spectral peaks was used and was able to largely correctly classify normal from pretreatment HNSCC samples, pretreatment from posttreatment, and normal from posttreatment samples. This showed the potential for use of this technology as a discovery platform in order to generate biomarker panels that potentially could be used for more accurate prediction of prognosis and treatment efficacies for HNSCC.

Another study used multidimensional LC-MS/MS to identify proteins that are differentially expressed in HNSCC for cancer biomarker discovery [53]. More than 811 proteins were identified which included structural proteins, signaling components, and transcription factors. They utilized a panel of the three best performing biomarkers, YWHAZ, stratifin, and S100-A7, to discriminate cancerous from noncancerous head and neck tissue. Their differential expression was verified by immunohistochemistry, immunoblotting, and RT-PCR and achieved a sensitivity of 92 % and specificity of 87 % in an independent set of HNSCC in discriminating tissue types. More recently, an analysis of samples from HNSCC patients with 2-DE and MALDI-TOF-MS revealed 181 proteins with differential expression between pretreatment and posttreatment samples [54]. Classification by disease status revealed significant differential expression of 16 proteins including several protease inhibitors and other molecules with direct implications on tumor survival. Another study attempted to validate DNA microarray results on a subset of genes that could potentially serve as biomarkers of oral SCC [55]. This group identified six potential biomarkers and used Q-RT-PCR to examine expression changes in oral SCC and normal control tissues, five of which were validated by this technique. TMA analysis then revealed that four of the six biomarkers (*SPARC*, *POSTN*, *TNC*, and *TGM3*) had differential expression and localization.

Biomarker clinical results from the EGOG 2303 phase II trial, where locally advanced stage III/IV resectable HNSCC was treated with induction chemo followed by CRT, were recently published [56]. Forty-two of the 63 patients had tissue samples available. A TMA was constructed and probed for the following proteins: EGFR, ERK ½, Met, Akt, STAT3, beta-catenin, E-cadherin, EGFR vIII, IGFR-1, NF-kB, p53, PI3Kp85, PI3Kp110a, PTEN, NRAS, and pRB. These protein biomarkers highlighted the important role that the MAPK and PI3K pathways play in HNSCC. Consistent with mutational analysis, overexpression of the peptides in these pathways were associated with inferior overall survival and inferior progression-free survival. Protein expression of ERK 1/2 had the most promising correlation with outcomes.

4.5.2 Surrogate Tissue Studies

Serum studies have been widely used in investigations of HNSCC given the challenges in obtaining repeat tumor samples. One study used MALDI on sera from 99 HNSCC and 143 controls to obtain serum protein patterns [57]. The mass spectra and linear discriminant analysis were used to select the top 45 spectral features. The subsequent spectral profiles from the sera of the HNSCC patients statistically significantly differed from the sera of control subjects. In a separate study, samples were analyzed by SELDI-TOF, and 80 common peaks or clusters were generated from the training set and used to create classification trees [58]. This algorithm correctly identified 91 % of HNSCC sera in the training set and 83 % of HNSCC samples in the test set, yielding an overall sensitivity of 83 % and an overall specificity of 90 %. Furthermore, they were able to identify a particular peak as the known biomarker metallopanstimulin-1 based on mass and whose relative intensity consistently correlated with levels detected by radioimmunoassay.

More recent research has sought novel surrogate tissue sources, which may be convenient for investigation. Alterations in the levels of biomarkers have been investigated in other body fluids that are near or bathe tumor sites. Accordingly, saliva is an ideal complementary resource for

developing HNSCC diagnostics, and more recent study attempts have focused on the use of salivary proteomics for oral cancer biomarker discovery. One analysis collected saliva from 64 oral SCC and 64 healthy subjects and utilized subtractive proteomics to find that several salivary proteins were differentially expressed [59]. Five candidate biomarkers were validated and demonstrated high sensitivity (90 %) and specificity (83 %) in detecting oral SCC. Another recent study found two proteins, alpha-1-B-glycoprotein and complement factor B proteins, to be present in patients with HNSCC but not in normal specimens, while cystatin S, parotid secretory factor, and poly-4-hydrolase beta-subunit proteins were detected in most normal saliva samples but not in HNSCC [60]. These results suggest that certain proteins are differentially found in patients and normal saliva and a small set of proteins may be useful for future validation for clinical investigation. Finally, another study built on prior data indicating that the expression of IL-6 and IL-8 are uniquely associated with oral SCC. They analyzed patients with newly diagnosed T1 or T2 oral cavity or histologically confirmed oropharyngeal SCC. Their analysis revealed that IL-8 was detected at higher concentrations in saliva and IL-6 was detected at higher concentrations in serum of patients with oral SCC, indicating that these markers and tissues hold promise for biomarker analysis in oral SCC [61].

Tandem mass spectrometry has also been used to identify proteins that may serve as biomarkers for neck disease. A recent study used serum from 40 patients, 18 without neck disease, and quantified 282 serum proteins [62]. Four candidate biomarkers (gelsolin, fibronectin, angiotensinogen, and haptoglobin) were identified, and the best one, gelsolin, had high validity for identifying node-positive HNSCC. Gelsolin is a cytosolic protein that regulates cytoskeleton assembly and disassembly. It is a protein that has been implicated in epithelial to mesenchymal transitions.

Table 4.2 Key advantages and limitations of DNA microarrays

Advantages
– Provide insight into fluctuations in gene transcription
– Capable of generating large amounts of expression data quickly
– Current microarrays give expression data from essentially the entire genome
– Technological advances have generated microarrays that can be implemented using automated, high-throughput strategies at reduced costs
Limitations
– High-quality RNA is required for the generation of good expression data
– Changes in RNA expression may not correlate with changes in protein levels
– Advanced biostatistics are necessary to process vast amounts of data generated

4.6 Challenges of HNSCC Oncogenomics/Proteomics

The application of these novel technologies offers many opportunities for advanced analyses of HNSCC (Table 4.2). With the completion of the Human Genome Project and advances in array technology, gene expression studies offer an opportunity to look at the full complement of genes expressed by a tumor. Gene expression profiling experiments have generated a tremendous amount of information regarding concomitant genetic events during disease. However, the functional consequences of disease are also regulated by the deregulation of protein products and protein networks so the information flow cannot be ascertained from gene analysis alone.

Furthermore, there are a variety of potential pitfalls in microarray analysis that may obscure the quantification of genes of interest. One of the most important variables relates to the quality of the transcripts utilized for the microarray, which may relate to initial and long-term tissue handling as well as processing of the transcripts for use in the microarray studies. A recent report indicated that there may be a storage time decrease in the predictive performance of tissue samples. There may be a decrease in the predictive performance of tissue samples based on their storage time. Other common causes of signal variations include errors with fluidics protocols, spoiled or omitted hybridization cocktail reagents, and inaccurate quantification of labeled samples. There are also a variety of factors inherent to the microarray technology such as intensity-dependent dye effect and spatial-dependent dye effect that can influence the quantification process. In addition, studies vary in the heterogeneity of the cell types included in the samples from 50 % tumor cells to the pure isolation of single tumor cells.

By contrast, proteins are dependent on highly regulated processes at the transcriptional, translational, and posttranslational level (Table 4.3). Many of the standard proteomic approaches rely on the usage of complex protein mixtures and the indirect assignment of spectra to identify target pro-

Table 4.3 Key advantages and limitations of proteomic approaches

Advantages
– Provide insight into fluctuations in transcribed and translated gene products as well as posttranslational modifications
– Capable of using a variety of tissue sources with minimal processing to analyze variations
– Increasingly offering high-throughput technologies
Limitations
– High-abundance proteins may obscure data
– Generally only analyze a minority of proteins within the entire sample
– Difficult to correlate individual spectral peaks/signatures with actual proteins

teins. These approaches are often hampered by the presence of large quantity proteins that may obscure quantification of the proteins of interest. Accordingly, there has been increasing interest in developing protein microarrays capable of identifying hundreds of protein events simultaneously; however, these arrays have a set of unique problems. Protein interactions are governed by complex associations between the target protein and the antigen-binding site on the antibody. Furthermore, proteins tend to denature with changes in pH or temperature, and antibodies must exhibit strong affinities and specificity to each of their respective substrates especially in the analysis of specific protein states such as phosphorylation or proteolytic cleavage. In addition, the variation in protein concentration in cells may vary widely, so detection methods must exist that can quantify protein concentration over many orders of magnitude.

These studies also require careful experiment planning starting with the selection of appropriate controls. Many studies use matched "normal" epithelium, but this may confound interpretations of gene expression changes occurring in HNSCC tumorigenesis. Although logistically difficult to achieve, the theoretically ideal control tissue would match for patient age, gender, smoking and drinking history, and other variables to minimize further confounding factors.

4.7 Conclusion and Future Directions

The goals of oncogenomics and proteomics are to improve diagnosis, therapy, and cure rates for cancer patients. A patient's genomic signature of a cancer may serve as the basis for choosing the most effective therapy for the individual patient to improve their chances of recovery and their quality of life. Oncogenomics and proteomics have progressed from molecular profiling to model systems, cancer pharmacology, and clinical trials. With whole-genome sequencing, personalized tumor profiles are now possible. Although it is unlikely that a single biomarker will accurately predict response to therapy, analyses that can detect multiple markers may have improved predictive value when used in combination. Imperfect biomarkers may still be clinically useful for serial testing of single individuals because acute changes in biomarker levels may signal the need for an aggressive search for the cause. An important challenge for biomarker validation is the considerable molecular heterogeneity of individual cancers and the low overall incidence of the disease in general population, making it difficult to validate the true prognostic potential of a biomarker or panel of biomarkers. Non-concordance of predictive gene lists is common in many microarray studies using different platforms and data mining tools and may represent differences in experimental design or data analyses but also may represent true differences in biology based on different subsites or other unknown factors.

Furthermore, although current oncogenomic and proteomic approaches may yield valuable information in the identification of novel diagnostic markers, gene and protein expression profiles may not be able to provide an alternative method of diagnosis on their own. It may become necessary to include other technologies such as metabolomics, peptidomics, glycomics, and lipidomics for better isolation and identification of molecular targets. In order to obtain reliable prognostic markers, these technologies will need to be combined with advanced bioinformatics tools to integrate and mine the data from basic and clinical research. Once molecular signatures are successfully validated, it will also be important to perform long-term clinical studies to determine the validity of using these signatures in independent cohorts of patients for the prediction of patient response to therapeutic options.

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Genetics and Epigenetics of Head and Neck Cancer

5

Jagtar Dhanda and Richard J. Shaw

Abstract

Our ability to explore the cancer genome is dependent upon, and limited by, the availability of representative tumour models, the high-quality tissue resource and the capacity of available technologies. Fortunately, there has been great progress in these areas in recent years with next-generation sequencing techniques enabling entire genome sequencing, using a fraction of the resources previously required. Carcinogenesis a multistep and multifactorial process that involves multiple genes with critical events occurring at the DNA level and DNA is a highly stable macromolecule and therefore an excellent resource for biomarker discovery. However, translational perspectives of genomics remain limited which is partly related to intratumour heterogeneity, in which subclones of cells can be present within the same tumour. New advances in therapy will rely upon a greater understanding of the molecular basis of this heterogeneity, and new therapies will have to target the specific characteristics of an individual's tumour, central to the modern concept of personalised medicine. There is however an emerging molecular classification of HNSCC, with prognostic significance, that is based upon the presence of human papillomavirus and the number of genomic alterations present.

In the last decade, interest has also grown in the epigenetics of cancer. The role of promoter hypermethylation has become a focus for research in many tumour sites, including HNSCC. Silencing of certain TSGs may occur in the absence of genetic change, via aberrant methylation of CpG islands. Several promising avenues exist in attempting to translate this research field into the clinical management of HNSCC. Several suggestions have been made that promoter methylation of specific genes may indicate a particular tumour's sensitivity to a drug. Epigenetic alterations are particularly interesting since they can potentially be reversed in drug treatment with mechanisms such as epigenetic reprogramming suggested. This opens the door for using epigenetic modifiers as therapeutic agents.

Keywords

Genetics • Epigenetics • Carcinogenesis • Techniques • Biomarkers • Therapies

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5.1 Introduction

Our ability to explore the cancer genome is dependent upon, and limited by, the availability of representative tumour models, the high-quality tissue resource and the capacity of available technologies. Fortunately, there has been great progress in these areas in recent years. Since the completion of the 15-year human genome project in 2003, the capability of the next-generation sequencing (NGS) techniques is such that an entire genome can be re-sequenced using a fraction of the resources previously required [1, 2]. In many respects DNA is an excellent resource for clinical biomarkers. Not only do many of the critical events occur at the DNA level but also it is a highly stable macromolecule that is simply extracted and less prone to degradation and artefact than the more labile RNA and protein alternatives.

With the development of these 'next-generation' or 'high-throughput' techniques, a new 'omics' language has emerged, and this technology has given us some novel insights into the genetics of head and neck cancer. For example, these whole-genome approaches have shown that tumour suppressor genes (TSGs) are the most commonly mutated genes associated with head and neck cancers, and NOTCH signalling pathways are the second most common oncogenic mutations. However, their translational perspectives remain limited, and this is partly related to the limited scope of druggable targets for TSG reactivation. These perspectives are also limited by intratumour heterogeneity with subclones of cells present within the same tumour, a feature that was also determined from NGS. This heterogeneity is one of the reasons why, despite the many innovations in cancer management, there has been only a relatively modest improvement in overall survival. To overcome this obstacle, new advances in therapy will rely upon a greater understanding of the molecular basis of this heterogeneity, and new therapies will have to target the specific characteristics of an individual tumour, central to the modern concept of personalised medicine. Understanding how tumours evolve, adapt and select subclones in the presence of therapeutic pressures will dictate how successful future biomarkers and therapeutics will become.

Although a diverse range of malignancies arises from the head and neck including the salivary and thyroid glands, paranasal sinuses and connective tissues tumours, over 90 % are head and neck squamous cell carcinomas (HNSCC). The genetic and epigenetics of head and neck cancer will therefore be discussed in relation to SCC, the principles of oncogenesis are nonetheless generically applicable. Cancer results from the accumulation of molecular lesions that occur and might be investigated, at the genetic, epigenetic, messenger RNA or protein level. The importance of genetic changes, and the frequency of the resultant disease, has led to cancer being labelled the most common human genetic disease. Often when we consider genetic diseases, we immediately think of inherited diseases. Fortunately, these inherited head and neck cancer syndromes are relatively uncommon, but these predisposition disorders offer a valuable window into the events that are also critical for sporadic cancers.

The great majority of sporadic cancers occur due to exposure to environmental mutagens. These mutagens cause genetic lesions that have a huge range of scale, from a single nucleotide to an entire chromosomal region being lost or gained. These genetic abnormalities occur more or less randomly rather than as an ordered sequence, and it is apparent that whilst some may be critical 'drivers' to carcinogenesis, others are 'bystander' events. Inherited predisposition to cancer can either be those rare single gene autosomal recessive syndromes with a greatly increased risk (i.e. inherited cancer syndromes), or they can more subtly represent single nucleotide polymorphisms (SNPs) that affect predisposition in the general population. In both cases, DNA damage and repair appear to be the common target. From the analysis of comprehensive sequencing for sporadic human cancers, it has also become apparent that the most common mutations are seen in relation to this DNA repair machinery.

In the last decade, interest has also grown in the epigenetics of cancer. The role of promoter hypermethylation has become a focus for research in many tumour sites, including HNSCC. Silencing of certain TSGs, central to the development of many solid tumours, may occur in the absence of genetic change, via aberrant methylation of CpG islands. Several promising avenues exist in attempting to translate this research field into the clinical management of HNSCC. The discussion in this chapter will present the genetic and epigenetic basis of HNSCC and the molecular techniques that have contributed to our understanding.

5.2 Tumour Heterogeneity and Molecular Classification in HNSCC

The clinical behaviour of head and neck SCC (HNSCC) varies greatly from patient to patient, site to site and even within individual subsites; this clinical diversity is a reflection of tumour heterogeneity. Clinical and biological diversity is most apparent between the different head and neck subsites with oropharyngeal squamous cell carcinoma (OPSCC), which is associated with the human papillomavirus (HPV), having a better prognosis than oral squamous cell carcinoma (OSCC), which is mainly HPV negative. HPV status, therefore, lends itself as a starting point for grouping an otherwise highly heterogenous disease. Additional distinct clinical features related to HPV status includes the age of the patient, the association with smoking and, most importantly, the prognosis. HPV-positive OPSCC

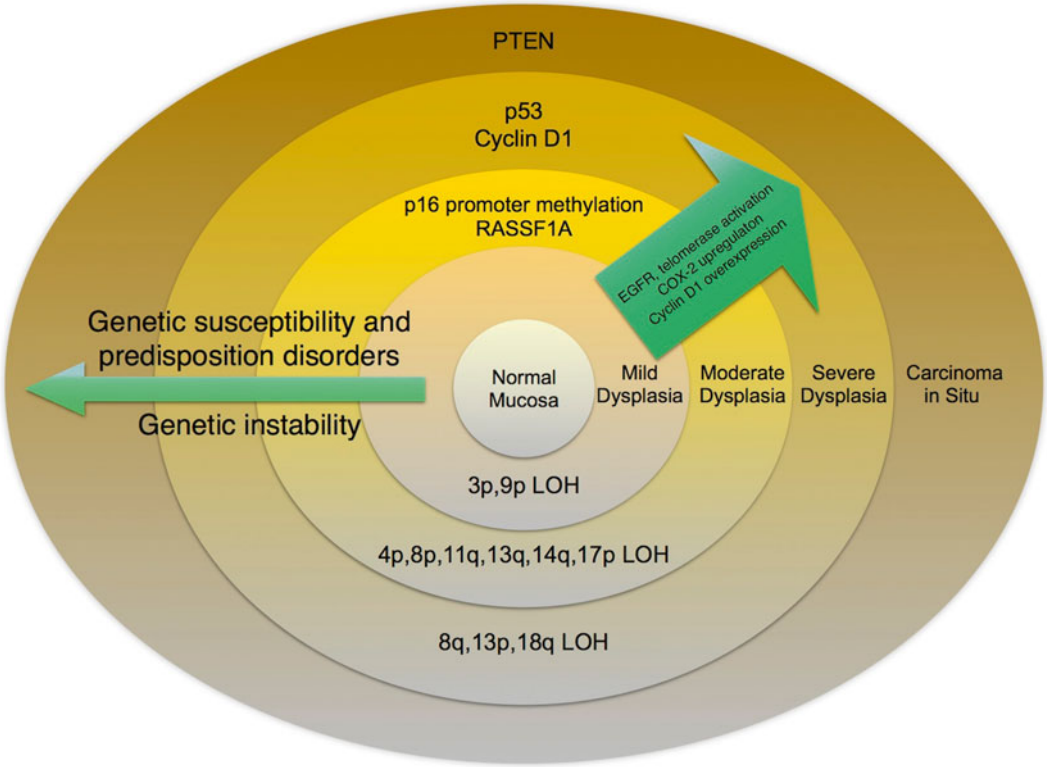

Fig. 5.1 Emerging molecular classification of HNSCC and prognostic significance. *CIN* chromosomal instability. The *line* demarcating prognosis overlaps the HPV-positive group which represents a subset of these cases with poor prognosis

occurs in younger non-smoking patients and has a better prognosis than OSCC although 15 % have distant metastasis with poor survival (see Fig. 5.1). These differences in the natural history of HPV-related HNSCC are well established, and they also have a genetic basis. The presence of viral oncogenes E6 and E7 and wild-type TP53 is associated with HPV-positive disease, and chromosomal instability (CIN) and TP53 mutations are more commonly associated with HPV-negative disease.

The differences in the clinical behaviour of tumours can also be found within the same sites. For example, tongue SCC behaves differently to other oral subsites with a higher rate of recurrence and poor local control. This has led some to suggest that it is a distinct biological entity [3]. Subgroups of HPV-negative HNSCC have emerged based on DNA copy number techniques such as karyotyping and comparative genomic hybridisation (CGH). Chromosomal or genomic instability is a consistent feature in 80 % of HPV-negative HNSCC and most likely results from loss of function of DNA repair mechanisms. High CIN can be used to predict progression of premalignant lesions as well as poor survival with high risk of metastasis [4–7]. 20 % of HPV-negative HNSCCs are associated with low CIN, have low numbers of genetic mutations and possess mainly wild-type TP53 (Fig. 5.1) [4].

Further studies have shown that heterogeneity can be taken one step further and exist within the same tumour itself, or intratumour heterogeneity [8]. These studies have shown that mutational events and chromosomal imbalances can vary spatially within the same tumour. This observation casts doubt over any interpretation of data obtained from single biopsies. Multiregional genetic analysis has shown that single sites analysis can often underestimate the number of genetic events. Although intratumour heterogeneity is a significant factor that has limited the development of therapies, the extent of this phenomenon can itself be used as a marker that has been linked to poor survival [8].

5.3 Genetic Principles in Carcinogenesis

Cancers arise from cells that have undergone heritable and non-heritable (somatic) genetic alterations and Theodor Boveri is generally credited as the father of the ‘somatic mutation theory’ of carcinogenesis [9]. There is considerable evidence to support many of the predictions he made in his theory on the origin of malignant tumours. These genetic alterations can involve activation of cancer-promoting genes or inactivation of cancer-suppressing genes. Multiple heritable changes are required for a normal cell to evolve into a

cancer cell; evidence showing that this may involve between three and ten genetic events, i.e. carcinogenesis, is a multistep and multifactorial process that involves multiple genes [10]. This is supported by histopathological observations revealing multiple stages of tumour progression during malignant transformation. It is also supported by animal models of carcinogenesis and cancer predisposition disorders in individuals with heritable syndromes. Mathematical models based on age-specific tumour incidence curves also consistently show that 3–7 independent hits are required for carcinogenesis [10]. The sequential accumulation of these genetic abnormalities develops in a Darwinian fashion, with those aberrations giving a selective advantage being propagated further.

One of the reasons for relapse in OSCC is the presence of abnormal or dysplastic epithelium at the margins of resection, and only macroscopic features can be used intraoperatively to determine the extent of disease and the margins to use. Slaughter et al. first coined the term 'field cancerisation', which partly explains this tendency for local recurrence [11]. The presence of clonal genetic changes associated with macroscopically 'normal' mucosa, and the tumour, led to this suggestion that these preneoplastic cells are present in the whole field. This could be related to, and propagated by, the presence of stem cells. The genetic features in these fields, such as LOH at chromosome 9p, have been suggested as a possible marker for recurrence [12, 13].

5.4 Oncogenes and Tumour Suppressor Genes

Genetic alterations, such as deletions, mutations, amplifications and chromosomal rearrangements, manifest with activation of cancer-promoting genes, otherwise known as oncogenes, which support cell survival and proliferation. They can also manifest with the inactivation of cancer-suppressing genes, or TSGs, thereby also promoting tumour development [14–16]. Oncogenes are derived from alteration of cellular proto-oncogenes, a term used to describe genes that are normally involved in cell growth or survival signals, i.e. an oncogene is an abnormally activated proto-oncogene. Oncogenes give cancer cells dominant gain of function with a selective growth advantage due to promoting uncontrolled cell proliferation. Most of the products of oncogenes override the normal cell cycle checkpoints allowing abnormal cell proliferation [17]. Oncogenes can be classified into one of five broad functional groups and represent the different stages at which their products are involved in the growth signal cascade. This includes extracellular proteins such as growth factors and their transmembrane receptors (EGFR, erbB), the subsequent intracellular signalling transducer (ras, raf) to the eventual intra-nuclear transcription factors (c-myc) [18]. Other oncogene products include cell cycle regulators (cyclin D1) and inhibitors of apoptosis (bcl-2).

The list of oncogenes associated with head and neck cancer is extensive. It includes EGFR, which is overexpressed in over 90 % of HNSCC. It is clinically used in targeted therapy with Cetuximab, a chimeric monoclonal antibody, directed against EGFR [19]. EGFR is a member of the ErbB protein family of cell surface receptors; it works through the tyrosine kinase cascade. It is activated by a number of ligands including EGF, TGFα and amphiregulin, and downstream effects include activation of kinases and signal transducers such as mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinases (ERK) and the JaK/STAT pathway. This results in activation of pathways involved in proliferation, apoptosis, invasion, angiogenesis and metastasis [20]. Genetic alterations in the EGFR pathway can provide predictive biomarkers since these alterations correlate with response to cetuximab therapy [21]. Interestingly, sensitivity to EGFR inhibition agents in other tumours has been shown to be accurately predicted by downstream Ras/Raf mutations which can cause downstream constitutive activation [22].

ΔNp63-α is another commonly associated oncogene in HNSCC and belongs to the p53 family. It is involved in Wnt signalling which is associated with proliferation and migration [23, 24]. The PI3KCA mutated gene is also commonly utilised in cancer therapies and is amplified in 20 % of HNSCC [25]. PI3Ks are activated by tyrosine kinases resulting in recruitment of pleckstrin-homology-domain-containing proteins including phosphoinositide-dependent protein kinase 1 (PDK1) and serine/threonine-specific protein kinase (AKT) to the plasma membrane. Conformational change of PIP_3 (phosphatidyl 1,4,5-triphosphate) causes AKT phosphorylation by PKD1 and mammalian target of rifampicin complex 2 (mTORC2). This AKT activation is found in 90 % of HNSCC cases [25]. Both PI3K and mTOR inhibitors are being investigated in phase II trials in HNSCC, but early results have been disappointing due to complex feedback loop interactions and crosstalk [26, 27].

There has been a recent interest in the NOTCH signalling pathway after it was shown to be the second most common mutation associated with HNSCC. Most mutations are missense, causing loss of function, although it can also be activated and therefore act as an oncogene [1, 2, 5, 28]. Ras mutations are found in a third of all cancers and 5 % of HNSCC and are also associated with the PI3K and MAPK signalling pathways [29, 30]. JaKs, nonreceptor tyrosine kinases, activate cell surface cytokine receptors by phosphorylation and are found in HNSCC. These can then dimerise STAT with subsequent nuclear translocation and activation of Ras and PI3K pathways [31].

TSG-encoded proteins have an inhibitory regulatory effect on growth, mediated via cell cycle, apoptosis, cell adhesion and DNA repair [32]. TSGs give cancer cells loss

of function, resulting in genomic instability with limitless replicative ability and immortalisation. They can be inactivated by genetic events such as mutation and deletions or by epigenetic events such as DNA methylation or chromatin remodelling [33]. TSGs require both alleles to be altered before manifestation (i.e. homozygosity) and are therefore recessive, unlike oncogenes, which can be activated by single allele activation (i.e. heterozygosity). This was first described by Knudson as the 'double-hit' theory for retinoblastoma [34, 35]. Upon TSG inactivation, cells lose their regulatory control leading to unchecked cell division and the development of cancer. TP53, the 'guardian of the genome', was one of the earliest TSGs discovered in a broad range of cancers including head and neck cancer [36–39]. Other important TSGs found in HNSCC include the CDKN2a locus and the DCC gene (deleted in colon cancer) on chromosome 18q21, a conditional TSG, which mediates it growth effects by binding to netrin-1. FAT1 has also recently been shown to be mutated in 23 % of HNSCC cases with inactivating mutations, and it also has a role in Wnt signalling. Loss of the FAT gene at 4p35 is thought to play a role in cell-cell adhesion [40, 41].

5.5 The Multistep Process of Carcinogenesis: The Genetic Progression Model

A 'genetic progression model' has been postulated in HNSCC during the transformation of normal cells to malignant, and this model reflects the multistep process of carcinogenesis (Fig. 5.2). Genetic events, such as loss of heterozygosity (LOH) at particular gene loci, can be found to be associated with specific histological features at different stages of this progression [18, 42]. For example, there is a high frequency of LOH at loci 9p, 3p and 17p in dysplastic lesions indicating that such events occur early in carcinogenesis. LOH at 13q and 8p is more frequently observed in carcinomas suggesting that they occur at later stages of carcinogenesis [42]. Although these phenotypic and genotypic changes manifest in a linear fashion, carcinogenesis may not be a simple linear event with a single end point, possessing features of a branched evolution. Data from heterogeneity studies show that several key genetic events can occur independently with selective pressures during growth and metastasis selecting several subclones through a process of natural selection [8].

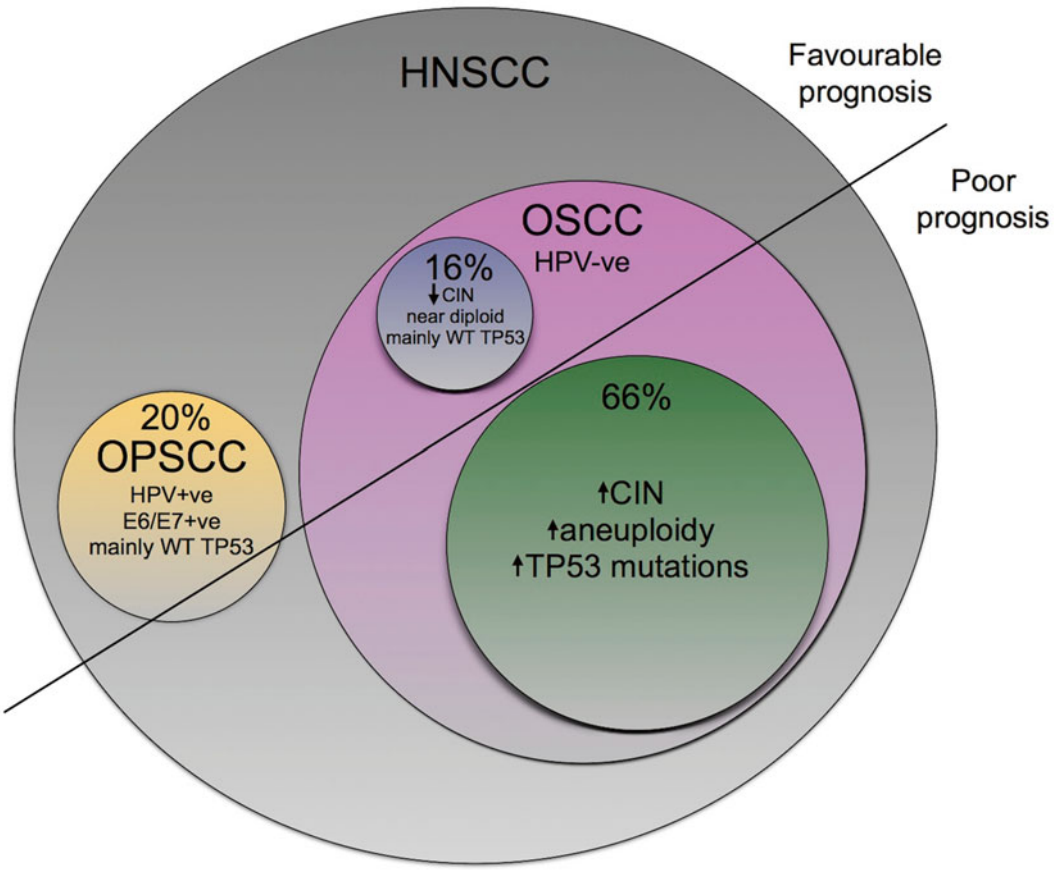

Fig. 5.2 The progression model for HNSCC. As genetic abnormalities (LOH and oncogene activation) accumulate over time, a corresponding histological progression is found. The rate of accumulation of these genetic changes is increased once genomic instability is established. The first stages of this progression axis may be heritable (susceptibility and predisposition disorders)

5.5.1 Earlier Events

5.5.1.1 Loss of 9p21 region (CDKN2A Locus)

The most common site for LOH associated with HNSCC is 9p21 with 71 % loss in preinvasive and invasive lesions suggesting this is an early event [43]. This gene locus harbours the CDKN2A gene and encodes the p16 and p14 (ARF) proteins that regulate cell cycle via the TP53-MDM2 axis [44]. CDKN2A is a negative regulator of MDM2 and so its loss indirectly influences TP53 function. In a series of 40 OSCC cases, 94 % were associated with genetic alterations in both CCND1 and CDKN2A [5]. The p16 gene encodes a cell cycle protein that inhibits cyclin-dependent kinases (CDK4 and CDK6) thereby preventing phosphorylation of Retinoblastoma (Rb) protein [45–47]. The Rb gene regulates cell cycle control through the G1 restriction point, by binding to the E2F transcription factor when it is in a hypophosphorylated state. The presence of mitogens causes complex dissociation with downstream activation of genes promoting cell cycle activation, such as $p21^{WAF-1}$ and Myc [48]. The retinoblastoma gene, or RB1, can itself be mutated or deleted in 5 % of HNSCC patients and its upstream regulator also includes CDKN2A thereby closely interacting with the TP53 pathways [49].

5.5.1.2 Loss of 3p Region

Loss of chromosome 3p region is another early event in HNSCC found in oral dysplasia [50, 51]. The region includes the tumour suppressor genes FHIT (fragile histidine triad gene) and RSSFIA, which is an effector molecule in the RAS-activated growth inhibition signalling pathway [52].

5.5.2 Late Events

5.5.2.1 17p Loss of Heterozygosity/p53 Mutation

Mutations (predominantly missense) or deletions of TP53 (or p53), which is located on chromosome 17p13, are associated with increased genomic instability that hastens the rate of further mutational events. Over half of HNSCC tumours have been found to have mutations of TP53, and this is associated with a reduced survival rate [2]. It is a transcription factor that is normally activated by stimuli that cause cellular stress such as radiation and carcinogenic toxins exposure. TP53 activation regulates cell growth and differentiation by influencing cell cycle control at the G1/S junction, a 'checkpoint' in the cell cycle. Actively dividing cells pass through this checkpoint to ensure progeny cells do not receive incomplete or damaged DNA. If the extent of genetic damage is beyond repair, then P53 will promote apoptosis or senescence to prevent propagation of the genetic insult. Loss of p53 function therefore results in transformation due to the propagation of abnormal DNA.

Upstream pathways inducing TP53 activation include ATM, CHK2, ATR and p14 pathways, levels of p53 are regulated by ubiquitination of MDM2, and resulting proteolytic degradation and p21 are amongst the many downstream regulators [53, 54]. TP53 inactivation can occur indirectly by MDM2 (mouse double minute 2 homolog) overexpression, an E3 ubiquitin protein ligase and a negative regulator which binds to TP53 promoting its degradation [33, 55]. Mutations of TP53 can also behave in an oncogenic manner by exerting a gain of function and promoting tumour growth. These mutant p53 proteins regulate metabolic pathways involved in aerobic glycolysis [56].

5.5.2.2 11q13 Amplification/Cyclin D1 Overexpression

The oncogenes bcl-1, int-2, hst-1, EMS-1 and cyclin D1/PRAD1 are implicated in 11q13 amplifications which are found in significant numbers of HNSCC cases [30, 40, 41, 57]. Cyclins are proteins involved in cell cycle regulation; the cyclin D1 (CCND1) gene product activates Rb by phosphorylation resulting in proliferation with cell cycle progression from G1 to S phase [58]. It is a cofactor for CDK4 and CDK6 and phosphorylates Rb, and the $p16^{IKN4a}$-cyclin D1-CDK6-RB axis is an important pathway of immortalisation in HNSCC. Other late genetic events in head and neck cancer include amplifications at 3q26, 13q21, 14q23 and 4q21–q25 and deletion at 5q13 [42].

5.6 Hereditary Conditions Predisposing to HNSCC

Accurate replication and repair of DNA are essential for genomic integrity, but somatic mutations can occur spontaneously during cell replication, even without exposure to carcinogens. This intrinsic tendency for errors in DNA replication is regulated by many cellular processes; failure to correct these errors contributes to carcinogenesis. These regulatory processes involve systems that can both detect and repair abnormal DNA. If this repair is not possible, then cells will undergo programmed cell death, or apoptosis [59]. Defects in any part of this chain of events of recognition, repair or apoptosis result in unresolved genomic instability. Our understanding of these processes has come from insights into hereditary conditions and genetic predisposition disorders (Fig. 5.3).

5.6.1 Fanconi Anaemia

Fanconi anaemia (FA) is a rare autosomal recessive disorder (incidence 1:350,000) that was first described in 1927 [60]. It is characterised by various congenital malformations, progressive bone marrow failure and tumour development [61]. The disease involves many organs and patients typically present with hyperpigmentation, skeletal anomalies, growth retardation, learning disability and risk of secondary malignancies including HNSCC

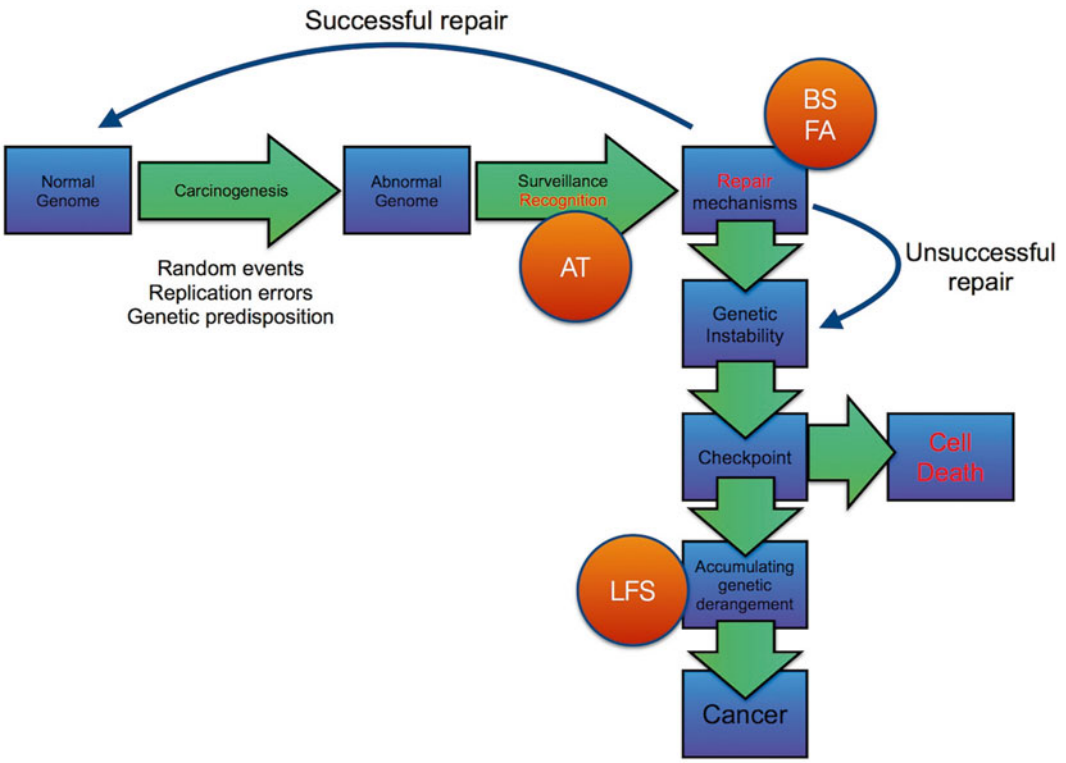

Fig. 5.3 Interaction of the hereditary conditions that predispose to HNSCC with the pathway of carcinogenesis. *AT* ataxia telangiectasia, *BS* Blooms syndrome, *FA* Fanconi anaemia, *LFS* Li-Fraumeni syndrome

at a young age. The genes associated with FA have a caretaker role in the protection against carcinogenesis, i.e. they maintain the integrity of the genome by DNA repair mechanisms. FA is defined by its cellular hypersensitivity to DNA cross-linking agents, and two genetic defects have been suggested that determine the development of cancer, defective chromosomal stability and immunodeficiency [62]. The genes associated with the FA including BRCA1, BRCA2 (also mutated in familial breast cancers), FANCD2 and FANCG. These genes can also be frequently associated with sporadic HNSCC suggesting similar pathways in non-FA sporadic cancer patients [63]. This is supported by differences in expression levels of Fanconi-related genes in sporadic OSCC of younger patients compared to older patients. It leads to the conclusion that sporadic tumours in younger patients also occur through defective carcinogen metabolism or DNA repair mechanisms.

5.6.2 Bloom's Syndrome

Bloom's syndrome (BS) is also an autosomal recessive disorder associated with Ashkenazi Jewish ancestry, and it is a 'chromosomal breakage syndromes'. It is characterised by marked genetic instability and is associated with a greatly increased risk of a wide range of cancers including head and neck malignancy and leukaemias/lymphomas. Features include growth retardation, hypersensitivity to sunlight, facial sun-sensitive telangiectatic erythema, skin pigmentation in non-sun-exposed skin and moderate to severe immunodeficiency. BS is characterised by a high level of sister chromatid exchanges, a feature that exists when two chromatids form during late prophase of mitosis, break and rejoin to allow switching of positions of genetic material. This increased frequency of chromosomal breakages or interchanges occurring spontaneously or following exposure to DNA damaging agents. The genetic instability arises through mutations in both copies of the BLM gene, located on chromosome 15q26. The BLM protein interacts with proteins involved in genomic maintenance and stability and a super complex of BRCA1-associated proteins named BASC (BRCA1-associated genome surveillance complex). This surveillance complex includes proteins involved in replication repair processes found in ataxia telangiectasia mutated (ATM), HNPCC (MLH1, MSH2) and some of the Fanconi complementation group of proteins (FANCA, FANCG) [64, 65]. There are also interactions between the BLM protein and TP53 [66].

5.6.3 Ataxia Telangiectasia

Ataxia telangiectasia (AT) is a debilitating and progressive neurodegenerative disease of childhood, and characteristic defects include neurodegeneration, immune dysfunction, radiosensitivity and cancer predisposition. The underlying cause of the disease is mutation in ataxia telangiectasia mutated

(ATM) gene located on 11q22–23, a common deletion site in HNSCC [67, 68]. It is a protein kinase involved in the cellular response to DNA damage and is also involved in immune system maturation and meiosis [69]. Cancer predisposition is mainly of the lymphoreticular system but is also linked to head and neck malignancy in younger patients [70]. The ATM gene is involved in surveillance of DNA damage with activation of repair enzymes or apoptosis if DNA damage is irreparable. After DNA damage it undergoes autophosphorylation initiating a signalling cascade that includes p53, BRCA1, p53-binding protein 1 (p53BP1) and the checkpoint kinase CHK2 [71].

5.6.4 Xeroderma Pigmentosum

Xeroderma pigmentosum (XP) is an autosomal recessive disease characterised by a severe predisposition to ultraviolet light-induced skin cancers. There are two major clinical forms, one involving progressive degenerative changes of the skin and eyes and the other also includes progressive neurological degeneration [72]. There is an extreme sensitivity to sunlight with cutaneous symptoms ranging from sunburn to overt carcinoma. The risk of squamous cell carcinoma is elevated by 100,000-fold with a median onset of skin cancer at 8 years of age. XP is the archetype of the family of nucleotide excision repair (NER) diseases deficient in a gene product required in the excision of damaged DNA [73]. The NER excises damaged single strands of DNA and replaces it with a new sequence of bases using the second intact strand of DNA as a template. Abnormalities in this repair system lead to high levels of chromosomal breakage in skin cells leading to cancer [73].

5.6.5 Li-Fraumeni Syndrome

Li-Fraumeni syndrome is a rare autosomal dominant syndrome characterised by a predisposition to cancers including sarcomas, leukaemias and brain tumours. The early-onset malignancy (<45 years), usually a sarcoma, is associated with family history of multiple cancers. There is frequently a germline mutation of the tumour suppressor gene TP53 and other TSGs such as CHEK2 [74]. These individuals have a 90 % lifetime risk of developing cancer and are at risk of developing both lung and laryngeal carcinomas [75].

5.6.6 Lynch Syndrome II

Lynch syndrome II, or hereditary non-polyposis colorectal carcinoma (HNPCC), is an autosomal dominant inherited familial cancer syndrome in which patients are susceptible to colorectal cancer without diffuse polyposis. Lynch syndrome II has additional features with an association with extracolonic cancers including laryngeal cancer [76]. These patients have a defect in the DNA mismatch repair enzyme hMSH2, an important enzyme in genetic instability and carcinogenesis of HNPCC [77].

5.7 Genetic Predisposition and Mutagen Sensitivity

Inherited chromosomal instability syndromes represent one end of a spectrum of DNA repair defects. There are individual variations in the efficiency of these DNA repair systems with some individuals having an increased tendency for DNA damage from carcinogen exposure. Consequently, they have an increased susceptibility to cancers [78]. There is not a simple relationship between carcinogen exposure and the development of cancer. Not all heavy smokers develop cancer and likewise not all cancer patients are exposed to alcohol or tobacco [78–80]. Individuals with an inherited genetic susceptibility have defects in systems used to maintain DNA after exposure to these carcinogens [79]. Mutagen sensitivity and polymorphisms in DNA repair enzymes or carcinogen-metabolising enzymes also explains the variable risk seen with carcinogen exposure.

Familial aggregation studies have demonstrated that family history is also a significant risk factor for head and neck cancer. Studies have demonstrated odds ratios of 1.5–2.5 for cancer development in those predisposed by mutagen sensitivity polymorphisms, with greater predictive power found when combining mutagen sensitivity tests with other risk factors such as alcohol and smoking [81]. These genetic polymorphisms in carcinogen-metabolising enzymes (xenobiotic metabolising enzymes) frequently occur in the population, with both phase 1 and phase 2 enzymes implicated. Phase 1 enzymes include the cytochrome P450 enzymes CYP1A1, CYP1B1, CYP2D6 and CYP2E1, and phase II enzymes include the glutathione S-transferase enzymes GSTM1, GSTT1 and GSTP1. Metabolic polymorphisms in the cytochrome P450 CYP1A1 gene, for example, are associated with oral cancer risks in some populations with relatively lower smoking exposure, and the GSTM1 null genotype is associated with increased susceptibility to oral cancer in Asians but not in Caucasians [82–84]. Other polymorphisms have been found to be protective including the GSTT1 null genotype [85].

5.8 Techniques Used to Detect Genetic Changes in Cancer

5.8.1 Cytogenetics

Cytogenetics, the study of chromosomal rearrangements, was one of the earlier methods of determining the site of genetic abnormalities related to the pathogenesis of cancer. With karyotype analysis, cultured cells are arrested in metaphase

and a visual analysis made of gross genetic changes such as translocations, breakpoints and areas of gain or loss. At metaphase, the chromosomes appear as long arms (p) and short arms (q) joined at the centromere. The disadvantage of employing these gross techniques is that DNA base level alterations are missed and the abnormalities found are only a snapshot in time. The most common areas of gain are on the short arm of chromosomes 1, 3, 8 and 15. The most common areas of losses are on the long arms of chromosomes 8, 13, 14, 15 and 11. Cytogenetics can be used as a screening technique to identify gross losses or gains, but subsequent identification of specific genes requires high-resolution techniques with functional studies to determine the genes properties.

5.8.2 Fluorescent In Situ Hybridisation and Comparative Genomic Hybridisation

Techniques have developed over time to improve the resolution of karyotype analysis with molecular cytogenetic technology such as fluorescent in situ hybridisation (FISH) and comparative genomic hybridisation (CGH) increasing the ability to identify genetic alterations in cancer cells. These higher-resolution techniques have found area of loss commonly in 1p, 3p, 4p, 5q, 8p, 10p, 11q, 13q and 18q and areas of gain at 1q, 3q, 5p, 7q, 8q, 9q, 11q, 12p, 14q and 15q [86, 87]. FISH is a technique in which sequence-specific fluorescent probes are detected after hybridisation using microscopy to detect gains (amplifications) or losses (deletions). It is an efficient and reproducible approach for precise localisation of specific sequences, and it allows visualisation of copy number per cell.

CGH is also a fluorescence in situ technique developed to look at chromosome losses or gains but at a genomic level. It allows mapping of chromosome imbalances using total genomic DNA as a probe. In this technique normal metaphase chromosomes are hybridised with differentially fluorescent-labelled DNA probes (tumour with green and normal with red), and fluorescence in different regions can be measured for increased or decreased intensity corresponding to over- or under-expression of tumour DNA. CGH can also be used in archival tissues for retrospective studies unlike conventional cytogenetic analysis. The most frequently observed changes are copy number changes on chromosomes 3 and 5. Examples of tumour suppressor genes found at these locations include VHL on 3p and FAP on 5q [58, 88, 89]. These studies also identified amplification of the region 11q13 in HNSCC as a late event in the progression axis and their association with aggressive tumour growth [90]. CGH arrays give a higher resolution and have revealed previously unknown oncogenes as well as predicting chemoradiosensitivity [63].

5.8.3 DNA Microarray Techniques

Edwin Southern, a British biologist, first described in 1975, using labelled nucleic acids in a known DNA sequence (or a probe) to identify complementary DNA fragments through hybridisation of base pairs, a process known as Southern blotting [91]. The DNA probes used were labelled with a radioisotope or a fluorescent tag. This method of probe detection for DNA has been miniaturised with microarray techniques enabling detection of several thousands of DNA or RNA sequences at a time. The process is the reverse of Southern blotting; a probe is being placed on an immobile surface such as glass, silicone or nylon that is exposed to free nucleic acid [92]. Microarray technology has increased CGH analysis by several orders of magnitudes with array CGH utilising several millions of probe sequences giving a much finer map of genetic abnormalities [63]. This technology has been used to identify specific regions of gain such as 8q22 and the LRP12 gene [50]. Microarray technology is also utilised in gene expression analysis with gene signatures associated with metastasis and poor outcomes identified [93, 94].

5.8.4 Single Nucleotide Polymorphisms and Microsatellite Analysis

Work on the human genome project led to the discovery of single nucleotide polymorphisms (SNPs), scattered areas of altered DNA sequences, which ultimately have no impact on protein expression and no adverse phenotype in normal individuals. Since these SNPs cluster in populations, they can be used as identification markers for genetic predisposition when they are located in DNA repair genes [86]. SNP analysis can also indirectly provide information on gain or loss of specific genomic regions, and the density and resolution of SNP analysis have also been increased using microarray technology.

Microsatellites are short repeating sequences of DNA (short tandem repeats or STRs) that are located in the non-coding areas of the genome or introns. These non-coding regions represent up to 98 % of the human genome. Polymerase chain reaction (PCR) techniques, which amplify small regions of DNA, or amplicons, are used to detect microsatellites associated with particular chromosomal regions. Microsatellite analysis can therefore be used to detect the presence, absence or partial absence (LOH) of genes of interest. Patterns of allelic loss or LOH can be analysed in relation to many clinical variable such as the presence of involved margins, the likelihood of recurrence and the association with the tumour progression in the multistep model of carcinogenesis [42].

5.8.5 Sequencing and Next-Generation Sequencing

Genomic sequencing has greatly progressed since dideoxy chain termination sequencing in the 1970s [95]. The automated sequencer accelerated the process, and subsequent development of the 'shotgun' technique saved more time by splitting the genome into smaller segments. In the past few years, another generation of sequencers has been launched that can read as much DNA in a day that would previously taken years. Next-generation sequencing is a technique central to the emerging field of personalised medicine and utilises large arrays of templates with multiple simultaneous reads. Millions of templates can be read at once with thousands of times the throughput of Sanger's technique. This parallel sequencing technique provides relatively inexpensive, quick and reliable reads of the whole genome. With the ever-reducing costs of the technology, there is the real prospect of developing biomarkers based on genome-wide mutational screens looking at patterns of mutations or genomic landscapes to stratify risk of cancer rather than looking at individual genetic mutations.

These approaches have given us a greater understanding of the genomics of head and neck cancer. Two recent studies in 2011, the Broad Institute in Harvard and the John Hopkins University, were the first to use whole-genome sequencing approaches to reveal some surprising insights [1, 2]. The key players in HNSCC such as TP53, CDKN2A and PIK3CA were confirmed, but the majority of genetic mutations were found to be associated with TSGs and NOTCH1 was the second most common mutated gene after TP53 (47–66 %). In some further whole-genome studies, FAT1 was also found commonly associated with HNSCC [5, 28, 49]. The clinical implications of these findings have focused translational research on strategies to restoring function of TSGs rather than selectively inhibiting oncogene activation. This restoration of function is difficult, but NOTCH1 could provide a new potential target for therapies.

5.9 The Epigenetics of Head and Neck Cancer: Epigenetics, the Role of DNA Methylation, Histone Modifications and the Nucleosome

As each cell in the body contains the same DNA code, but the morphology and behaviour of these cells differs greatly, it can readily be appreciated that much of this variation arises from the way that the DNA is interpreted. This change in interpretation is known as epigenetics, providing an extra layer of processing in addition to the basic genetic paradigm of DNA → RNA → protein proposed by Crick and Watson. Epigenetic changes are heritable modifications of DNA with information content that influence phenotype but that are not associated with changes in nucleotide sequence. The regulation of gene expression is by the controlling influence of the proteins surrounding the DNA molecules known as histones. Chemical modifications of both histones (the 'histone code') and DNA (the 'DNA methylome') control the availability of genes for transcription and in turn have a fundamental influence on cell differentiation. It is now beyond doubt that epigenetic dysregulation has a major part to play in carcinogenesis; however, before attempting to understand the changes seen in cancer, it is important to review the normal physiological role of epigenetics.

The most important aspects of epigenetic regulation are methylation of gene promoters and modification of histone proteins. Gene promoter regions are particularly interesting stretches of DNA usually leading up to the transcriptional start sites. From the four nucleotides seen in DNA (A, C, T and G), it might readily be assumed that the frequency of any particular dinucleotide combination in any particular stretch of DNA might be approximately 1/16th. However, one particular combination, CG, has a very characteristic pattern. For much of the genome, the CG dinucleotide has been evolved out because it is highly mutation prone. In contrast the CG content within certain defined stretches of DNA is particularly high, upwards of 50 %, and these regions are called CpG islands (the 'p' merely refers to the phosphor-diester bond seen between all nucleotides in DNA). Definitions of CpG islands vary but typically refer to stretches of around 200 base pairs with >50 % CpG content upstream of mammalian genes. Chemical modification of the cytosine by methylation tends to occur in concert along the gene promoter. This is associated with transcriptional silencing via conformational changes in the surrounding histones (Fig. 5.4).

The 'default' CpG methylation pattern of humans is in two different states depending on the location. For scattered CpG not associated with gene promoters, almost all are methylated. Within CpG islands, most are normally unmethylated. Changes in methylation are brought about by a balance of two coordinating influences: firstly, waves of de novo methylation sweeping the genome and, secondly, active 'resetting' demethylation, probably mediated through histone modifications [96, 97]. This DNA methylome is reset early in embryogenesis and then re-established around the time of implantation. Further targeted alterations subsequently occur throughout differentiation and are associated with the loss of pluripotential state. The embryonic stem cell is principally characterised by its epigenetic signature.

The interplay between chromatin and DNA methylation is somewhat complex and is currently the focus of much research. It appears that in some circumstances, the DNA methylation pattern creates changes in histones, but in others the reverse relationship is found. In a highly simplified model

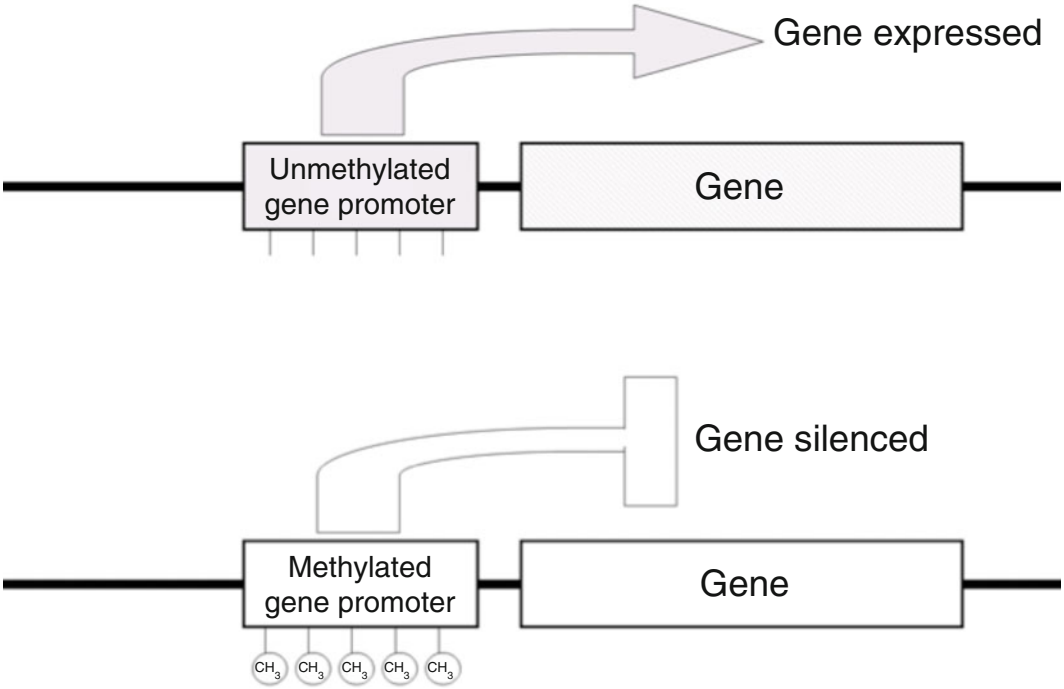

Fig. 5.4 Effect of gene promoter methylation on gene expression

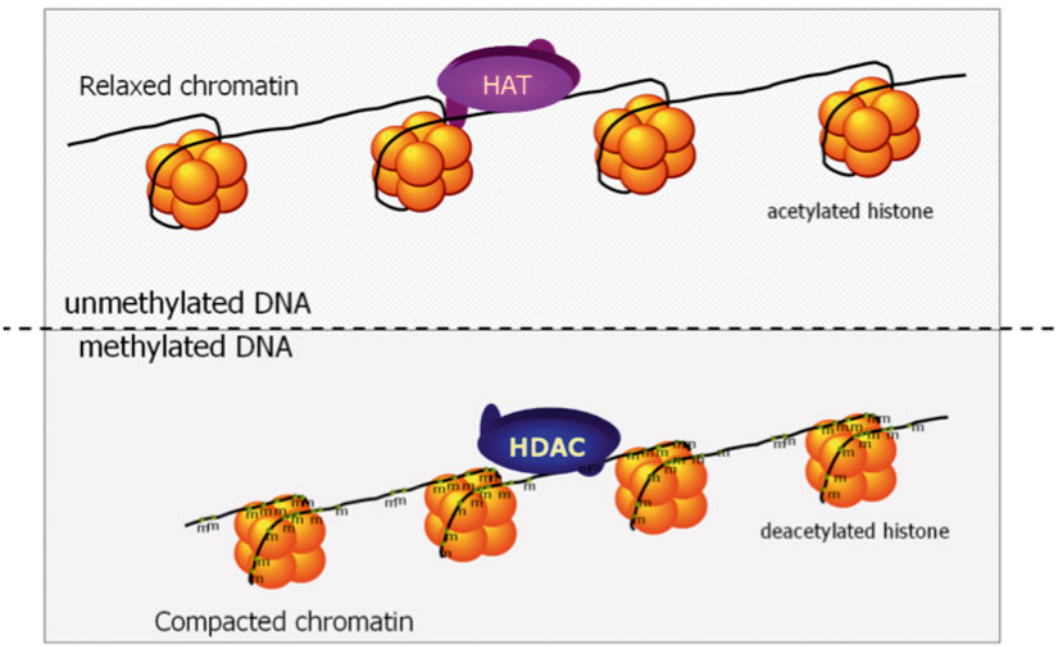

Fig. 5.5 Methylation and histone acetylation coordinate transcriptional availability. *HAT* histone acetyltransferase, *HDAC* histone deacetylase, *m* methylated CpG dinucleotide

of transcriptional regulation, unmethylated DNA is found in association with acetylated histones with a relaxed chromatin structure amenable to transcription. In methylated DNA, histone deacetylase is recruited creating a much tighter conformation of deacetylated histones which are not available for transcription and hence the gene is silenced (Fig. 5.5).

A pair of each of the core histones (H2A, H2B, H3, H4) make up an octamer which DNA is wound around to from a nucleosome. The N-terminal tails of histones are subject to a wide variety of covalent modifications such as acetylation, methylation and phosphorylation, which have influence over conformation and subsequent gene expression.

Heterochromatin is the term used to describe highly packed regions which are transcriptionally silenced. Methylation of histone H3 at lysines 9 (H3K9) and 27 (H3K27) is an important modification in heterochromatin. Gene repression induced by histone methylation and heterochromatin formation is readily reversible and common in cellular differentiation. Gene repression induced by DNA methylation leads to permanent gene silencing and is seen in various physiological and pathological processes such as imprinting and cancer [98]. It is likely that the DNA methylation pattern of a cell might be the template used to reconstitute the epigenetic programme following cell division. A third epigenetic mark worthy of consideration is nucleosome occupancy. Nucleosomes are known to be dynamic structures and tend to be depleted in promoter regions [99]. Removal of nucleosomes correlates with transcriptional activation, and often this can be related to only one or two nucleosomes near the transcriptional start site [100]. Presumably this is because transcription binding sites become more accessible.

5.9.1 Epigenetic Drivers of Carcinogenesis: Challenging the Genetic Paradigm

It has become increasingly apparent that cancer is as much a disease of misdirected epigenetics as genetic mutations and losses. As an illustration, recent results suggest that as many as 5 % of known gene promoters (i.e. 1500–2000 genes) are methylated in a typical solid tumour compared with, typically, 11 gene mutations [101, 102], whilst it is now beyond dispute that silencing of many TSGs important to cancer occurs through DNA methylation. The models available to explain an overall contribution of epigenetics to cancer have evolved with the technologies available to study them. Initially it was understood that the principal change in cancer was hypomethylation of genome-wide CpGs, but eventually it was realised that the functional significance of promoter methylation of a smaller number of TSGs might have greater relevance [103, 104]. One model is that methylation patterns arise through a process of selection. Some evidence suggests that tumours have upregulation of DNA methyltransferase enzymes and that those cells gaining a growth advantage form the clones of cells primed for malignant transformation [105]. These epigenetic events may then occur in preinvasive lesions, involving disruption or over-activation of key developmental pathways and cell signalling properties. This, so-called, epigenetic addiction may then predispose to later genetic mutations and genomic instability ultimately causing malignant transformation [106]. In this model, one may hypothesise that epigenetic events may be the most valuable in predictive modelling in potentially malignant head and neck lesions. Advances in genome-wide methylation technologies have, however, revealed that not all epigenetic events appear to occur in the tumour suppressor genes expected. It is seen that many methylation events occur in gene promoters not previously implicated in cancer and with no obvious mechanistic links. An alternative hypothesis is that certain genes are earmarked for methylation and it has been shown that genes frequently methylated in cancer have specific trimethylation of lysine 27 in histone H3 in their nucleosomes [107]. This suggests that cancer-targeted de novo methylation may be programmed by a preordained epigenetic code that physiologically has a role in marking embryonic genes for repression. Many hypermethylated genes in adult cancers are polycomb group marked (H3K27 me) in embryonic stem cells, and there are many, and unexpected, similarities in higher-order chromatin conformation between stem cells and adult cancers [108].

5.9.2 Interactions of Genetic and Epigenetics Events in Carcinogenesis

It is now clear that epigenetic events such as DNA methylation occur frequently in DNA repair pathways, encouraging the accumulation of mutations in key cellular pathways. Examples of this are DNA methylation and silencing of one allele of MLH1 and CDKN2a causing defective DNA mismatch repair and cell cycle control [106]. Another example is epigenetic-genetic cooperation in WNT signalling pathway, as an example through methylation of WNT repressors such as secreted frizzled-related proteins (SFRP) which mediate proliferation and survival advantages [109]. As a corollary, mutations of genes in the epigenetic machinery are also common, for example, in components of the DNA methyl transferases (DNMTs), the histone acetyltransferases (HATs)/deacetylases (HDACs) and the polycomb group (PcG) of repressor proteins. These genetic changes then mediate widespread epigenetic changes, including aberrant DNA methylation, histone modifications and nucleosome positioning, in turn leading to cancer [110].

Next-generation sequencing has shown, perhaps unexpectedly, that mutations in genes that control epigenetic machinery are frequent in cancer. These mutations had previously been overlooked, but it is now clear that their resulting epigenetic effects act as a pinnacle of the hierarchy of gene control mechanisms on many pathways relevant to the cancer phenotype [111]. Genetic and epigenetic somatic alterations in head and neck squamous cell carcinomas appear to be hierarchically and functionally highly coordinated without being necessarily locally targeted [112]. The coexistence and interdependence of multiple genetic and epigenetic aberrations suggest that novel cancer therapies may only be effective when combined with epigenetic strategies.

5.9.3 Molecular Assay of Epigenetic Alterations in Cancer

As the technological platforms which support detection of methylation have generally lagged behind other genomic methods, the translational potential of the DNA methylome has remained relatively unexplored. Much of the previous HNSCC literature has concentrated on a known published cohort of methylated genes clearly limiting progress. Methylation assays have previously relied upon methylation-sensitive restriction enzymes or methylcytosine antibodies, which greatly limits the number of samples analysed and precision of resulting data [113, 114]. Probably the largest breakthrough in methylation assays was bisulphite conversion, in which the methylation code is converted to a C/T polymorphism. This then allows the creation of methylation-specific PCR reactions, and a similar process might be made semi-quantitative by using real-time PCR [115, 116]. Methylation-specific PCR can be criticised as being only as specific as the primers and conditions allow, and without doubt some of the applications previously suggested push the envelope of reliable and reproducible performance of PCR. It must also be appreciated that the loss of sequence complexity accompanying bisulphite conversion also predicates towards loss of specificity. Methods previously described for SNiP analysis might then be 'borrowed' for methylation assays, such as pyrosequencing [117–119]. Alternative methods use standard Sanger's sequencing of bisulphite-converted DNA, but the impact of massive parallel sequencing has yet to be realised in epigenetics. Additionally more indirect methods have been improvised to detect potential methylation targets using pharmacological unmasking. It is possible to shortlist those genes upregulated by the use of demethylating agents in cancer cell lines using expression arrays [120–122]. In order to detect histone modifications, where methods of chromatin immunoprecipitation predominate, effective scaled-up assays are not currently available.

Up until recently, only around 1 % of the genomic CpG sites have been analysed in cancer, but now recently several array and next-generation sequence-based assays have become available. Bead arrays have been successfully applied with bisulphite-treated DNA to large numbers of samples with increasing numbers of previously selected CpGs across the genome [112, 120, 123]. Microarrays, employed with either restriction enzyme or enrichment methods, can provide relative levels of methylation across the genome. Most recently next-generation sequencing methods can assess tens of millions of DNA fragments, DNA methylation detection in a truly genome-wide approach [124].

5.9.4 Clinical Application of Epigenetics in Head and Neck Cancer

A comprehensive list of genes subject to promoter methylation in HNSCC is not yet available, and the previously published candidates are subject to regular additions [113, 114]. The genes and pathways subject to methylation are spread across the broad range of cellular functions. It may be that some of the methylation events seen as being relatively frequent in HNSCC are not critical mechanistic determinants of progression; however, others such as promoter methylation of p16 (CDKN2) appear to be highly likely to have functional relevance [118, 125]. Whether this is of importance to a suggested clinical application is highly dependent on the intended use of the assay, and this brushes on broader issues concerning on molecular biomarkers as discussed below. Studies in several tumour sites (in particular colorectal cancer) highlight the significance of the CpG island methylation phenotype (CIMP), with distinct features of histology, biological aggression and outcome [126]. A cluster of tumours with a greater degree of promoter methylation than would be predicted by chance alone are designated CIMP positive showing an association with worse prognosis [123]. The exact mechanisms underlying CIMP remain obscure; one may now speculate that the affected genes are histone H3K27 targets for EZH2-containing polycomb complex [107]. Epigenetic deregulation of NOTCH4 signalling in OSCC is also seen as part of a possible methylation signature for recurrence, with parallels to recently discovered NOTCH mutations in HNSCC [123].

Differences in methylation profiles between HPV-positive and HPV-negative HNSCC have been explored in several groups and recently summarised in a systematic review [127]. Interestingly several studies show the absence of p16 methylation in any of the HPV-positive samples. Studies investigating CCNA1 methylation show consistent association with HPV status (and wild-type P53), which is reinforced by work in gynaecological HPV-driven malignancies. Overall, HPV-positive tumours seem to have a greater association with global promoter methylation, possibly explained by DNA methyltransferases DNMT1 and DNMT3b as targets of HPV oncoproteins.

5.9.5 Epigenetic Biomarkers in HNSCC

The intended use of biomarkers can vary quite dramatically between assays. Biomarker research can resemble an uncertain navigation of the minefield between the discovery of an interesting observation in the research lab and the adoption of a proven biomarker for the benefit of patients in the clinic. Predictive biomarkers are designed to help make treatment

decisions as they predict for response to certain treatments, whereas prognostic biomarkers give an indication of the likely outcome for survival. A further class of biomarkers predicts for the mere presence of disease in surrogate specimens such as saliva, blood or surgical margins. In many regards DNA methylation appears to be a very promising aberration for biomarker applications as it can be detected with great specificity and sensitivity in many biological specimens, including saliva [128, 129]. Further, it may be present in a relatively high proportion of tumours encountered (e.g. cyclinA1 methylation in 50 % of HNSCC) which is in contrast to specific TP53 mutations which are, individually, relatively uncommon [118, 122]. Whereas mutations are irreversible events, there is the possibility of pharmacological reversal of methylation and histone changes. The ability to detect tumour-specific methylation events with great sensitivity results from methylation-specific assays which can detect methylated DNA, certainly in 1:1000 concentrations and may be in much lower proportions [116, 130]. It is possible then, at least in theory, to screen populations for cancer-specific events in saliva, perhaps using panels of methylation events, or to offer surveillance to post-treatment patients using their previous cancer's epigenetic fingerprint [131, 132]. It is also possible to search for tumour-specific methylation in histologically negative resection margins in order to optimise adjuvant treatment [133–135]. In a recent study, two-gene methylation combinations amongst the genes DCC, EDNRB and HOXA9 were predictive of recurrence and survival although not all studies were equally promising, and other conventional tumour staging variables (e.g. extracapsular spread in region lymph nodes) are known to be highly correlated with local recurrence [136–138]. With more refined panels of genes, and use of instantaneous assays, it is possible to envisage intraoperative use of methylation in margins helping head and neck surgeons in obtaining more reliably clear surgical margins.

Management of the patient with dysplasia of the head and neck depends on accurate prediction of transformation, and pathological grading fails in some regards. Bringing together the promise of epigenetic biomarkers within non-invasive sampling and also the mechanistic relevance of epigenetics in priming the molecular field for further genetic events seems logical in this setting. It has now been established that 3p and 9p losses represent very effective genetic biomarkers of progression within H&N dysplastic lesions [42]. Early evidence suggests that methylation may have some promise in this field, and one longitudinal study has found p16 methylation to be a specific predictor of malignant progression in oral dysplasia [139, 140]. The correlation between p16 methylation and HNSCC appears to be consistently strong in a recent systematic review [141]. It may be possible to make a prognostic evaluation of a tumour prior to definitive treatment by epigenetic analysis of the biopsy. In this way the patient's treatment may be individualised by the methylotype. The full impact of genome-wide methylation profiling and its prognostic value has yet to be evaluated. Realising the potential in order for any of these applications to be clinic-ready is self-evidently a painstaking process.

5.9.6 Epigenetically Directed Therapy in HNSCC

Several suggestions have been made that promoter methylation of specific genes may indicate a particular tumour's sensitivity to a drug. Such studies have yet to make an impact in the treatment of HNSCC. In the treatment of gliomas, it has been found that MGMT promoter methylation is a useful predictor of the responsiveness to alkylating agents such as temozolomide [142]. Perhaps of more relevance is that CHFR methylation predisposes cancer to increased sensitivity to taxanes which may be a useful line of investigation as TPF induction chemotherapy gains ground in HNSCC [143]. Epigenetic alterations are particularly interesting as characteristics of cancer as they can potentially be reversed in drug treatment. A great number of epigenetically directed drugs are now entering clinical trials, particularly in the field of haematological malignancy. Demethylation agents such as 5-azacytidine and decitabine are now licenced for the treatment of myelodysplasia. The use of histone deacetylase inhibitors as single agents has limited usefulness but shows promise in combination with demethylating agents. The emergence of drug-resistant clones accompanying loss of DNA mismatch repair with MLH1 hypermethylation has been identified as a frequent issue in treatment failure in ovarian cancer. At least in vitro, this has been addressed by combination therapy with both demethylating agents and standard chemotherapy [144]. Clearly this field is in its infancy, and provided that epigenetic therapy can be administered with acceptable toxicity, methylation assays are readily available to demonstrate adequate pharmacodynamic effects.

More recently, a serendipitous epidemiological association has been made between the use of the HDAC inhibitor and epileptic agent sodium valproate and a reduction in the risk of HNSCC by about one third [145]. Although the mechanism of this protective effect is as yet unproven, this may be through epigenetic reprogramming, which has been seen in other cancers and in in vitro preclinical models with valproate. This finding opens the door to studies investigating epigenetic modifiers, possibly as long-term but non-toxic-repurposed drugs, being used to prevent transformation in high-risk populations such as those with oral epithelial dysplasia or previous history of HNSCC.

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Immunology of Head and Neck Cancer

6

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Abstract

The immune system plays a key role in the development, establishment, and progression of head and neck cancer. A greater understanding of the dysregulation and evasion of the immune system in the evolution and progression of head and neck cancers provides the basis for improved therapies and outcomes for patients. Head and neck cancer evades the host's immune system on different levels: (1) manipulation of its own immunogenicity, (2) production of immunosuppressive molecules, and (3) promotion of immunomodulatory cell types. Through the tumor's influence on the microenvironment, the immune system can be exploited to promote metastasis, angiogenesis, and growth. In this chapter, we review basic immunology as it relates to head and neck cancer and discuss the theory of cancer immunosurveillance and immune escape. A brief overview to key components in the tumor microenvironment is provided. Current research on cytokines as biomarkers, cancer stem cells, tumor antigens, and immunotherapeutic strategies is presented.

Keywords

Immunology • Immunotherapy • Head and neck cancer • Biomarkers • Immune evasion • Immune surveillance • Monoclonal antibodies

6.1 Introduction

The immune system plays a key role in the development, establishment, and progression of head and neck cancer. A greater understanding of the important contribution of the dysregulation and evasion of the immune system in the development and evolution of head and neck cancers should lead to improved therapies and outcomes for patients. Head and neck cancer evades the host's immune system on different levels: (1) manipulation of its own immunogenicity, (2) production of immunosuppressive molecules, and (3) promotion of immunomodulatory cell types. Through the tumor's influence on the microenvironment, the immune system can be exploited to promote metastasis, angiogenesis, and growth. In this chapter, we review basic immunology as it relates to head and neck cancer and discuss the theory of cancer immunosurveillance and immune escape.

There has been a recent renaissance in the idea that nascent cancer cells are destroyed by the immune system before tumor formation can occur (termed immune surveillance). Derangements in the immune system or alterations in the transformed cells may allow immune escape that enables the cancer to become manifest. In the progress, the tumor interacts with the immune system in manifold ways: transcription factors such as NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells) and STAT3 (signal transducers and activators of transcription), which are usually deregulated in tumor-promoting inflammatory states in

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response to cytokine stimuli, are aberrantly activated in tumor cells and are intensively studied as possible targets for therapeutic intervention. Tumors themselves produce cytokines such as transforming growth factor-beta (TGF-β), interleukin (IL)-6, and IL-10, which suppress cell-mediated antitumor immunity. In response to inflammatory stimuli, head and neck cancer cells also can express ligands which are involved in lymphocyte and dendritic cell migration. Expression of these ligands by tumor cells, such as CCR7 and CXCR4, constitutes immune exploitation of established signals intended for immune cells and has been associated with tumor invasion, metastasis, and cell survival, leading to treatment resistance. Another recently espoused theory is the idea that tumors are comprised of a heterogeneous cell population in the tumor microenvironment that includes a special subpopulation of cancer stem cells (CSC) that are able to recreate the entire tumor phenotype and potentially evade immune recognition. These cells appear to be more resistant to conventional chemotherapy and radiation and may not possess the same tumor antigen expression or T cell recognition as non-CSC.

In head and neck cancer patients, there appear to be global alterations in the functional state of the immune system, as evidenced by changes in serum cytokines, chemokines, and other immune-related biomarkers. We discuss investigations on the identification of serum biomarkers to monitor cancer progression, prognosis, treatment response, and relapse. Finally various immunotherapeutic strategies designed to utilize the immune system to stimulate elimination of cancer are described. These include cancer vaccines using tumor peptide antigens or viral, bacterial, and DNA-based vectors—as well as tumor antigen-specific monoclonal antibodies (mAb). The recent clinical efficacy of these FDA-approved mAb, including cetuximab (anti-EGFR) and bevacizumab (anti-VEGF), has stimulated research of immunological mechanisms that enhance antitumor activity.

6.2 Brief Overview of the Immune System

The immune system has traditionally been divided into two major arms: innate and adaptive immunity. This dichotomy is somewhat artificial since there is tremendous interaction between the two components. Innate immunity refers to the part of the immune system that provides antigen nonspecific, first-line protection. The effectors of innate immunity include natural killer (NK) cells, neutrophils, macrophages, dendritic cells (DC), and monocytes that attack/ingest extracellular debris or pathogens. Innate immunity also utilizes pattern recognition systems that recognize molecules that are not normally present in the human body: double-stranded RNA, bacterial cell wall components, lipopolysaccharides, and microbial membranes. These pattern recognition systems can be represented by enzymes like lysozyme, antimicrobial peptides (defensins), soluble factors (complement, C-reactive protein, mannose-binding lectin), and cell surface receptors (Toll-like receptors, scavenger receptors). Innate immunity is more static and nonspecific, showing less adaptation in magnitude or efficacy after repeated exposure to antigenic challenges. However, innate immune signals effectively trigger the adaptive immune system. DC and other antigen-presenting cells link the two systems. They ingest and process tumor antigens, after effectors of innate immunity have destroyed the tumor cell. DC then present these antigens to cytolytic and helper T lymphocytes, causing clonal expansion of antigen-specific T cells. Activation of the adaptive immune system (T lymphocytes) provides immunologic memory responses against these antigens. Thus, key effectors in tumor immunology are B cells, T cells, NK cells, and DC.

6.3 B Lymphocytes

Early in the field of immunology, humoral immunity was believed to be the primary effector mechanism; in 1948 plasma cells were identified as the source of antibodies. Plasma cells are one of the two endpoints for B cells, the other being the memory B cell. B cells can be activated via T cell-dependent or T cell-independent antigens. Tumor antigens are T cell-dependent antigens which require binding of the antigen to the B cell receptor and a secondary activation signal via CD40 on an activated helper T cell. It is well established that B cells in cancer patients are capable of recognizing and producing antibodies to tumor antigens [1, 2]. In head and neck cancer, circulating serum antibodies have been found against p53 [3], MUC1 [4], p40 [5], p73 [6], and HPV E6 and E7 [7]. However, levels of circulating antibody have not been correlated with clinical outcome other than high postoperative levels of anti-p53 antibody which have been correlated with poor prognosis [8]. Interestingly, it has been noted that there is an increased frequency of immunoglobulin (Ig) E subtype in head and neck cancer [2, 9]. The significance of this finding, if any, is unclear.

6.4 T Lymphocytes

T lymphocytes were defined in the early 1960s when mice were thymectomized in an attempt to prevent lymphoma. When the initial experiments in adult mice failed to have any effect, neonatal thymectomized mice were found to have profoundly decreased lymphocyte numbers and were unable to generate antibodies despite having plasma cells. Based on these data, Miller theorized that the thymus must be the source of a "helper" cell that is required to produce antibody

[10–12]. In later experiments, CD8 T cells were identified as a primary effector of specific tumor/allograft rejection.

T lymphocytes are defined by the presence of T cell receptors (TCR) on their cell surface. TCR are part of the immunoglobulin superfamily and undergo germline DNA rearrangement to produce diversity much like immunoglobulin genes in B cells. TCR recognize tumor antigens which are short peptide fragments bound to or "presented by" major histocompatibility complexes (MHC). There are two main classes of MHC: MHC I molecules, found on the cell surface of all nucleated cells, and MHC II, found only on professional antigen-presenting cells such as macrophages and dendritic cells. MHC class I and II bind with peptides, which are derived from (tumor) proteins and "processed" within the cell. Hereafter, MHC molecules present these (tumor) peptides on the cell surface for recognition by T cells. The TCR can only recognize peptide antigens when presented by a particular self-MHC molecule, a phenomenon known as MHC restriction, which led to the Nobel Prize in 1996 to Doherty and Zinkernagel. Therefore, CD8 T cells can recognize syngeneic (self) but not allogeneic (from someone else) tumor cells. MHC I binding tumor peptides are usually 8–10 amino acids in length, are derived from endogenous proteins processed via the proteasome, and are presented to CD8 T cells [13]. MHC II peptides are longer (11–16 amino acids), are derived from exogenous proteins taken in by endocytosis, and are presented to CD4 T cells.

T lymphocytes are generally divided into $CD4^+$ or $CD8^+$ T cells. While it remains unclear how T cells are selected to become CD4 or CD8 cells, there are usually twice as many CD4 T cells as CD8 T cells released. Once antigen is encountered along with the appropriate costimulatory signals, T cells become activated and differentiated. CD4 T helper (T_H) cells usually differentiate into one of two major subclasses, T_H1 and T_H2. This differentiation depends on the cytokine milieu in the environment at the time of activation. These two subsets of CD4 cells are differentiated by function and cytokine secretion profile. The T_H1 subset is responsible for most cell-mediated immune functions such as activation of CD8 T cells, inflammation and delayed-type hypersensitivity, as well as production of complement-activating IgG antibodies. Macrophages or dendritic cells will produce IL-12 in response to intracellular pathogens. IL-12 along with interferon-gamma (IFN-γ) and IL-18 drive the T_H1 response. T_H1 cells secrete IL-2, IFN-γ, and tumor necrosis factor (TNF)-α and are considered to be the strongest antitumor subtype.

On the other hand, IL-4 drives a T_H2 response [14]. The T_H2 response stimulates B cells to produce IgM, IgE, and non-complement-activating IgG, as well as activating eosinophils, in response to parasitic invasion. T_H2 T cells are strongly implicated in allergy and are considered to be tumor permissive. T_H2 cells secrete granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-3, IL-4, IL-5, IL-10, and IL-13. More recently, other subsets of CD4 T cells have been identified. T_H17 cells require TGF-β and IL-6 for differentiation and are defined by their production of IL-17. IL-17 is known to induce the production of several chemokines that attract proinflammatory cells, and IL-17 expression is greatly increased in autoimmune diseases [15]. The final subset of CD4 T cells is the regulatory T cell (Treg) that was originally defined as a $CD4^+CD25^+$Foxp3 (Forkhead box P3)$^+$ T cell. Tregs are thought to be a reciprocal subtype to T_H17 cells in that both are induced by TGF-β, but Tregs are immunosuppressive as opposed to T_H17 cells which are proinflammatory. Tregs have recently been strongly correlated with disease status in SCCHN patients [16, 17].

6.5 Natural Killer Cells

NK cells were discovered in 1975 when experiments studying tumor lysis by lymphocytes from immunized animals found lysis that was independent of previous immunization or activation [18]. This was thought to be an artifact until the NK cell was isolated and given the name "natural killer" cell for its ability to kill tumors without previous activation. NK cells kill much in the same way as cytotoxic T cells, through the interaction Fas ligand on their surface with Fas on target cells inducing apoptotic cell death. They also constitutively possess perforin and granzyme granules and degranulate causing cytolysis. Unlike T cells that are self-MHC restricted and require self-MHC for activation, NK cells can be suppressed by the presence of self-MHC via killer cell immunoglobulin-like receptors (KIR) that can inhibit NK killing when bound by self-MHC [19]. These inhibitory signals dominate functional responses as to activating receptors, and therefore, presentation of self-MHC on the target's surface is protective. Activation receptors on the NK cell include NKD2D and FcγIII receptor. NKD2D binds ligands produced by cells stressed by DNA damage or infection. FcγIII receptor is a high affinity receptor for IgG which provides a mechanism by which NK cells can recognize targets bound by antibody. Activating Fcγ receptors mediate antibody-dependent cell-mediated cytotoxicity (ADCC) by NK cells, macrophages, monocytes, neutrophils, and eosinophils.

6.6 Dendritic Cells

DC are antigen-presenting cells and as such are potent initiators of the immune response. They use several mechanisms for efficient antigen uptake, including phagocytosis, macropinocytosis, and adsorptive endocytosis. After uptake, antigen is shunted into lysosomes and degraded for presentation on MHC II. DC also possess B7 molecules on their

surface that provide a necessary secondary activation signal to T cells after engagement of the MHC-peptide complex with the TCR. Because DC are such potent activators of T cells and initiators of adaptive immunity, they have been intensely studied as a possible therapeutic for cancer immunotherapy.

Another important process mediated by DC is cross-presentation of antigen derived from tumor cells or shed tumor products/vesicles. Exogenous antigen is processed via the exogenous pathway and presented to CD4 cells by DC via MHC II. However, DC are able to move exogenous antigen to the endogenous pathway and present these antigen to CD8 cells via MHC I. This surrogate presentation of exogenous antigen to the endogenous pathway is defined as cross-presentation. Cross-presentation serves a very important function because it allows DC to activate cytotoxic T cells against virally infected cells and tumor cells and has recently been harnessed in cancer vaccine trials.

6.7 Cancer Immunosurveillance and Immunoediting

The idea of immune control of malignant cells was first proposed by Paul Ehrlich in 1908, but it was not until the 1950s that greater understanding of the immune system gave rise to a formalized hypothesis. This "cancer immunosurveillance" hypothesis was introduced by Burnet and Thomas and stated that tumor cells must have recognizably different antigens than normal cells and therefore have the potential for immune clearance. Also at that time, the phenomenon of allograft rejection via cellular immunity was observed. Because grafting of allogeneic tissue is not a naturally occurring event, Thomas proposed that the actual primary function of cellular immunity was not to protect against allografts but rather to protect against tumors. Conflicting experimental results led many to abandon the idea of cancer immunosurveillance for several decades, until several key discoveries have led to a revival of the hypothesis. First was the discovery of the NK cell in the late 1970s which seemed to provide innate immune protection from tumor [20]. The discovery of IFN-γ and its proapoptotic effect on tumor growth gave additional support to the potential for immune clearance of cancer cells [21]. Mice lacking IFN-γ receptors produced more tumors with decreased latency after methylcholanthrene challenge, and addition of IFN-γ was protective against transplanted, spontaneous, and induced tumors in another experiment. Studies in mice lacking perforin, a key component of cytolytic granules in T cells and NK cells, recapitulated the results in IFN-γ receptor knockout mice with more frequent tumors and lower latency of formation [22]. Mice with genetically induced immunodeficiency were found to be more susceptible to both spontaneous and chemically induced tumors. In humans, epidemiologic data from AIDS patients demonstrate increased risk of lymphoma, Kaposi's sarcoma, and virally induced carcinomas of the genitourinary tract. There also appears to be a higher risk of HPV-associated HNC in HIV+ patients [23]. These data confirm the unchallenged idea that immune protection from viral infections reduces risks of cancer associated with viruses.

But what about tumors without viral etiology? Data gathered from transplant patients who are immunosuppressed to avoid organ rejection demonstrate increased risk of many tumors with no known viral etiology such as lung, head and neck [24], pancreatic, endocrine, and colon cancer and melanoma [25]. The cancer immunosurveillance hypothesis has given rise to the theory of cancer immunoediting which represents the idea that immune surveillance of cancers provides selective pressure on tumor cells and negatively selects for cells that can evade the immune system. One study showed that many tumors grown in immunocompromised mice are rapidly cleared when injected into immunocompetent mice, whereas cancers from immunocompetent mice continue to grow when transplanted into other immunocompetent mice, indicating a qualitative difference in the cancer cells that was dependent on the immune environment [26]. The theory contends that successful tumor formation can occur only after the cancer has discovered a means by which it can evade the immune system.

6.8 Immune Escape and Immunosuppression in Head and Neck Cancer

In order to establish effective immunotherapies, it is of utmost importance to understand the different pathways of the tumor's scopes for immunoevasion. Two primary evasion means are distinguished: firstly, the cancer cells' ability to reduce their innate immunogenicity and, secondly, their suppression of the immune response (Fig. 6.1). To date, various mechanisms through which the tumor cells achieve this immunoevasion have been identified, partly depending on the tumor's characteristics (e.g., site, differentiation, and host). A key component for the immune system's recognition of different or altered cells is the human leukocyte antigen (HLA) system. The HLA system is the human display of the MHC classes. As previously described, T cells interact with the MHC/HLA molecules. Tumor cells can reduce T cell-mediated recognition by altering HLA class I expression. It has been noted that some tumor cells have a complete loss of HLA expression due to defects in β_2-microglobulin expression or function. Alternatively, chromosomal defects in the HLA-encoding genes themselves can cause selective loss of HLA expression. This process has been noted in approximately 50 % of head and neck squamous cell carcinomas

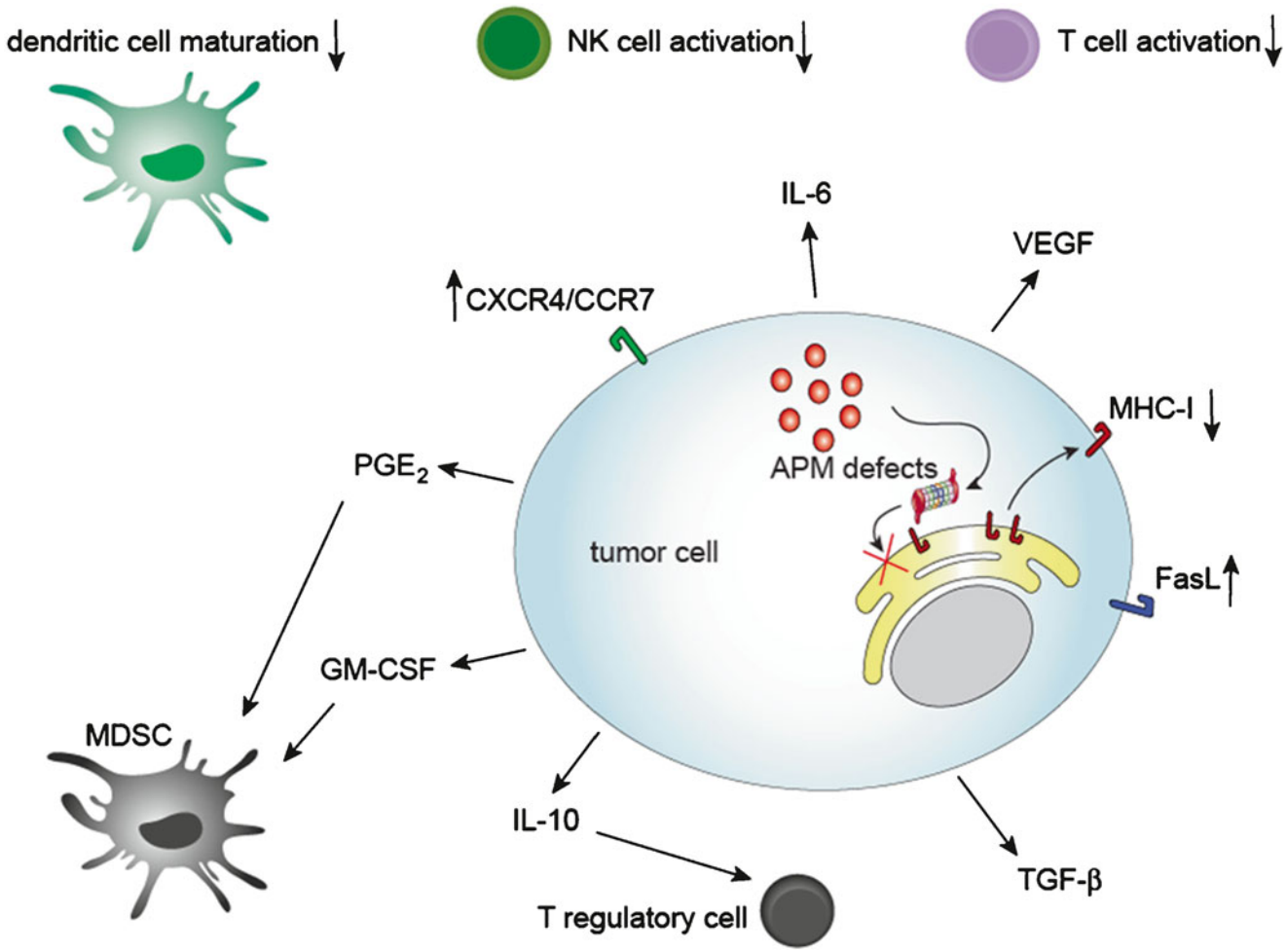

Fig. 6.1 Tumor cell immune evasion and exploitation. Tumor cells secrete several small molecules and cytokines that depress NK, DC, and T cell function and induce immunosuppressive MDSC and regulatory T cells. MHC downregulation and defects in the antigen presentation machinery impairs T cell recognition. Fas ligand is expressed which kills T cells. Chemokine receptors aid in metastasis of the cancer cell to lymph nodes

[27] and was correlated with poor prognosis in esophageal squamous cell cancer [28] and laryngeal squamous cell cancer [29].

On the other hand, cells with complete loss of HLA may evade immune response by T cell recognition but represent a strong trigger for NK cell activation as the absence of HLA removes a key inhibitory signal for NK cells. Therefore, tumor cells must employ multiple mechanisms to realize immunoevasion. One proposed explanation for the lack of NK cell killing is that cancer cells possess defects in their antigen presentation machinery (APM) for HLA molecules that are tumor antigen specific. Endogenous antigens are processed through the cytoplasmic immunoproteasome which consists of various subunits including low molecular weight proteasome (LMP) 2, LMP7, and LMP10. Antigenic peptides are transported to the endoplasmic reticulum by the transporter associated with antigen processing (TAP) where they are associated with HLA class I heavy chains by tapasin [30]. The observation that T cell recognition could be reconstituted with either exogenous peptide or upregulation of APM expression [31] confirms the biological significance of this immune escape mechanism. This reduces selectively tumor antigen-HLA peptide completely without reduction in overall surface HLA density. Thus, SCCHN cells that express HLA I and whole tumor antigen can evade T cell recognition through decreased expression of LMP2, TAP1, TAP2, and tapasin but still maintain nonspecific HLA I expression in order to avoid recognition by NK cells.

In addition to altered expression of HLA, SCCHN tumor cells express Fas ligand which can interact with Fas and transduce a powerful apoptosis signal to activated T cells allowing immune evasion [32] by eliminating tumor-infiltrating T lymphocytes.

Another important group of molecules that emerged in the focus of research is the group of immune checkpoint receptors (ICR). Being part of the immune system's control mechanisms against overreactive functions in inflammatory response and thus limiting autoimmunity, this mechanism is exploited in the tumor microenvironment. Several receptors have been identified that are expressed on exhausted cells

and/or show inhibitory regulation upon stimulation, including cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), lymphocyte activation gene-3 (LAG-3), T cell immunoglobulin and mucin protein-3 (TIM-3), B and T cell lymphocyte attenuator (BTLA), and programmed death-1 (PD-1). Its ligand PD-L1 (B7-H1, CD274) induces a loss of function of cytotoxic T cells (CTL) [33]; PD-L1 is upregulated in multiple tumor cell lines including HNSCC [34]. CTLA-4 is a member of the B7 receptor family expressed by $CD4^+$, $CD8^+$, and regulatory T cells (Treg) [17], which competes with CD28 to stimulatory ligands CD80 and CD86. LAG-3 is another receptor that was shown to enhance Treg function [35]. If TIM-3 is rather a marker or a mediator for immunosuppression is still investigated, studies correlated TIM-3 expression levels with poor clinical outcome [36]. BTLA and its ligand herpesvirus entry mediator (HVEM) are receptors from the immunoglobulin superfamily and were first receptors that demonstrated cross talk between TNF and Ig ligands [37]. It is mainly expressed on B lymphocytes and can induce inhibitory and stimulatory pathways depending on its ligands, although the inhibitory function was shown to be the dominant pathway in knockout mice [38].

As described, these pathways play an important role in tumor immune escape. In the recent years, tremendous advances in the understanding of these described mechanisms have been made, allowing further establishment of immunotherapies that we will outline at the end of this chapter.

6.9 The Establishment of a Cancer-Promoting Tumor Microenvironment

We discussed pathways for the reduction of immune response in direct cell-to-cell contact between tumor cells and two of the main effector cells, T and NK cells. But the points of action through which the tumor cells generate a tumor-promoting environment are much more versatile. They include and are realized through direct (tumor cells) and indirect (induced) cytokine secretion. Many of the cytokines play an important role in cancer formation and can be localized in the setting of chronic inflammation. The fact that some cancers arise at sites of chronic inflammation was first noted by Virchow over a century ago. Since then, chronic inflammatory states have been linked to a myriad of tumors: *Helicobacter pylori* infection and gastric cancer, inflammatory bowel disease and colon cancer, chronic irritation of the aerodigestive tract by tobacco/alcohol, and SCCHN. Studies of the tumor microenvironment demonstrate infiltration of inflammatory mediators and a complex milieu of cytokines including TGF-β, IL-6, IL-10, GM-CSF, IL-1β, IL-23, and TNF-α as well as chemokines, which are "chemotactic cytokines" that direct immune cell migration. More recent developments link many of those cytokines to the formation of suppressive immune cells like myeloid-derived suppressive cells (MDSC), regulatory T cells (Treg), tumor-associated macrophages (TAM), and their effectors, which are exploited and promoted by the tumor microenvironment.

6.10 Cytokines

Cytokines and other molecules that suppress immune function such as IL-10, TGF-β, IL-6, PGE_2, VEGF, and GM-CSF are known to be produced by SCCHN cells. IL-10 reduces activation of cytotoxic T cells and has been correlated with advanced stage head and neck cancer [39]. TGF-β suppresses T cell and NK activation and is a key cytokine in the differentiation of regulator T cells [40]. TGF-β production is increased in preneoplastic oral cavity lesions and promotes angiogenesis and a protumorigenic microenvironment linking it to early tumor formation [41]. IL-6 signals via STAT3 to inhibit DC maturation, NK cell, T cell, neutrophil, and macrophage activation [42] and has been correlated with recurrence and survival in SCCHN [43]. Reduced DC numbers and function have been observed in this disease [44]. STAT3 is a transcription factor that is also involved in several other immunosuppressive pathways such as IL-10 signaling [45], suppression of dendritic cells [46], downregulation of IL-12 [47], and generation of regulatory T cells [48]. PGE_2 is a prosurvival, proangiogenic molecule that is produced by many cancers including SCCHN [49, 50]. It is also a potent immunomodulator that decreases T cell proliferation, inhibits Th1 T cells, decreases B cell proliferation, and inhibits maturation and antigen presentation of DC [51]. VEGF, which is primarily thought of as a promoter of angiogenesis, is overexpressed in 90 % of SCCHN [52] and functions to increase the ratio of immature to mature DC in the tumor microenvironment which is thought to lead to T cell anergy [53]. GM-CSF, when produced in large quantities by tumors, recruit MDSC [54, 55] which have been identified in SCCHN.

6.11 Chemokines

Chemokines are a family of small heparin-binding cytokines that direct the movement and migration of leukocytes. There are four groups of chemokines based on the arrangement of cysteine residues near the N-terminus of the proteins: C, CC, CXC, and CX3C. The G-coupled transmembrane chemokine receptors are also divided into these four groups based on their cognate ligand [56]. SCCHN cells have aberrant expression of several chemokines. They overexpress CXCL1 which has been implicated in tumor angiogenesis, nodal metastasis, and leukocyte infiltration. CCL2 is also overexpressed in squamous cell cancer and is thought to have similar functions. CXCL5 is found in metastatic SCCHN and is involved in tumor migration and tumorigenesis. CXCL8, also found in metastatic SCCHN, promotes matrix metalloprotease

secretion and subsequent extracellular matrix breakdown and tissue invasion.

Of the chemokine receptors, CXCR4 and CCR7 are of particular interest as these two receptors are overexpressed in malignant cells including SCCHN cells. Increased expression of CXCR4 and its ligand, CXCL12, is associated in SCCHN cells with nodal metastasis, tumor recurrence, and overall survival. Studies of CXCR4 activation have shown increased metastatic potential, induction of matrix metalloprotease and collagenase expression, decreased cell adhesion, and increased cell mobility. CCR7 appears to have similar biological actions. High CCR7 expression is clinically associated with tumor stage, lymphatic invasion, nodal metastasis, and poorer prognosis [57]. A study of chemokine receptor expression differences between primary and metastatic SCCHN cell lines found that only CCR7 was consistently upregulated in metastatic SCCHN [58]. CCR7 also provides tumor survival and invasion signals via the PI3 kinase signal transduction pathway [59]. These actions in tumor cells are similar to the action of CCR7 in dendritic and $CD8^+$ cells where they mediate chemotaxis to lymph nodes and antiapoptotic signals and may explain the predilection of SCCHN to metastasize to lymph nodes where there is a high concentration of chemokines. The production of chemokines and their receptors by SCCHN tumor cells represents exploitation of the immune system to promote tumor survival and metastasis.

A key regulator of the inflammatory response in cancer is the transcription factor NFκB [60] which stimulates many cancer-promoting cytokines and chemokines in SCCHN [61]. NFκB sits downstream of several soluble factors including TNF-α, IL-1, and reactive oxygen species that are produced by macrophages and granulocytes that infiltrate tumor. Of interest in relation to SCCHN, NFκB activation can also be elicited by cigarette smoke condensate, betel nut extract, and EGFR signaling [62–64]. Activation of the NFκB pathway induces several tumor-promoting processes in SCCHN [65]. NFκB is traditionally thought of as a stress response transcription factor because it controls expression of several prosurvival genes such as mdm2, TRAF1, TRAF2, IAP, and Bcl-XL. These act as antiapoptotic signals for tumor cells and confer resistance to natural death pathways for aberrant cells. NFκB also promotes tumor cell proliferation and expansion through regulation of a key cell cycle modulator, cyclin D1. Angiogenesis is promoted by NFκB through VEGF production, and several cytokines including TNF-α, IL-1, IL-6, and IL-8 are induced causing a positive feedback loop. Tissue invasion is promoted by the upregulation of heparinase, matrix metalloprotease, and urokinase. It has also been suggested that NFκB mediates resistance to treatment with chemotherapy and radiation via regulation of growth arrest and DNA damage (GADD) and glutathione S-transferase [66]. The activation of NFκB by inflammatory immune mediators demonstrates yet another subversion and exploitation of the immune system by cancer to promote key aspects of tumor formation and progression.

6.12 Immune Mediators as Cancer Biomarkers

Because of the derangements in production of cytokines and other immunomodulatory molecules caused by cancer, there has been investigation into the possibility of using cytokine profiles as biomarkers. Biomarkers are of considerable interest because they could be useful in early detection of cancer, determination of prognosis, as a marker of treatment response, and selection of optimal treatment regimen. Cytokines as biomarkers have been investigated in SCCHN in several studies. An older study found that serum TNF-α was 100-fold higher in cancer patients than in disease-free controls [67]. A subsequent study linking serum TNF-α levels to cancer status was published, but that paper found IL-6 to be a more sensitive marker than TNF-α [68]. Another cytokine commonly cited in papers as a possible biomarker for detection of tumor is IL-8 which is elevated in recurrent or metastatic cancer [69]. In a study of over 300 subjects encompassing those with active disease, no evidence of disease and healthy smokers, 60 cytokines were measured and a panel of 25 including IL-8, IFN-α, IFN-γ, IL-1, and RANTES could correctly identify active disease with a sensitivity of 84.5 % and a specificity of 92 % [70]. This provided a proof of principle that the immune system may serve as a biosensor of malignancy and disease status. In another study, IL-6, IL-8, VEGF, and hepatocyte growth factor were elevated in cancer patients and decreases over treatment correlated with improved survival. Interestingly, elevated pretreatment VEGF was a good prognostic factor [71]. This is in contrast to a study in non-small cell lung cancer [72] and head and neck cancer (ASCO 2009 A6035) which demonstrated low pretreatment VEGF as a predictor of better treatment response and longer progression-free survival. A large study of 444 patients found that high pretreatment IL-6 is an independent predictor of poor prognosis [43].

6.13 Key Components of the Tumor Microenvironment: Myeloid-Derived Suppressor Cells, Regulatory T Cells, Tumor-Associated Macrophages, and Cancer Stem Cells

Myeloid-derived suppressor cells (MDSC) are a diverse family of myeloid origin with T cell suppressive functions that express surface molecules such as $Gr1^+$(murine) $CD11b^+$, $CD33^+$, and $CD34^+$ [73]. They are increased in almost all cancer patients and, indeed, were first characterized in SCCHN [55] where their link to VEGF and GM-CSF was

discovered. In addition to VEGF and GM-CSF, MDSC are induced by IL-6, IL-1β, PGE_2, and complement C5a. Initial studies in SCCHN found that MDSC inhibit IL-2 secretion by activated T cells which is a key step in T cell proliferation and escalation of cell-mediated immunity. Also, they deplete the tumor microenvironment of arginine and cysteine which are essential for T cell activation. MDSC produce nitric oxide and reactive oxygen species that catalyze the nitration of the TCR which inhibits TCR-MHC interactions and subsequent activation. Downregulation of the TCR ζ chain which also interferes with T cell activation is mediated by MDSC along [74] with downregulation of L-selectin which is important for migration of naïve T cells to lymph nodes. Data on the effect of MDSC on NK cells has been conflicting with reports of both enhancing as well as suppressive action on NK cells which may be a function of the heterogeneity of MDSC populations. MDSC also promote induction of Tregs via production of IL-10, TGF-β, and arginase [73]. Treatments such as antibody depletion, retinoic acid, gemcitabine, and STAT3 blockade diminish MDSC, restore immune surveillance, increase T cell activation, and improve efficacy of immunotherapy. The basal levels of MSDC increase with age and may contribute to increased tumor frequency and growth rate increase with age [75].

Though it was long suspected that a subset of T cells was immunosuppressive, the characterization occurred relatively recently when it was found that this subpopulation represented $CD4^+$ cells that also expressed CD25 [76]. So far, four subtypes of regulatory T cells have been identified: naturally occurring thymus-derived $CD4^+CD25^{high}FoxP3^+$Tregs, antigen-induced IL-10-dependent Tregs (Tr1), IL-4-dependent Tregs (Th3), and antigen-specific Tregs [16]. There is also a $CD8^+CD25^+$ variant which also appears to have immunosuppressive ability, but their biological significance is unclear and they are thought to be overshadowed by the much more abundant $CD4^+$ Tregs [77]. Tregs cause anergy, apoptosis, and cell cycle arrest of activated T cells via production of IL-10, TGF-β, and direct cell-to-cell contact [78]. They also inhibit the action of dendritic cells, NK cells, and B cells [79]. In SCCHN patients, Tregs are increased in frequency in peripheral blood and among T cells infiltrating the tumor and draining lymph nodes resulting in an immunosuppressed state [17, 80, 81]. Also, Treg numbers are inversely proportional to DC and $CD8^+$ T cell numbers in SCCHN [82, 83]. Treg frequency as a prognostic indicator is unclear as one study linked increased Tregs with better locoregional control [84] while another study found increased Tregs associated with early recurrence [85]. Additionally, Treg frequency is elevated in SCCHN patients after treatment, indicating that oncologic treatment increases Treg numbers [17].

A different cellular component in the tumor microenvironment is represented by macrophages. They can engage different phenotypic functions depending on environmental conditions. Two main subsets are distinguished. On the one hand, the M1 phenotype is being activated by IFNγ and Toll-like receptors (TLR), producing proinflammatory cytokines such as TNF-α with a T cell-stimulating effect resolving in a T_{H1} response. On the other hand, the alternatively activated macrophages (M2) force a T_{H2} response, with production of interleukins such as IL-4 and IL-13. Obviously, there is no black and white in a plastic cell population such as the macrophages, but there have been several studies linking the number of TAM in tumor to a worse clinical outcome and characterizing their phenotype closely associated to the M2 population. TAMs have been demonstrated to produce EGF, IL-6, and IL-10 and have been associated with angiogenesis, local tumor progression, and metastasis [86].

Additionally to these immunosuppressive cell types with origin from the immune system, a hypothesis about treatment-resistant and adoptive tumor cells—so-called cancer stem cells—that provide another challenge is being investigated. Recently, there has been growing interest in the cancer stem cell hypothesis. Heterogeneity in tumor cells has long been accepted, and this theory postulates the existence of a subpopulation of tumor cells that are pluripotent and able to effectively recapitulate the entire heterogeneous tumor when transferred to another site. They are known to be more resistant than other tumor cells to chemotherapy as well as radiation [87]. Several defining markers of these stem cells have been proposed. The first marker proposed was CD44 [88], a cell surface glycoprotein which binds hyaluronate but may also inhibit the action of the p53 tumor suppressor in cancer cells [89]. However, CD44 expression is abundant in normal epithelia, and its utility as a cancer stem cell marker is questionable [90]. Another proposed marker is aldehyde dehydrogenase 1 (ALDH1) which is found in many embryonic stem cells and was identified as the responsible protein in conferring resistance to chemotherapeutic agents in stem cells [91]. Because these cancer stem cells are able to reconstitute the entire tumor, many believe that, ultimately, it is treatment of this small population of resistant cells that determines the success or failure of oncologic therapy. If this is the case, it is important that these cells be addressed in any treatment regimen. Because ALDH1 is not highly expressed in normal tissues, its potential as a tumor antigen target has been recently explored [92].

These data indicate that SCCHN induces an immunosuppressed state via multiple potent mechanisms which is a barrier to effective cancer immunotherapy. They secrete immunosuppressive cytokines and molecules. Cytokine levels are aberrant in SCCHN patients indicating deregulation or dysregulation of cytokine pathways [93]. There is increased frequency of immunosuppressive regulatory immune cells, and there is a global dysfunction of almost every facet of the immune system in SCCHN patients.

6.14 Head and Neck Cancer Immunotherapy

As described, the tumor's interactions with the immune system and the evasion strategies are manifold. Therefore, therapeutic approaches have to be versatile as well. They include vaccination therapies and monoclonal antibody (mAb)-based therapies for multiple, different targets. Playing a central role in immunology, vaccination approaches for tumor therapy have been developed in the past years.

There are several strategies for delivering tumor vaccines with each having inherent advantages and disadvantages. All methods depend on delivering an antigen to the host in an effort to elicit an adaptive cellular immune response to the tumor antigen. Most methods require the use of a specific known tumor antigen, but some can use entire tumor cells as part of the vaccine to activate the immune system against multiple unspecified and unknown tumor antigens.

DNA vaccines utilize delivery of naked DNA encoding a known tumor antigen to the patient. This DNA is taken up by cells, and the antigen is expressed for subsequent processing and presentation by DC. DNA vaccines are safe, inexpensive, and easy to deliver and do not induce the formation of neutralizing antibodies allowing repeated administration. However, they have low transfection efficiency and elicit a very weak immune response and therefore are often engineered to encode proteins that target DC or are given with adjuvant agents that increase DC activation. Currently in SCCHN, a DNA vaccine encoding an HPV-16 E6/E7 fusion protein is under development for HPV-positive SCCHN [94], and another vaccine encoding Hsp65 has been tested in a phase I trial [95] and demonstrated clinical response in 4 out of 14 patients with recurrent unresectable SCCHN.

Bacterial/viral vaccines can deliver tumor antigen and function as an immune adjuvant because the immune system responds to a perceived infection. They are very immunogenic, relatively inexpensive, and easy to manufacture but have the downsides of potential toxicity, preexisting neutralizing antibodies, or the formation of antibodies against the bacterial or viral vector limiting repeat dosing or effectiveness. Also, these tend to elicit a stronger humoral rather than cellular immune response which is less desirable. Several such vaccines are currently under development: HPV-16 E7 Listeria vaccine [96], Vaccinia-based E6/E7 vaccine [97], and a Vaccinia-based E2 [98].

Peptide vaccines consist of synthesized peptides that have been designed to correspond to an epitope on a tumor antigen that binds well to the cleft of an HLA molecule. They are similar to DNA vaccines in that they are safe and inexpensive with low immunogenicity but have the added drawback of being restricted to the HLA subclass for which they were designed. The popular HLA subclass used in vaccine design is HLA-A2 as this is the most common subclass found in Caucasians. Clinical trials are under way with a MAGE-A3/HPV-16 peptide (NCT00257738) and an LMP2 peptide for EBV-related nasopharyngeal carcinoma (NCT00078494).

To circumvent HLA restriction, whole proteins can be used as a vaccine. Whole proteins can be processed by the antigen-presenting cells and presented on self-MHC to cause activation of T cells. However, the vast majority of identified tumor antigen proteins are self-proteins, and therefore, the patient's immune system is tolerant to these proteins. Therefore, there is tremendous difficulty in producing an effective immune response with protein vaccines.

Tumor cell vaccines are similar to whole protein vaccines in that they are not HLA restricted and specific epitopes need not be known for their use. Often the tumor cells are given with adjuvant agents or modified by viral infection to improve their immunogenicity. A Newcastle disease virus-infected tumor cell vaccine was found to induce a specific T cell response and [99] that correlated with better clinical outcome. These vaccines tend to be labor intensive because the tumor has to be isolated and processed before it can be used as a vaccine.

Dendritic cells are the most potent activators of antigen-specific T cells, and consequently, DC vaccines are the most widely studied cancer vaccine strategy. This is an extremely labor-intensive method in which dendritic cells are isolated from each patient and they are loaded with tumor antigen ex vivo. This loading can be in the form of peptides, proteins, DNA transfection, tumor cell lysates, apoptotic tumors, necrotic tumors, or cell fusion. After DC are loaded with tumor antigen, they undergo maturation and activation with various cytokine cocktails to prime them for presenting the tumor antigen to T cells. These DC are then introduced to the patients, usually into the tumor or into lymph nodes. Several DC-based vaccines are currently being developed for SCCHN: intratumoral injection of DC (NCT00492947), multivalent p53 DC vaccine [100], and lysyl oxidase-like-4 transfected DC [101]. Efforts to reverse the immunosuppression associated with cancer include stimulating cocktails of multiple cytokines delivered systemically to improve immune competence.

Besides cytokines, different drugs imply a strong stimulating potential for immunomodulation in anticancer therapy. A group that is investigated in clinical trials of HNSCC is the group of TLR agonists. TLR are pattern recognition receptors (PRR) that can recognize so-called pathogen-associated molecular patterns (PAMPs) from external pathogens such as viral RNA, bacterial DNA, or surface molecules. Therefore, they are closely associated to the innate immune response and stimulate upon activation various parts of the immune system, notably cells from myeloid origin. This effect is utilized in anticancer therapy. TLR agonists induce the maturation and cross-priming of dendritic cells (DC) and have been shown to induce NK cell-dependent lysis of tumor

cells in combination with mAb such as antiepidermal growth factor receptor (EGFR) cetuximab [102]. Clinical trials of TLR agonists in combination with mAb are evolving and include HNSCC-specific trials like a neoadjuvant phase Ib trial (NCT02124850) or adjuvant trials in patients with locally advanced, recurrent, or metastatic HNSCC (NCT01836029, NCT01334177).

6.15 Monoclonal Antibody-Based Immunotherapy of SCCHN

Today the most widely used form of cancer immunotherapy is mAb therapy. Therein, the different targets are distinguished, aiming the previously discussed different mechanisms of tumor-promoting effects: Tumor antigen (TA)-targeted mAbs, cytokine-targeted mAbs, tumor necrosis factor receptor (TNFR)-family costimulatory targeted mAbs and immune checkpoint-targeted mAbs. Currently available mAbs that are circumstantially investigated in head and neck cancer are listed in Table 6.1. The most extensively studied of these is cetuximab, a mouse-human chimeric IgG1 antiepidermal growth factor receptor mAb [103]. EGFR is an attractive target in SCCHN because it is overexpressed in 80–90 % of SCCHN and leads to tumor cell proliferation, invasion, angiogenesis, tumor survival, and, consequently, poor survival and prognosis [104, 105].

It is becoming clear that anti-EGFR mAb mediate antigen-specific immune responses to targeted tumors (Fig. 6.2). There are two major mechanisms by which mAb can activate the immune system against a tumor target, direct killing via lytic immune cell (NK cell or monocytes) and complement fixation, or opsonization of tumor for phagocytosis and subsequent antigen processing. The latter would induce TA-specific cytotoxic T lymphocytes (CTL) to recognize and lyse tumor cells. One of the most direct methods by which antibodies can cause tumor lysis is via antibody-dependent cellular cytotoxicity (ADCC) mediated by NK cells and probably monocytes and neutrophils. Panitumumab and cetuximab both mediate ADCC [106], and the extent of ADCC is heavily influenced by genetic polymorphisms in FcγRIIIa, also known as CD16 [107]. Complement activation via the classical pathway is another major effector of humoral immunity and is activated by IgM, IgG1, IgG2, and IgG3. A combination of cetuximab and matuzumab can elicit complement-dependent cytotoxicity in vitro [108]. In addition to direct activation of NK cell lysis of tumor cells, TA-specific mAbs can elicit $CD8^+$ T cell responses to tumor-derived antigens through interaction with FcγRs on antigen-presenting cells (APC). In human cells, there are three activating FcγRs, FcγRI, FcγRIIa, and FcγRIII, and one inhibiting FcγR, FcγRIIB [109] with FcγRIIa being the dominant receptor on APC. This antigen-specific T cell activation was noted in 78 % of patients treated with trastuzumab for breast cancer,

Table 6.1 Trials of monoclonal antibodies in head and neck cancer

Drug (company)	Target	IgG subclass	HNSCC development
Tumor antigen-targeted monoclonal antibodies			
Cetuximab (Bristol-Myers Squibb, Eli Lilly)	EGFR antagonist	IgG1	Phase III/IV
Panitumumab (Amgen)	EGFR antagonist	IgG2	Phase II/III
AV-203 (Aveo)	HER3 antagonist	IgG1	Phase I (monotherapy; cetuximab combination)
Cixutumumab (Eli Lilly)	IGFR antagonist	IgG1	Phase 0–II (neoadjuvant monotherapy; cetuximab combination)
Cytokine-targeted monoclonal antibodies			
Bevacizumab (Genentech)	VEGF neutralizer	IgG1	Phase III (platinum chemotherapy +/−)
Ficlatuzumab (Aveo)	HGF neutralizer	IgG1	Phase I (cetuximab combination; cisplatin-radiation combination)
TNF receptor-targeted monoclonal antibodies			
OX40 mAb (AgonOx, Providence Health)	OX40 agonist	IgG2	Phase Ib
Urelumab (Bristol-Myers Squibb)	CD137 agonist	IgG4	Phase I
PF-05082566 (Pfizer)	CD137 agonist	IgG2	Phase I
Immune checkpoint-targeted monoclonal antibodies			
Ipilimumab (Bristol-Myers Squibb)	CTLA-4	IgG1	Phase I (cetuximab-radiation combination)
Tremelimumab (Pfizer)	CTLA-4	IgG2	Phase I
MEDI4736 (AstraZeneca)	PD-L1	IgG1	Phase II
MK-3475 (Merck/Schering-Plough)	PD-1	IgG4	Phase I
Nivolumab (Bristol-Myers Squibb)	PD-1	IgG4	Phase III

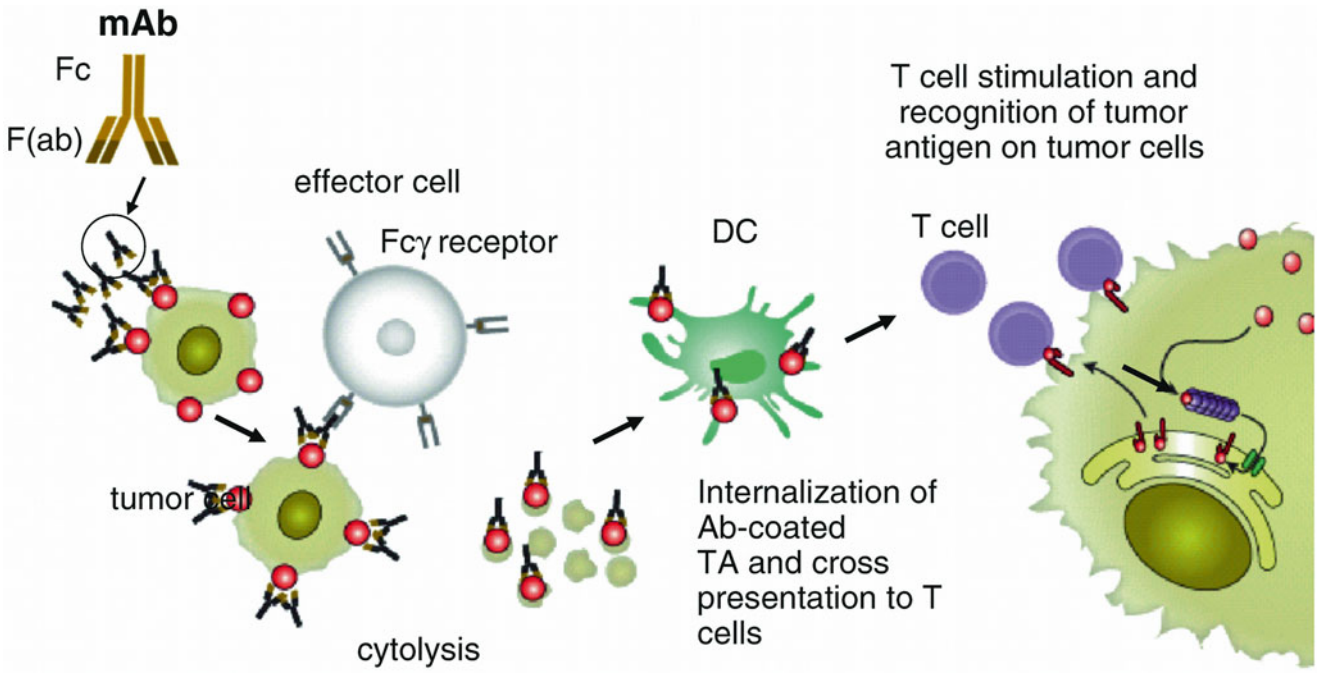

Fig. 6.2 Schematic representation of ADCC; the effector mAb has a constant fragment [Fc] that interacts with immune effector cells and a variable fragment [F(ab)] that is antigen (EGFR) specific. During cross-presentation, tumor antigens are degraded in the cytoplasm of dendritic cells (DC) and presented to T cells producing a cellular immune response [Reprinted from Lee S, Lopez-Albaitero A, Ferris RL. Immunotherapy of head and neck cancer using tumor antigen-specific monoclonal antibodies. *Current Oncology Reports.* 2009;11(2), 156–162. With permission from Springer Science + Business Media]

and this activation seemed to correlate positively with clinical response [110]. Specific T cell activation has been demonstrated in a model using glioma and cetuximab [111], and it is likely that similar T cell activation also occurs in SCCHN patients treated with anti-EGFR mAbs [112].

The mechanism for TA-specific T cell induction may actually be enhanced by ADCC and NK cell activation. In addition to their ability to mediate ADCC, activated NK cells, particularly $CD56^{bright}$ NK cells [113] have also been shown to secrete cytokines, such as IFN-γ, TNF-α, and chemokines, such as macrophage inflammatory protein-(MIP)-1α, MIP-1β, and RANTES, that inhibit tumor cell proliferation, enhance antigen presentation, and aid in the chemotaxis of T cells [107, 114]. Indeed, NK cells can interact with other innate immune cells that are present during the early phases of inflammatory responses [115]. This so-called NK cell-DC cross talk follows the recruitment of both NK cells and DC to sites of inflammation [116, 117], resulting in potent activating bidirectional signaling. NK cells in the presence of cytokines released by DC become activated, regulating both the quality and the intensity of innate immune responses. Also, activated NK cells release cytokines that favor DC maturation and select the most suitable DC for subsequent migration to lymph nodes and efficient T cell priming. In addition, IFN-γ secreting NK cells can be recruited directly to the lymph nodes to enhance T cell induction [117]. Elevated levels of the NK cell-derived chemokines IL-8, macrophage inflammatory protein-1, and RANTES have been detected within the sera of trastuzumab-responding cancer patients [114]. These NK cell factors could induce the chemotaxis of naive and activated T cells, as indicated by the correlation of their presence with the infiltration of tumor tissue by $CD8^+$ CTL. These data suggest that NK cell cytokine and chemokine production may enhance DC cross-presentation and T cell induction, with the potential to spread it to other TA [118].

In order to face the immunosuppressing cytokines of the tumor microenvironment (NK cell cytolysis, induction of Treg [119]) that are associated with prognosis and clinical outcome [71], cytokine-targeted mAbs are developed. One of them is bevacizumab, which is a humanized IgG1 specific against VEGF-A (FDA approved for NSCLC and colon cancer). A phase II trial of a combination of bevacizumab and erlotinib in SCCHN demonstrated a response rate of 14.6 % and an overall mean survival of 6.8 months [52]. A phase II trial that investigated bevacizumab in combination with docetaxel and radiation in locally advanced HNSCC showed tolerability and effectiveness (3-year PFS 61.8 %) [120]. Ficlatuzumab is a humanized anti-hepatocyte growth factor (HGF) mAb that is currently in phase I trial in combination with cetuximab.

So far, the investigation of TNFR-targeting mAb in clinical trials for HNSCC is in phase I. Because of the important costimulatory pathways for immune cell activation, substances

like CP-870,893 (Pfizer), an IgG2 CD40 agonist; OX40 mAb (AgonOx, Providence Health), an IgG2 OX40 agonist; or urelumab (Bristol-Myers Squibb), an IgG4 CD137 agonist, have been investigated in multiple anticancer trials [121].

Other strategies target specific inhibitory molecules. To reduce T cell anergy, anti-CTLA-4 antibodies are developed to block the inhibitory signal [94] alone or in combination with other mAb such as cetuximab (NCT01935921). The same accounts for the previously described PD-1 [95], and antagonistic antibodies to this protein have demonstrated efficacy in phase II trials [96]. Based on promising results of the use of PD-1 blocking monoclonal antibodies (mAb) in different cancer subsets (phase I-III), clinical trials of phase I and phase II have emerged for advanced recurrent or metastatic HNSCC [6]. A different group of receptors with a modulating effect on immune cells is the killer cell immunoglobulin-like receptors (KIRs). They interact with MHC I molecules and regulate immune response. Most of the receptors have a suppressing effect on the cytotoxicity. Anti-KIR antibodies remove the major inhibitory signal on NK cells. Ongoing trials are investigating an anti-KIR mAb in combination with the anti-CTLA-4 mAb ipilimumab (NCT01750580) or anti-PD-1 mAb nivolumab (NCT01714739).

6.16 Conclusion

Cancer immunology is a rapidly evolving field, and it is only recently that we have begun to understand the complex interaction between cancer and the host immune system. Tumor cells demonstrate several methods to exploit the immune system to help promote angiogenesis, derive prosurvival and proliferative signals, and induce metastasis and tumor progression. At the same time, cancers are able to cloak themselves from the immune system by self-modification and by immunosuppression of the host. Recent results from clinical trials show evidence for effective anticancer immunotherapies. Because of the manifold tumor evasion strategies and hence different response rates for treatments, combinational therapies urge into focus for cancer treatment. These insights and better understanding of the workings of the immune system have allowed the recent explosion of several promising immunotherapeutic agents that are currently in clinical use as well as under development.

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Biomarkers in Head and Neck Cancer

7

Hyunseok Kang, Christine H. Chung,
and Arlene A. Forastiere

Abstract

Biomarker research provides the opportunity to risk stratify patients based on identified prognostic and predictive markers. The need for such biomarkers is evident to improve response and survival outcomes in head and neck cancer through more rational patient selection for intensive curative regimens as well as palliative treatments. Advances in our understanding of genomics, epigenetics, and immunology of head and neck cancer are accelerating the discovery of new biomarkers. With the increasing availability of molecularly targeted therapeutics, it is very important to identify and validate biomarkers in the appropriate clinical setting to translate the advances into improved clinical outcome. This chapter focuses on human papillomavirus (HPV) status as a validated prognostic biomarker and discusses emerging prognostic and/or predictive biomarkers with potential for testing through prospective clinical trials. The availability of validated diagnostic assays and required multi-institutional trials for selected patients presents logistical challenges in biomarker research for head and neck cancer.

Keywords

Molecular biomarkers • Head and neck cancer • Therapeutic targets • Predictive and prognostic markers

7.1 Introduction

Head and neck cancer is a heterogeneous disease which includes cancers arising from the paranasal sinuses, nasal cavity, oral cavity, pharynx, larynx, salivary glands, and thyroid. Head and neck squamous cell carcinoma (HNSCC) refers to a major subset of head and neck cancer that arise in the mucosal epithelium of the oral cavity, pharynx, and larynx. The management of patients with HNSCC has changed dramatically over the past 30 years from a surgically dominated specialty to a multidisciplinary decision-making approach. Nearly all patients presenting with locally advanced cancers now receive chemotherapy combined with radiotherapy as a part of their treatment, often as a strategy to preserve organ function or as an adjuvant therapy following surgery. Advances have also occurred in radiation technology for treatment planning and dose delivery to improve local control and reduce the volume of normal tissue treated and risk of late effects. The introduction of novel therapeutics including molecularly targeted therapy and immune therapy offers an exciting opportunity to improve upon the outcomes achievable with standard cytotoxic chemotherapy and radiotherapy.

The National Cancer Institute defines biomarker as "a biological molecule found in the blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition." [1]. Biomarkers can be prognostic or predictive; prognostic biomarkers provide long-term outcome of a disease process independent of treatment, whereas predictive

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biomarkers offer information on outcome associated with a specific treatment. A biomarker can be both prognostic and predictive. Successful implementation of a biomarker requires an extensive validation process to ensure robust clinical performance, a streamlined assay process to ensure a short turnaround time, and reasonable cost to ensure feasibility [2].

The current standard for assessing risk in HNSCC largely depends on clinical tumor staging which encompasses histopathology and imaging; the approach has limited ability to stratify patients for specific risk of metastasis, local–regional recurrence, or development of a second primary. The human papillomavirus (HPV) has been established as a prognostic biomarker in oropharyngeal squamous cell carcinoma (OPSCC) [3], but no validated predictive biomarkers have been identified in HNSCC yet. Further identification of prognostic and predictive markers is a logical and rational next step to achieve improvement in outcome without increasing acute and chronic toxicity associated with treatment. Recent advances in genomics have provided detailed data on genetic alterations in HNSCC from large genome-wide sequencing studies [4–7]. Most of the mutations were found in tumor suppressor genes (TSGs), which are harder to target, rather than oncogenes. Some of these mutations, such as *TP53* and *CDKN2A*, were consistent with previously known alterations in a multistep model of tobacco-related HNSCC carcinogenesis, but novel mutations such as *NOTCH1* were also identified [8]. These genetic alterations have great potential to serve as reliable predictive biomarkers against targeted therapy as each of them may represent a distinct biological process in individual cancer.

This chapter will focus on an established biomarker in HNSCC, HPV, and p16 and emerging biomarkers including predictive biomarkers to existing treatments, genomic alterations, gene-expression profile, and immunotherapy-related biomarkers.

7.2 Established Biomarker: HPV and p16

HPV is associated with a subset of HNSCC that is biologically very distinct from non-HPV-related HNSCC [9]. Among greater than 100 subtypes of HPV, HPV 16 is the subtype most frequently associated with HNSCC; it is also associated with cervical and vulvar cancers in women, anal cancer in men and women, and penile cancer [10]. Over the past decade, the incidence of oropharynx cancers has been rising, especially in younger individuals in the US and Europe who have little or no history of exposure to two major risk factors, tobacco and alcohol [11].

HPV, which is a circular double-stranded DNA virus, causes inactivation of p53 and retinoblastoma (RB) mediated by two viral oncoproteins, E6 and E7, respectively [12, 13]. HPV integrates its DNA into the host cell genome, encodes for E6 and E7 genes, and dysregulates the cell cycle. The E6 oncoprotein promotes ubiquitination and degradation of p53, promoting cell survival. The E7 oncoprotein binds and inactivates the retinoblastoma tumor suppressor protein leading to upregulation of p16, low expression of cyclin D1, cell-cycle disruption, proliferation, and malignant transformation (Fig. 7.1).

Patients with HPV-related OPSCC are more likely to be nonsmokers and nondrinkers. As HPV is a sexually transmitted virus, the major risk factors appear to be a high number of lifetime sexual partners, younger age at first intercourse, a history of genital warts, and possibly marijuana use [18]. Patients with HPV-positive head and neck cancer commonly present with large cystic neck nodes and a small primary (low T stage) in the tonsil or base of the tongue [19]. Histologically, these cancers are usually nonkeratinizing, poorly differentiated squamous carcinomas with basaloid features [20].

HPV status in a tumor tissue can be determined by detection of the presence of HPV DNA or mRNA or by detection of p16 which is overexpressed by the downstream effect of viral oncoprotein E7. The gold standard for detection of HPV in a tumor is detection of high-risk HPV E6/E7 oncogene expression through reverse transcriptase–polymerase chain reaction (PCR), which is currently not available in most clinical laboratory settings [21]. Commonly used detection methods include HPV DNA in situ hybridization (ISH), HPV RNA ISH, and p16 immunohistochemistry (IHC) [22]. It has been shown in multiple studies that p16 IHC or ISH/FISH are very sensitive and specific at least in OPSCC (Table 7.1).

The presence of HPV or p16 has been consistently shown to be a strong prognostic factor of favorable outcome with significant improvement in both overall survival and progression-free survival in locally advanced OPSCC in multiple phase 2–3 clinical trials (Table 7.2) [3, 23–26]. The presence of p16 in OPSCC appears to remain as an important prognostic factor for patients who had surgery followed by adjuvant concurrent chemoradiotherapy or patients who develop recurrent and/or metastatic disease. A recent study showed that patients with HPV-positive OPSCC had better locoregional control and longer survival after postoperative platinum-based concurrent chemoradiotherapy regardless of p53 expression (by IHC) and the presence of extracapsular extension [27]. Another study reported that patients with p16-positive OPSCC had better overall survival (HR 0.48, 95 %CI 0.31–0.74), independent of initial tumor stage, progression type (distant versus locoregional), salvage surgery, and smoking status compared to p16-negative patients after progression of disease in a combined analysis of two large prospective clinical trials [28]. Even in non-OPSCC tumors, p16 expression was shown to be associated with better progression-free survival (HR 0.63, 95 %CI 0.42–0.95) and overall survival (HR 0.56, 95 %CI 0.35–0.89) in analyses of three phase 2–3 clinical trials [29]. These trials, though, did

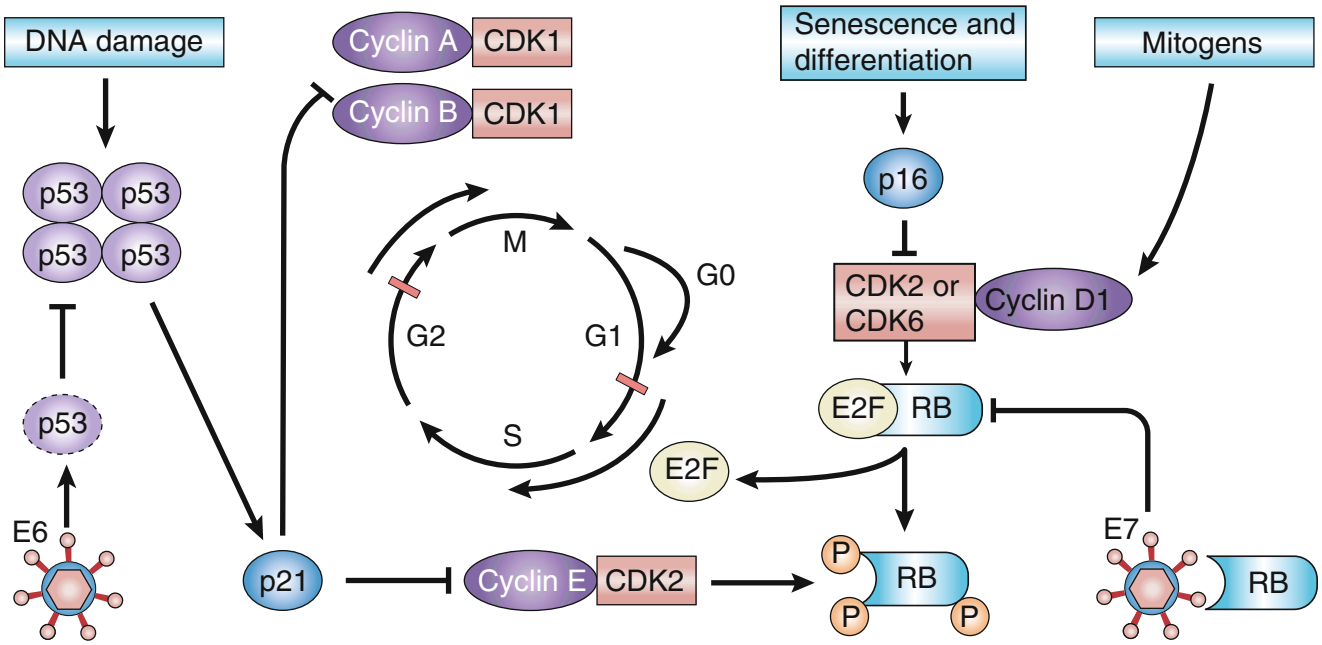

Fig. 7.1 Cell-cycle deregulation by human papillomavirus. Schematic diagram of molecular pathogenesis of HPV-related HNSCC. HPV can cause cell-cycle dysregulation and result in genomic instability and therefore promote malignant transformation. (1) Ubiquitination by viral E6 leads to p53 degradation [13, 14]. (2) Ubiquitination by viral E7 leads to pRb degradation [15, 16]. (3) Increased expression of $p16^{INK4A}$ as a consequence of increased S-phase gene expressions from the absence of pRb function [17]. *Abbreviation*: *CDK* cyclin-dependent kinase [Reprinted from Leemans CR, Braakhuis BJM, Brakenhoff RH. The molecular biology of head and neck cancer. Nature Rev Cancer 2011;11(1):12. With permission from Nature Publishing Group]

Table 7.1 Comparison of HPV detection methods in OPSCC[a]

Study	Number of samples	HPV-DNA PCR		ISH/FISH		$p16^{INK4A}$ IHC		$p16^{INK4A}$ IHC interpretation		
		Sens.	Spec.	Sens.	Spec.	Sens.	Spec.	Intensity	%	Pattern
Smeets et al. [115]	19	100 %	92 %	83 %	100 %	100 %	70 %	≥1+	>10	N or C
Shi et al. [116]	111	NA	NA	84 %	92 %	89 %	81 %	Strong	N/A	N and C
Schache et al. [117]	95	97 %	87 %	88 %	88 %	94 %	82 %	Strong	>70	N and C
Schlecht et al. [118]	21	NA	NA	38 %	100 %	90 %	100 %	≥2+	≥75	N and C
Rotnaglova et al. [119]	109	100 %	89 %	NA	NA	94 %	96 %	≥1+	>50	N or C
Jordan et al. [21]	235	99 %	63 %	88 %	95 %	97 %	84 %	≥2+	>70	N and C
						92 %	90 %	H score[b] ≥ 60		

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C cytoplasmic, *FISH* fluorescence in situ hybridization, *HPV* human papillomavirus, *IHC* immunohistochemistry, *N* nuclear, *OSCC* oropharyngeal squamous cell carcinoma, *Sens.* sensitivity, *Spec.* specificity

[a]Sensitivities and specificities are based on gold standard of E6 mRNA qRT-PCR

[b]H score is derived from cross product of the intensity score (0–3) and from the percentage of tumor staining at the highest intensity (0–100 %)

not include oral cavity squamous cell carcinoma (OCSCC), 6 % of which can be positive for HPV16. In OCSCC, p16 expression by IHC has a poor positive predictive value [30] for HPV infection and thus should not be used as a surrogate marker for the presence of HR-HPV. Also, the prognostic role of either p16 or HPV DNA/RNA has not been established in OCSCC [31].

Although HPV status or p16 expression have been well established as a strong prognostic marker for OPSCC, whether it can serve as a predictive biomarker for certain therapies is still not clear. HPV-negative tumors tend to have higher total and phosphorylated epidermal growth factor receptor (EGFR) protein expression than HPV-positive tumors [32]; thus, there is a possibility that EGFR-targeting

Table 7.2 Impact of HPV status on outcome of HNSCC

Study	Site	Detection method	Number of patients	PFS rate			OS rate		
				HPV^+	HPV^-	HR	HPV^+	HPV^-	HR
Fakhry et al. [23]	OP; L	DNA ISH	96	86 % at 2 years	53 % at 2 years	3.57 (1.33–9.09)	95 % at 2 year	62 % at 2 year	2.86 (1.25–6.67)
Ang et al. [3]	OP	DNA ISH	323	73.7 % at 3 years	43.4 % at 3 years	2.50 (1.75–3.45)	82.4 % at 3 year	57.1 % at 3 year	2.63 (1.82–3.85)
Rischin et al. [24]	OP	$p16^{INK4A}$ IHC	185	87 % at 2 years	72 % at 2 years	2.56 (1.35–5)	91 % at 2 year	74 % at 2 year	2.78 (1.35–5.88)
Posner et al. [25]	OP	DNA PCR for E6/E7	111	78 % at 5 years	28 % at 5 years	NA	82 % at 5 year	35 % at 5 year	5.00 (2.63–10.00)
Lassen et al. [26]	OP; OC; L; P	$p16^{INK4A}$ IHC	794	68 % at 5 years	57 % at 5 years	1.52 (1.14–2.04)	62 % at 5 year	47 % at 5 year	1.61 (1.28–2.04)

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HNSCC head and neck squamous cell carcinoma, *HPV* human papillomavirus, *HR* hazard ratio, *ISH* in situ hybridization, *IHC* immunohistochemistry, *L* larynx, *NA* not available, *OC* oral cavity, *OP* oropharynx, *OS* overall survival, *P* pharynx, *PFS* progression-free survival

therapy may work better for HPV-negative HNSCC. In a retrospective subset analysis of the SPECTRUM study, in which patients received panitumumab, a monoclonal antibody against EGFR, in combination with cisplatin and 5-FU, a survival benefit from the addition of panitumumab was limited to p16-negative patients [33]. Another study, comparing MEHD7945A, a dual-action antibody against EGFR and HER3, and cetuximab in a second-line systemic therapy of recurrent or metastatic HNSCC, showed that the response to either MEHD7945A or cetuximab is limited to HPV-negative patients [34]. However, a retrospective analysis of the EXTREME study demonstrated that the benefit of cetuximab is not limited to HPV-negative patients [35]. As these studies are all retrospective, unplanned analyses of prospective studies of limited numbers of patients, a prospective study will be required to address this question.

As the long-term survival of patients with HPV-positive HNSCC treated with current standard of care multimodality regimens is excellent, current clinical trials are focused on de-intensification of multimodality treatment [36]. HPV status may become a biomarker for less intensive curative intent treatment if randomized controlled de-intensification trials demonstrate comparable outcome. Also, HPV status may become a predictive biomarker for HPV-targeted therapies in the future, such as therapeutic HPV vaccines [37].

7.3 Emerging Biomarkers

Recent advances in tumor biology and multiplex genomic analysis have enabled us to access expansive information on genetic and epigenetic alterations of HNSCC. Comprehensive genome-wide sequencing data from several studies available to date have shown that there are more alterations in tumor suppressor genes (TSGs) rather than in oncogenes (Fig. 7.2) [4–6, 38, 39]. TSG mutations are more difficult to target than oncogene mutations, as it is harder to restore loss of function than to suppress gain of function. In addition, while oncogene mutations tend to occur in certain hotspots, TSG mutations tend to occur scattered throughout the gene [40].

Genomic analyses clearly demonstrate distinct biologic difference between HPV-positive and HPV-negative tumors. HPV-positive tumors tend to have fewer mutations per tumor and frequently have helical domain mutations of the oncogene, *PIK3CA*. This is not very surprising given that all HPV-positive tumors have already altered p53 and Rb pathways from actions of viral oncoproteins, E6 and E7. Almost all HPV-negative tumors show loss-of-function *TP53* mutations and *CDKN2A* inactivation which leads to $p16^{INK4A}$ functional loss (Table 7.3) [38]. These biological differences support clinical observations and may provide further insight on development of specific treatments for each type of HNSCC.

7.3.1 Epidermal Growth Factor Receptor

The epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein and a member of the human epidermal receptor (HER) family receptor tyrosine kinases. EGFR is composed of an extracellular ligand-binding domain, a transmembrane region, and an intracellular domain that includes the tyrosine kinase enzyme. When a ligand binds to the receptor, it undergoes a conformational change and dimerization with another EGFR or other HER family members such as HER2, HER3, or HER4. Dimerization results in activation of intracellular tyrosine kinase, protein phosphorylation and stimulation of various cell signaling pathways that mediate cell-cycle progression, angiogenesis, inhibition of apoptosis, tumor invasion, and metastasis [41].

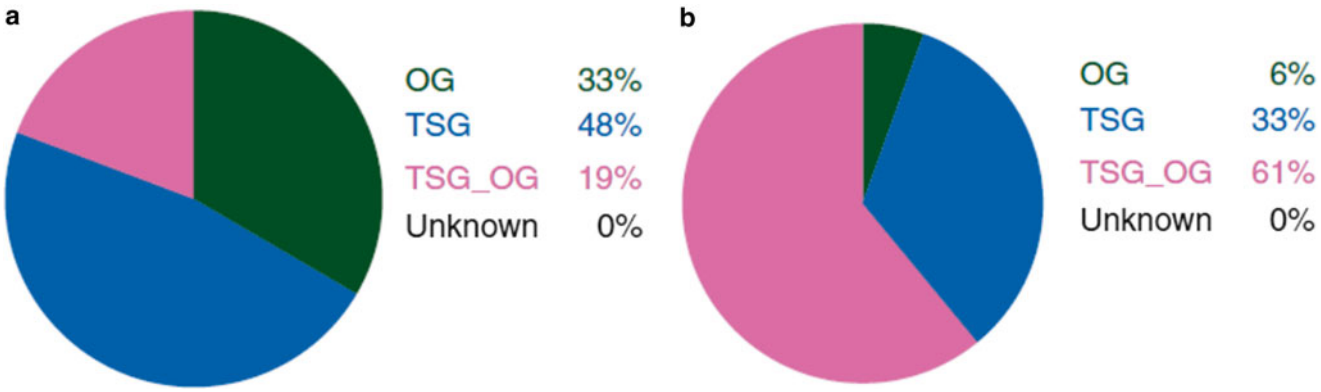

Fig. 7.2 Tumors with alterations in oncogenes (OG), tumor suppressor genes (TSG), or both (TSG and OG) based on selected 236 cancer-related gene sequencing, (**a**) HPV-positive HNSCC, (**b**) HPV-negative HNSCC [Reprinted from Chung CH, Guthrie VB, Masica DL et al. Genomic alterations in head and neck squamous cell carcinoma determined by cancer gene-targeted sequencing. Ann Oncol 2015 2015 Jun;26(6):1216–23. With permission from Oxford University Press]

Table 7.3 Frequently mutated genes in HPV-positive and HPV-negative tumors in selected studies

HPV-positive HNSCC				HPV-negative HNSCC			
Gene	TCGA (*N*=36) [38]	Chicago (*N*=51) [6]	Foundation medicine (*N*=84) [39]	Gene	TCGA (*N*=243) [38]	Chicago (*N*=69) [6]	Foundation medicine (*N*=168) [39]
PIK3CA	56 %	35 %	30 %	*TP53*	84 %	80 %	87 %
SOX2	28 %	NA	11 %	*CDKN2A/B*	57 %	32 %	54 %
MLL2 (KMT2D)	17 %	20 %	13 %	*FGF19*	32 %	NA	23 %
RB1	6 %	24 %	7 %	*FGF3*	31 %	NA	22 %
BCL6	25 %	18 %	1 %	*FGF4*	31 %	NA	22 %
EP300	14 %	12 %	10 %	*PIK3CA*	34 %	29 %	16 %
NOTCH1	11 %	18 %	6 %	*CCND1*	32 %	13 %	24 %
PTEN	3 %	8 %	15 %	*NOTCH1*	21 %	26 %	16 %
FGFR3	11 %	24 %	1 %	*LRP1B*	22 %	30 %	6 %
ASXL1	19 %	10 %	5 %	*SOX2*	21 %	NA	8 %

Modified from Chung CH, Guthrie VB, Masica DL et al. Genomic alterations in head and neck squamous cell carcinoma determined by cancer gene-targeted sequencing. Ann Oncol 2015 2015 Jun;26(6):1216–23. With permission from Oxford University Press
TCGA The Cancer Genome Atlas

EGFR has been a major therapeutic target in the treatment of HNSCC, as the majority of HNSCC (~90 %) overexpresses EGFR relative to normal tissue [42]. High EGFR expression has been associated with worse outcome in patients who were treated with resection or radiotherapy [43, 44]. However, EGFR expression detected by IHC has not been widely adopted as a biomarker because there is no standardized anti-EGFR antibody, staining protocol, or quality control measure for the assay. Furthermore, EGFR expression assessed by IHC has not been shown to be predictive of response to EGFR-targeting therapy, such as cetuximab, a chimeric monoclonal IgG1 antibody directed against EGFR [45].

EGFR amplification has been investigated as a prognostic factor in HNSCC. *EGFR* is amplified in 10–58 % of HNSCC and is measured by fluorescence in situ hybridization (FISH) and quantitative PCR and was associated with worse progression-free and overall survival in two independent studies [46, 47]. However, there is no evidence correlating gene amplification with response outcome to EGFR-targeting therapies in HNSCC. The Cancer Genome Atlas (TCGA) showed that only 15 % of HPV-negative HNSCC and 6 % of HPV-positive HNSCC have mutations or amplifications of *EGFR* [38], which suggests that the previous studies may have overestimated *EGFR* mutations or copy number variations. More investigations are needed to clarify the role of *EGFR* alterations as a predictive biomarker.

The resistance mechanisms against EGFR-targeting therapy provide insight into potential prognostic and predictive biomarkers and therapeutic targets. These include increased nuclear localization of EGFR, transactivation and dimerization with other HER family receptors, activation of other receptor tyrosine kinases such as MET or IGF-1R, or activation of downstream signaling molecules (Fig. 7.3) [48].

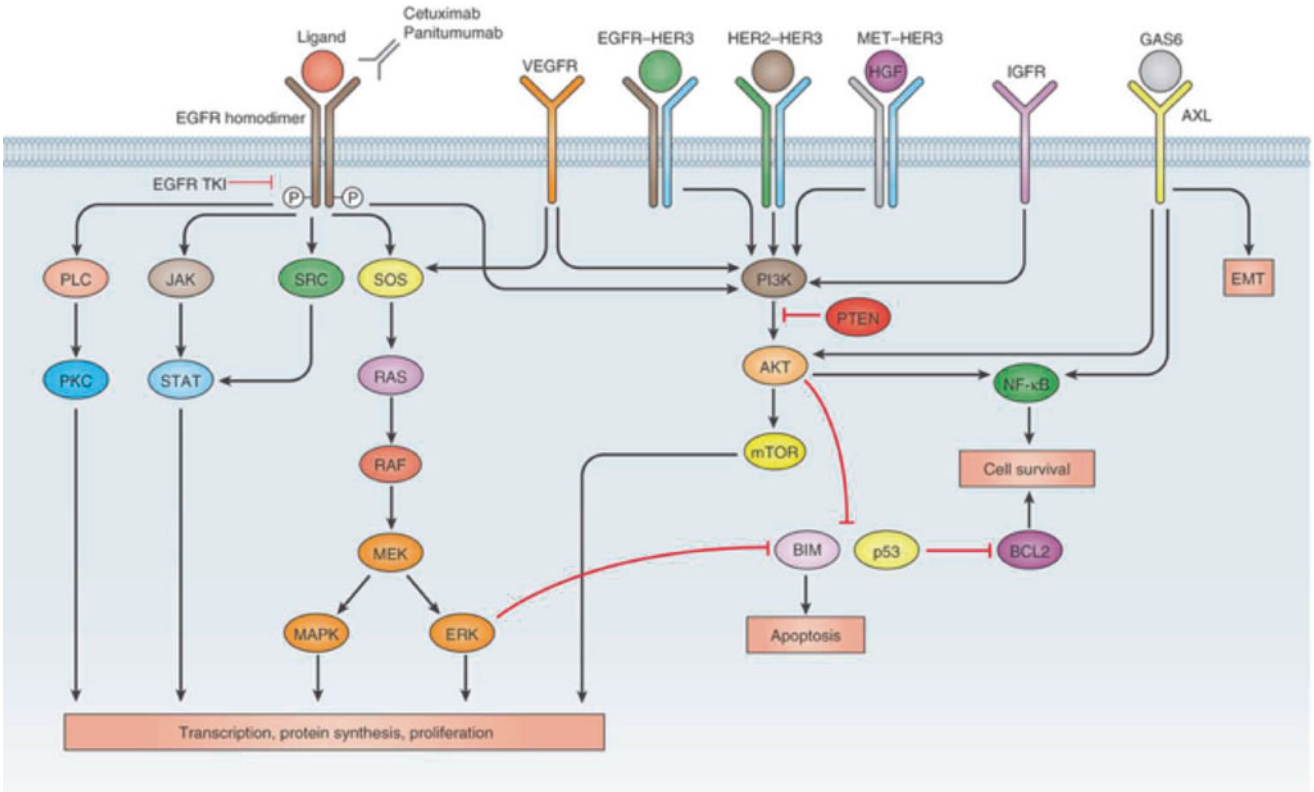

Fig. 7.3 EGFR and receptor tyrosine kinase signaling in head and neck cancer. Resistance to EGFR inhibitors can arise via signaling from redundant receptor tyrosine kinases, such as HER family members, MET, or IGF-1R, as well as the activation of downstream signaling intermediaries [Reprinted from Chong CR, Janne PA. The quest to overcome resistance to EGFR-targeted therapies in cancer. Nat Med 2013;19(11):1390. With permission from Nature Publishing Group]

7.3.2 *PIK3CA*

PIK3CA encodes p110α, a p110 catalytic subunit of phosphoinositol 3-kinase (PI3K), which is a family of lipid kinases that integrate signals from growth factors, cytokines, and other environmental cues, and relays them to intracellular signaling for such functions as cell growth, proliferation, and survival [49]. An example of a signaling cascade mediated by activated PI3K is shown in Fig. 7.4. PI3K activates AKT, which subsequently leads to the activation of the mammalian target of rapamycin (mTOR), triggering downstream effects on transcription, protein synthesis, metabolism, proliferation, and apoptosis (Fig. 7.4) [50].

PIK3CA is the most commonly mutated gene in HPV-positive HNSCC, and the mutation tends to be located in the helical domain (E542K and E545K), while *PIK3CA* mutations in HPV-negative HNSCC are more diverse throughout the gene [38, 51]. The distinctive mutation loci may result in functionally different mutant proteins that could serve as novel therapeutic targets and predictive biomarkers. In a comparative protein array study, HPV-positive and HPV-negative OPSCC differentially activate PI3K/AKT/mTOR pathway—*PIK3CA* mutations in HPV-positive OPSCC were associated with activation of mTOR but not AKT [32], suggesting that an mTOR inhibitor may have activity against HPV-positive *PIK3CA* mutant OPSCC. In a preclinical study, dual inhibition of mTOR/PI3K was shown to be effective in controlling a *PIK3CA* mutant patient tumor-derived xenograft mouse model [51].

Numerous clinical trials of drugs targeting the PI3K pathway are currently on-going. Early data from phase I/II trials have suggested limited efficacy as monotherapy in tumors with PI3K pathway activation partly because of lack of specificity and activation of alternate signaling pathways [52]. Clinical trials in nonselected RM-HNSCC population with an irreversible oral PI3K inhibitor, PX-866, in combination with either cetuximab or docetaxel did not show any improvement in the response rate or progressive-free survival [53, 54]. There was no correlation between the response and the PI3K mutation status, although only small number of patients harbored PI3K mutations (17 % and 8 %). Further development should account for the specific characteristics of *PIK3CA* mutations in HNSCC.

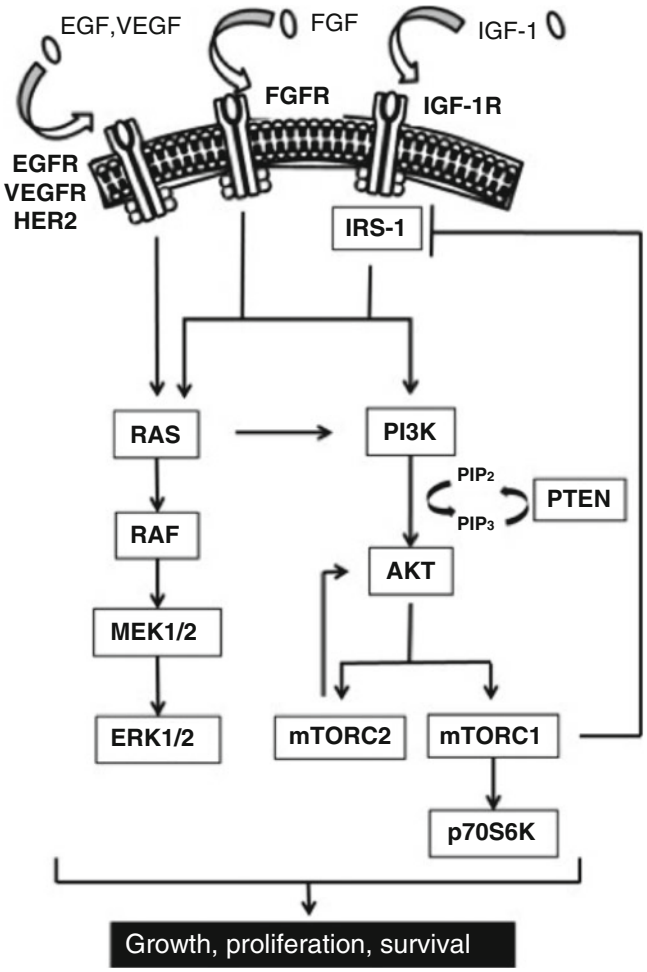

Fig. 7.4 The PI3K/AKT/mTOR pathway and associated signaling pathways. *AKT* protein kinase B, *EGFR* epidermal growth factor receptor, *ERK 1/2* extracellular signal-regulated kinase 1/2, *FGFR* fibroblast growth factor receptor, *HER2* human epidermal growth factor 2, *IGF* insulin-like growth factor, *IRS-1* insulin receptor substrate 1, *MEK 1/2* mitogen-activated protein kinase 1/2, *mTORC* mammalian target of rapamycin complex, *PI3K* phosphatidylinositol 3-kinase, *PIP2* phosphatidylinositol 4,5-bisphosphate, *PIP3* phosphatidylinositol (3,4,5)-trisphosphate, *PTEN* phosphatase and tensin homolog, *p70S6K* p70S6 kinase, *VEGFR* vascular endothelial growth factor [Reprinted from Simpson DR, Mell LK, Cohen EE. Targeting the PI3K/AKT/mTOR pathway in squamous cell carcinoma of the head and neck. Oral Oncol 2015;51(4):292. With permission from Elsevier]

7.3.3 Cyclin D1

Cyclin D1 is a protein expressed in a cell-cycle-dependent manner and plays an important role in regulating G1-S transition by forming a complex with cyclin-dependent kinases (CDKs), such as CDK4 and CDK6. This complex phosphorylates Rb and activates transcription factors, promoting proliferation through the expression of S-phase proteins [55]. Cyclin D1 also has non-catalytic functions independent of CDKs and can interact with various transcription factors [56] and regulate histone acetylation and methylation [57]. *CCND1*, which encodes for cyclin D1, was shown to be amplified in 28 % of HNSCC in TCGA, mostly in HPV-negative tumors (32 %) rather than in HPV-positive tumors (6 %) [38].

Overexpression of cyclin D1 or amplification of *CCND1* has been associated with poor outcome and resistance to EGFR-targeted therapy in HNSCC [58, 59]. This interaction may be further perturbed by inactivation of $p16^{INK4a}$, an inhibitor of CDK4 and CDK6. Inactivation of $p16^{INK4a}$ by deletion of *CDKN2A* (which is documented in 57 % of HPV-negative HNSCC) has been associated with poor prognosis [58, 60]. Increased cyclin D1 expression and loss of $p16^{INK4a}$ expression is associated with particularly poor clinical outcome in HNSCC [61], and there seems to be an inverse correlation between expressions of cyclin D1 and $p16^{INK4a}$ [62, 63]. As direct targeting of cyclin D1 is very difficult at this time, indirect targeting through inhibitors for CDK4/CDK6 is in development and might play role in patients with *CCND1* amplification.

7.3.4 Fibroblast Growth Factor Receptor

The FGF and fibroblast growth factor receptor (FGFR) pathway regulate developmental pathways, angiogenesis, wound repair, proliferation, differentiation, and survival. FGFRs are a family of highly conserved transmembrane tyrosine kinase receptors (FGFR1–4), which are activated by 18 ligands (FGFs) [64, 65]. The activated FGFR phosphorylates FGFR substrate 2 (FRS2) on several sites, allowing recruitment of the adaptor proteins, which in turn activate RAS–RAF–MAPK pathways and PI3K–AKT–mTOR pathways [64].

In HPV-negative HNSCC, *FGFR1*, *FGFR2*, *FGFR3*, and *FGFR4* are amplified or mutated in 10 %, 2 %, 2 %, and 0.4 %, respectively. HPV-positive HNSCC did not demonstrate any alteration in *FGFR1* and *FGFR2*, but *FGFR3* mutation or fusion was seen in 11 %, and *FGFR4* mutation was seen in 3 % [38]. In a preclinical study, FGF2 and FGFR2 and FGFR3 were found to be frequently expressed in HNSCC cell lines, forming an autocrine signaling network [66]. In a predominantly HPV-negative cohort primarily treated with surgery followed by radiation, FGF2 overexpression was shown to be independently associated with worse outcome after adjusting clinical factors and HPV status [67]. Inhibition of FGFR1 was shown to suppress cell growth and reverses epithelial–mesenchymal transition (EMT) features in HNSCC preclinical models [68]. Further investigation will be needed to validate this target.

7.3.5 *KRAS* Variant

KRAS is a well-known oncogene, although its alteration is rarely reported in HNSCC (amplification or mutation in 3 % of samples in TCGA) [38, 69]. A single nucleotide polymorphism

(SNP) in its 3′ UTR, *rs61764370*, has been associated with increased risk of non-small cell lung cancer [70], ovarian cancer [71], and triple-negative breast cancer [72]. The variant *KRAS* has altered *let*-7 miRNA complementary site (LCS) and is thought to cause decreased degradation of *KRAS* mRNA. The presence of *KRAS* variant was shown to be associated with higher mortality from ovarian cancer and a greater chance of platinum resistance [73].

In HNSCC, prevalence of the *KRAS* variant was reported to be around 20–30 % [74, 75] and associated with reduced survival [74]. A retrospective analysis of several prospective studies showed that the *KRAS* variant was associated with worse progression-free survival when treated with platinum-containing chemotherapy (cisplatin ± cetuximab). However, in patients treated with non-platinum-containing chemotherapy (docetaxel + bortezomib), no difference was observed in PFS between the *KRAS* variant group and the *KRAS* wild-type group [75]. This observation suggests that the *KRAS* variant may serve as a predictive biomarker for platinum response, and further studies are warranted.

7.3.6 *TP53*

Discovered in 1979 and characterized as a tumor suppressor in 1983, p53 is a highly studied, critical element of cell-cycle regulation and is mutated in over half of all human malignancies [76]. The normal role of p53 is to respond to an enormous variety of stress signals by modulating cellular responses, including transient cell-cycle arrest, cellular senescence, and apoptosis (Fig. 7.5) [77].

TP53 is the most commonly mutated gene in all cancers [78], and the mutation is found in 84 % of HPV-negative HNSCC tumors [38]. Including the inactivation of p53 by HPV viral oncoprotein E6 in HPV-positive OPSCC, functional loss of p53 occurs in more than 90 % of HNSCC [13, 79]. The majority of *TP53* mutations in human cancers are missense mutations (80 %) [80], leading to the substitution of a single amino acid in the p53 protein that can be stably expressed in the tumor cell. These mutations can occur anywhere in the gene but are most commonly found in the DNA-binding domain of p53 [81]. Diverse mutations may function differently in the different context, reflecting diverse expression patterns of target proteins of p53 [82]. Besides mutations resulting in loss of wild-type p53 functions, certain missense mutations exhibit gain-of-function properties [83], which is described to be oncogenic in HNSCC cell lines through inhibition of tumor-suppressive AMP-activated protein kinase (AMPK) signaling [84].

Loss of p53 function has been investigated as a prognostic biomarker in HNSCC, but early studies were confounded by poor assays, small sample size, and a lack of distinction between functional and nonfunctional alterations [85]. In several studies, disruptive *TP53* mutations which cause truncated p53 have been associated with worse clinical outcome in HNSCC patients [86, 87]. A recent study reported an evolutionary action score of *TP53* (EAp53) that identified high-risk mutations associated with decreased survival and increased distant metastases in HNSCC patients [88]. Cells harboring the high-risk *TP53* mutations tended to have decreased expression of certain p53 target genes, such as p21, Notch1, and BTG2. The same authors reported that high-risk *TP53* mutations identified by EAp53 were associated with decreased sensitivity to cisplatin in both preclinical tumor models and in patients treated with platinum-based chemotherapy [89]. These findings highly suggest that the functional status of p53, rather than the presence or absence of *TP53* alteration, may act as a prognostic biomarker in HNSCC.

Traditionally TSGs such as *TP53* have been regarded as hard to target. Recently, the concept of synthetic lethality in which a combination of mutations in two or more separate genes leads to cell death [90] has gained attention as a way to target TSGs. Synthetic lethality can be exploited when a maladaptive genetic change, not lethal by itself, makes cancer cells vulnerable to specific targeted therapies [91]. A high-throughput RNA interference functional genomic screen of the human kinome in HNSCC cell lines has shown that inhibition of WEE1, a G2-M cell-cycle-regulating protein, can render synthetic lethality in *TP53*-mutated tumors [92]. A WEE1 inhibitor, MK-1775, has been shown to sensitize platinum-resistant HNSCC cells with *TP53* mutations to cisplatin treatment in vitro and in vivo [93]. A similar approach can be taken by inhibiting CHK1, another G2-M cell-cycle-regulating protein, and a Chk inhibitor, AZD7762, has been shown to sensitize HNSCC cells with loss of functional p53 to cisplatin (Fig. 7.6) [94]. *TP53* mutations can be a potential predictive marker for these synthetic lethal approaches, in the context of functional disruption of p53.

7.3.7 Excision Repair Cross Complementing Group 1

The excision repair cross complementing group 1 (ERCC1)/xeroderma pigmentosum-complementation group F (XPF) is a heterodimeric DNA structure-specific endonuclease complex. This enzyme plays a key role in several DNA-repair pathways, particularly in repairing ultraviolet-induced lesions and intra- or interstrand cross-linked DNA adducts created by alkylating agents, such as cisplatin [95]. As platinum-based chemotherapy is routinely used in the management of HNSCC, ERCC1 has been investigated as a potential predictive biomarker.

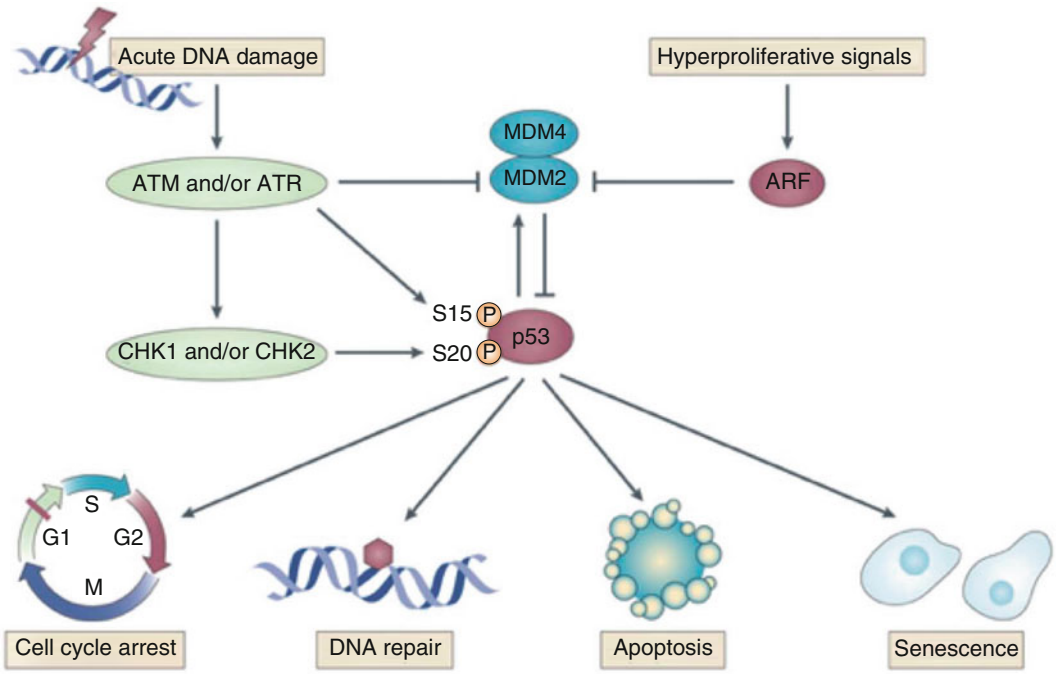

Fig. 7.5 p53 activation and response. In response to acute DNA damage, ataxia telangiectasia mutated (ATM) and/or ataxia telangiectasia and RAD3 related (ATR) is recruited and activates CHK1 and/or CHK2. ATM, ATR, CHK,1 or CHK2 can phosphorylate p53 and then stabilize it. MDM2 and MDM4 can bind to the transcriptional activation domain of p53 and can inhibit p53 transactivation function. Activation of p53 regulates crucial cellular processes by modulating cell-cycle arrest, DNA repair, apoptosis, and senescence [Reprinted from Bieging KT, Spano Mello S and Attardi LD. Unraveling mechanisms of p53-mediated tumor suppression. Nat Rev Cancer 2014;14(5):361. With permission from Nature Publishing Group]

Overexpression of ERCC1 determined by IHC has been associated with lower response rates to cisplatin-containing chemotherapy [96]. Results from various studies have not been consistent as there were inconsistencies in assay and interpretation, although there has been a strong signal that ERCC1 may be a useful predictive biomarker to platinum therapy [97]. A recent study with improved assays using specific antibodies and automatic quantitative analysis (AQUA) has shown that low ERCC1 expression was associated with improved outcome in patients treated with surgery followed by concurrent chemoradiation with cisplatin. There was no difference in survival between ERCC1 high and ERCC1 low group in patients treated only with surgery [98]. A retrospective analysis of patients treated with cisplatin-based concurrent chemoradiotherapy showed that higher ERCC1 expression determined by AQUA was associated with inferior PFS, irrespective of HPV status [99]. Similarly, low expression of XPF, a binding partner of ERCC1, has been associated with poor clinical outcome in HNSCC patients treated with platinum-based induction chemotherapy [100]. ERCC1 is a promising potential predictive biomarker for response to platinum chemotherapy, but these findings are needed to be validated in prospective studies.

7.3.8 Classification by Gene Expression Profiles

HNSCC can be classified based on gene-expression profiles using expression arrays. Four distinct subtypes have been identified as "basal," "mesenchymal," "atypical," and "classical" to reflect specific molecular characteristics [101]. This classification was validated in two independent cohorts [102]. These studies included only a small number of HPV-positive tumors which were classified in the "atypical" subtype. Recent analysis of an HPV-positive tumor-enriched cohort has led to the revision of the classification into five categories—"basal HPV," "classic HPV," "classic non-HPV," "mesenchymal HPV," and "mesenchymal non-HPV" [103]. Regardless of HPV status, the mesenchymal subtype was associated with the expression of immune response genes such as *CD8*, *ICOS*, *LAG3*, and *HLA-DRA* which could be used as predictive biomarkers for immune-based therapy in the future. In addition, a meta-analysis with a publicly available nine microarray gene-expression dataset in HNSCC showed a robust association of a 172-gene-expression signature with prognosis of patients regardless of HPV status [104]. Future studies will focus more on pathway-based analyses that integrate genomic data.

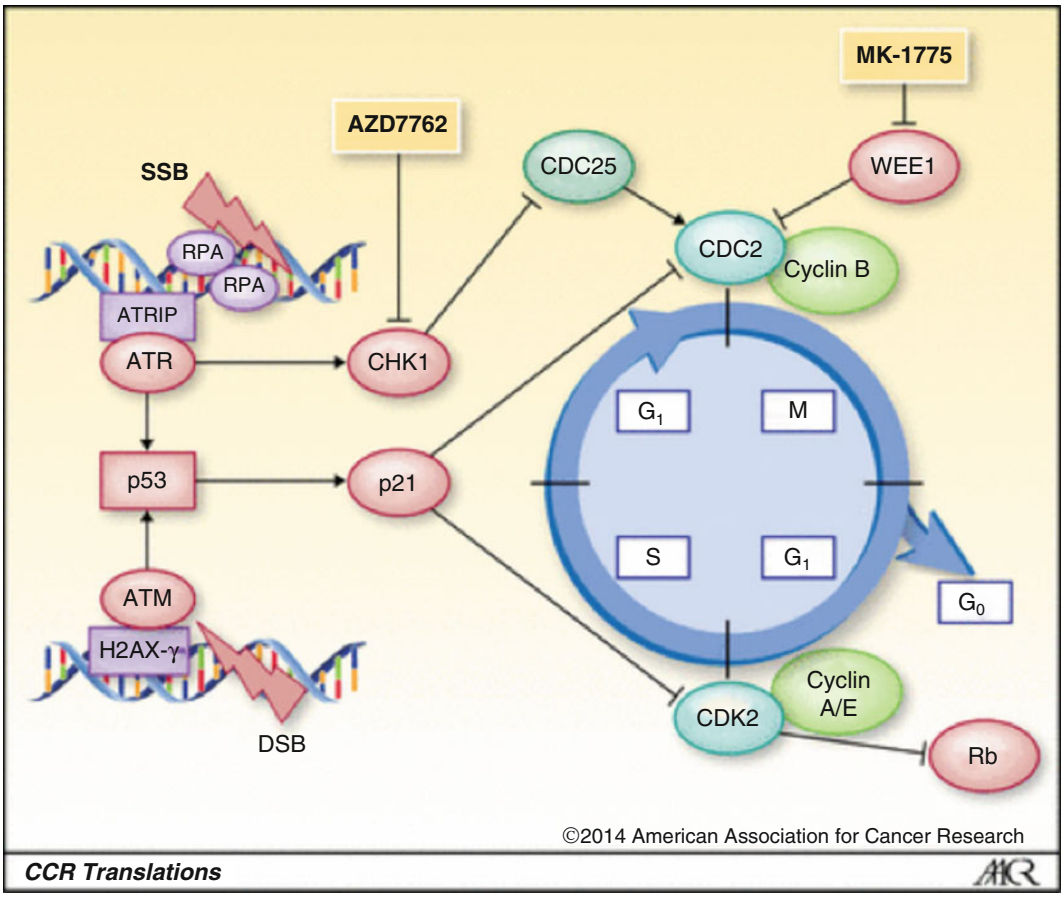

Fig. 7.6 Synthetic lethal approach for p53 dysfunctional tumors. Following DNA damage, ATR, and ATM initiate cell-cycle arrest, following their respective activation sites of single-strand (SSB) or double-strand breaks (DSB). ATR directly phosphorylates checkpoint kinase 1 (CHK1), whereas ATM activates p53 and CHK2, although there is extensive cross talk between these pathways. At the G2 checkpoint, G2-M arrest is triggered when CHK1 inhibits the activator of CDC2 and CDC25 or when WEE1 directly inactivates CDC2 [Reprinted from Bauman JE, Chung CH. CHK it out! Blocking WEE kinase routs TP53 mutant cancer. Clin Cancer Res 2014;20(16):4174. With permission from American Association for Cancer Research]

7.3.9 Immune-Related Biomarkers

Head and neck cancer is recognized as an immunosuppressive disease. Most patients demonstrate low absolute lymphocyte counts, impaired natural killer cell activity, and decreased antigen-presenting function [105–107]. Immune system evasion is mediated by several different mechanisms. The antigen-processing molecules, TAP 1/2, and the major histocompatibility complex (MHC) 1 are downregulated [108]. At the same time, co-inhibitory receptors, programmed death ligand 1 (PD-L1), and cytotoxic T-lymphocyte antigen 4 (CTLA-4), which induce immune tolerance to HNSCC, are frequently expressed on tumors [109, 110]. Immunosuppressive cytokines such as TGF-beta, VEGF, IL-6, and IL-10 are upregulated in the tumor microenvironment [111].

The recent success of immune checkpoint inhibitors in solid tumors along with the increased incidence of HPV-positive HNSCC has raised enthusiasm for novel immunotherapeutic approaches and identification of corresponding predictive biomarkers. Indeed, HPV-positive HNSCC arises from the deep crypts in lymphoid tissues of the lingual and palatine tonsils, and characteristic tumor-infiltrating lymphocytes (TILs) are found in the stroma and tumor nests [112]. Expression of PD-L1 is noted within deep tonsillar crypts as well as 70 % of HPV(+) HNSCC tumor cells. These PD-L1-expressing tumors were associated with an increased number of TILs [113]. High PD-L1 expression in the tumor or the tumor microenvironment, especially when it is expressed in tumor-infiltrating immune cells, seems to correlate with the likelihood of response in early clinical studies with PD1 pathway-targeting therapies [114]. Thus, the presence of TILs and expression of PD-L1 are promising candidates as predictive biomarkers for immune checkpoint inhibitors, but further evaluation is necessary.

7.4 Conclusion

Current research and patient care are influenced by the rapidly advancing knowledge of the molecular biology of head and neck cancer and of complex interconnecting pathways from cell surface receptors to transcriptional activation of genes that mediate uncontrolled cellular proliferation and survival. Molecular target identification and an array of new therapeutics present challenges to the standard methodologies for clinical trial designs, evaluation of efficacy, and toxicity. Risk stratification based on molecular prognostic and predictive markers is next on the horizon for advancing the field. This chapter has focused on markers with potential for testing in large-validation clinical trials. As yet, no predictive biomarker has been validated in the selection of therapy for individuals with head and neck cancer. HPV status, determined by p16 expression, HPV DNA, or RNA ISH, has been confirmed to be prognostic for better outcome. It is our responsibility to critically appraise and validate emerging biomarkers in prospective clinical trials to deliver optimal individualized care to patients with HNSCC.

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HPV and EBV in Head and Neck Cancer

8

Jeffrey Brumbaugh, Robert L. Ferris, and Shen Hu

Abstract

The focus of this book chapter is to discuss the role of human papillomavirus (HPV) in head and neck squamous cell carcinoma (HNSCC) and Epstein–Barr virus (EBV) in nasopharyngeal carcinoma (NPC). We have summarized the main events of HPV and EBV life cycle, potential mechanisms of HPV- or EBV-mediated carcinogenesis, and the implications of HPV and EBV in head and neck cancer, with an emphasis on disease diagnosis, prognosis, and therapeutic treatment. The potential of proteomics and metabolomics for studying these virus-associated cancers has also been discussed. A mechanistic understanding of HPV-associated HNSCC or EBV-associated NPC would require profound analysis of these tumors using advanced molecular analysis technologies, which will facilitate the development of preventive and therapeutic strategies for these diseases.

Keywords

Human papillomavirus • Head and neck squamous cell carcinoma • Epstein–Barr virus • Nasopharyngeal carcinoma • Proteomics • Metabolomics

8.1 Head and Neck Cancer

Cancer of the head and neck, including oral, laryngeal, and pharyngeal sites, is the sixth most common malignancy in the world [1]. Each year, almost 650,000 patients worldwide receive the diagnosis of head and neck cancer and some 350,000 die from this disease [1]. Nearly 90 % of these cancers are head and neck squamous cell carcinoma (HNSCC) in histology. Traditionally, HNSCC is causally associated with tobacco use and alcohol consumption. In addition, many studies are identifying an etiological role for infectious agents, such as human papillomavirus (HPV) and Epstein–Barr virus (EBV) in subsets of HNSCC, occurring mainly in the oropharynx and nasopharynx, respectively [2, 3]. In this chapter, we will give an overview about HPV-associated HNSCC and EBV-associated nasopharyngeal carcinoma (NPC).

8.2 HPV and Its Life Cycle

HPV is known as the virus that causes common warts and a host of other more serious conditions, from anogenital and aerodigestive diseases to cervical cancer and laryngeal papillomas. On a molecular level, HPVs are circular, nonenveloped, double-stranded DNA viruses, measuring about 7.9 kb in size. They belong to the *Papillomaviridae* family, all of whose members have a notable similarity in genomic organization [4], and were first isolated in rabbit papillomatosis in 1933 [5]. Early studies of the virus allowed researchers to observe its life cycle, most notably the transition of the benign papillomas in rabbits as they progressed toward

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malignancy [6]. More than 150 different types of HPVs have been isolated and there may be additional types that have not yet been identified [7–9]. The many types of HPVs are categorized into several groupings, based on tropism for infection site (cutaneous or mucosal) and on their risk for malignancy (high, intermediate, or low). The mucosal subgroup of HPVs contains more than 40 identified subtypes, making it the largest subgroup, predominantly infecting the genital and respiratory tracts [4], while the cutaneous type is mostly benign. The risk level of an HPV reflects its association with malignancy, with low-risk HPVs inducing benign hyperplasias, such as papillomas or warts, and with high-risk HPVs strongly linked to malignancy and the possibility of carcinogenesis [10].

The life cycle of an HPV virion is greatly dependent on both its own genetic mechanisms and those of the host cells that it infects. The genome of HPV is comprised of nine open-reading frames, which are divided into seven early-phase genes (E) and two late-phase genes (L) [6]. The early-phase genes encode proteins that regulate viral DNA replication, RNA transcription, and cell transformation, while the late-phase genes encode proteins that are involved in viral spread, such as the structural components of the capsid [11]. During an infection, HPVs typically target the cells in the basal layer of the squamous epithelium, integrating its genome into a host cell and eventually replicating. First, the virus enters and infects the basal cells of the epithelium through either a wound or microabrasions. As these epithelial cells divide and proliferate, the viral DNA also proliferates as a low-copy number plasmid, maintained in the nuclei of the daughter cells. The virus then becomes latent, exhibiting no signs of infection, for an unspecific amount of time. This latency period can last anywhere from several months to the lifetime of the host patient, and the infected tissue is both clinically and histologically normal during this time. In a subset of infected host cells, the HPV may become active, depending on the host's stage of differentiation. Due to a strong association between the HPV and the stage of differentiation of the host cell, the HPV DNA replicates to a high copy number only when epithelial cells move from a basal position to a more suprabasal position and become terminally differentiated. It is also in these suprabasal epithelial cells that the L1 and L2 HPV proteins, which constitute the viral capsid, are synthesized and that the progeny is produced and released. Normally, the suprabasal epithelial cells would not be able to support such DNA replication, but the E1 and E2 proteins allow for productive viral DNA replication and, along with E5, papilloma formation [7, 12]. Once the dead squames of the host epithelium are sloughed off, the viral life cycle continues as the process begins anew.

8.3 Mechanisms of HPV-Mediated Carcinogenesis

After an HPV virion infects a host and begins to form benign papillomas, there is a small chance that a subset of these papillomas will turn malignant. The transformation from a benign papilloma to carcinoma is a rare event, but in the case that it does occur, HPV DNA replication is ceased, and the life cycle of the virus is effectively terminated [12]. From this point, the functioning of several E genes will affect differentiation of the host epithelium, and HPV-mediated carcinogenesis can occur. The genome of high-risk HPVs contributes a vital component to its malignant potential (Fig. 8.1).

Currently, high-risk HPVs are understood to contribute to carcinogenesis mainly through the actions of the two viral oncogenes E6 and E7 [13–15]. E6 and E7 are responsible for inactivating and preventing the accumulation of the human tumor-suppressing proteins p53 and pRb, respectively [16]. It has been observed that E6 proteins of high-risk HPVs bind and form a complex with p53, subsequently marking the tumor suppressant for ubiquitination and degradation [14, 15]. Conversely, small interfering RNA (siRNA) knockdown of HPV-16 E6 results in accumulation of p53 [17]. E7, on the other hand, binds and destabilizes the Rb tumor suppressor protein and related proteins [13, 18]. Accordingly, it has been suggested that E6 is mainly responsible for offsetting the increased levels of p53, and E7 produces a necessary function in promoting cell cycle progression and viral DNA replication in differentiated keratinocytes. It has also been theorized that E6 may not assist in complete p53 degradation but merely diminish its effects [19]. As such, both E6 and E7 play crucial roles in immortalization and transformation, and each has been shown to have these capabilities to some extent independently of each other [20]. Furthermore, HPV DNA integration with host cells has been shown to cause extensive genomic amplifications and rearrangements, by which viral–host DNA concatemers may cause a "looping" effect and amplification of E6 and E7. HPV may directly promote genomic instability in such a way, which is often characteristic of human cancers [21].

Though the E4 protein is not necessary for transformation or episomal persistence of viral DNA, its RNA has been detected most abundantly in benign HPV-induced papillomas, implying that it may play a significant role in the life cycle of the virus [12, 20]. The E4 protein is found exclusively in the differentiating layer of the host epithelial cells and promotes the collapse of the cytokeratin network. Similarly, the E5 protein is assumed to take part in the early stages of HPV infection, but it is not necessary for malignant transformation [20]. In other papillomaviruses, E5 is the

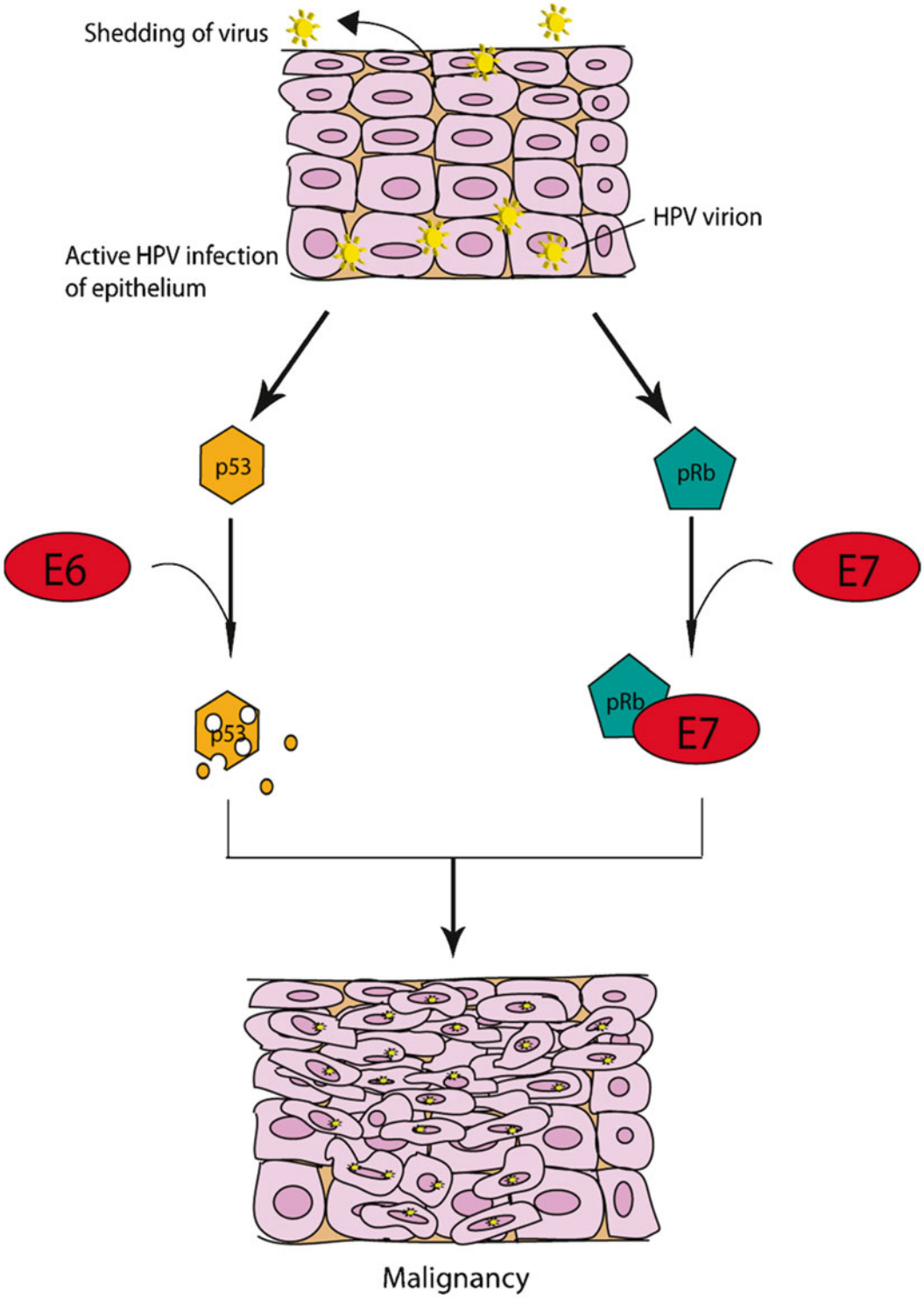

Fig. 8.1 Possible carcinogenic mechanisms of HPV in HNSCC. An active infection of HPV in the basal layer of the epithelium encodes the oncogenic proteins E6 and E7, which degrade the tumor-suppressing proteins p53 and pRb, respectively. E6 marks p53 for degradation by ubiquitination, and E7 binds and destabilizes pRb. The loss of p53 and pRb allow for unchecked growth and eventually to malignant carcinoma

major transforming protein, but in HPV, it only has weak transforming activity [4, 20].

Low-risk HPVs have not been studied as thoroughly as high-risk types, due to their infrequent role in HPV-mediated carcinogenesis. The E6 and E7 oncogenes of low-risk HPV types also target p53 and pRb, but with less ability to perturb their host's cellular functions than in high-risk types [19]. Consequently, they have less capability of inducing carcinogenesis.

By any means, the molecular mechanisms of HPV-mediated carcinogenesis are still not completely understood, and additional studies are warranted. To compound this lack of knowledge, it may also prove difficult to separate the molecular mechanisms and etiological role of HPV in carcinogenesis from the many cofactors of the disease. Studies have suggested HPV is not a sufficient cause for cancer, only recognized as a necessary one [4, 22]. For instance, evidence suggests that the transformation of HPV-infected cells into malignancies require cellular mutations as an impetus, such as carcinogenic agents like tobacco or UV irradiation [12]. One study of self-reported data has identified a correlation between tobacco use and HPV-16 infection. In current tobacco users, including environmental, smoking, and smokeless tobacco use, oral HPV-16 prevalence was higher than in never or former tobacco users. Current tobacco users were more likely to have a higher number of oral sexual partners, which was also shown to be significantly associated with HPV-16 infection [23]. However, partners of patients with HPV-associated HNSCC do not appear to have higher rates of HPV-16 infection than those of the general population [24]. Several other studies have even shown that HPV-transformed cells are noninvasive, implying the need for a cellular cofactor to be present in order for carcinogenesis to occur [4].

8.4 HPV in Head and Neck Precancer

Commonly, HPV itself is recognized in the context of carcinogenesis as the virus is associated with cervical cancers as well as several other anogenital carcinomas. However, current clinical studies are presenting convincing evidence for a causal role of the virus in a subset of HNSCCs [3, 25]. The HPVs of most concern in HNSCC are the mucosal, high-risk types that can infect the epithelium of the aerodigestive tract. Most frequently, HPV-16 and, to a lesser extent, HPV-18 have been detected and identified as two such types, playing important roles in head and neck carcinogenesis [26]. Since HPV infection of the cervix follows a genetic progression from benign papillomas to malignant lesions, the detection of HPV in the precancerous lesions of HNSCC may be an important indicator of the potential presence of the disease.

In the precancerous stages of HNSCC, dysplastic lesions undergo a series of molecular and genetic alterations that eventually lead to malignancy. In order to implicate HPV with an etiological role in head and neck carcinogenesis, it is important to know whether the prevalence of HPV DNA present in early dysplastic lesions increases as malignancy develops. For this purpose, numerous studies have measured the HPV DNA in premalignant lesions and the reported results are conflicting, with HPV prevalence ranging from 0 % to 88 % [27–30]. Even in biopsies of normal mucosa, HPV has been found to exist in low levels. Yet others report that HPV prevalence, especially of high-risk HPVs, is typically higher in oral precancerous lesions such as leukoplakia or proliferative verrucous leukoplakia [31]. The observed discrepancies may be attributed to the variation in examined samples and the sensitivity of the applied methodologies. Overall, HPV may in fact play a role in precancerous lesions, but this has not been histologically or morphologically defined and the progression from precancer to cancer is unclear.

8.5 HPV in Head and Neck Cancer

Though the evidence of HPV involvement in precancerous lesions is varied, the evidence of HPV in HNSCC is well established. HPV-positive HNSCCs comprise a heterogeneous group of squamous cell carcinomas (SCCs) of the oral cavity, pharynx, and larynx [32], each with varying biological/clinical characteristics and unique etiology. Tracing the rates of oropharyngeal cancers from 1983 to 2002, one study marked a noted increase in incidence worldwide mainly in developed countries in younger patients, highlighting a potential role for HPV infection [33]. Specifically, oropharyngeal and tonsillar carcinomas have emerged as an area of particular interest due to their notably strong association to HPV.

A systematic review of the data from 60 published studies revealed an overall HPV prevalence of 25.9 % in HNSCC based on a total of 5046 cancer specimens examined. HPV prevalence was found significantly higher in oropharyngeal SCCs (35.6 % of 969) than oral SCCs (23.5 % of 2642) or laryngeal SCCs (24.0 % of 1435). HPV-16 accounted for a larger majority of HPV-positive oropharyngeal SCCs (86.7 %) compared with HPV-positive oral SCCs (68.2 %) and laryngeal SCCs (69.2 %) [34]. It has also been identified recently in tonsil-related cancers [35]. HPV-18, on the other hand, was very rare in HPV-positive oropharyngeal SCC (2.8 %) compared to other head and neck sites of oral SCCs (34.1 %) and of laryngeal SCCs (17.0 %) [r34]. A case–control study of 100 patients with newly diagnosed oropharyngeal cancer and 200 control patients without cancer concluded that HPV-16 DNA was detected in 72 % of 100 paraffin-embedded tumor specimens, and 64 % of patients with cancer were seropositive for the HPV-16 oncoproteins E6, E7, or both [36]. To further separate HPV-positive oro-

pharyngeal SCCs from other HNSCCs, known risk factors for the disease seem to be markedly absent [37]. Thus, increasing evidence supports that HPV-associated oropharyngeal carcinomas are in fact a separate malignancy, distinct from other HNSCCs in terms of both risk factors and biology [35, 37].

The distribution of specific HPV type and infection sites in laryngeal papillomas and tonsillar infection in oropharyngeal SCC suggests "specific virus–tissue interactions" that only allow for HPV infection in certain sites of the head and neck [34]. While HPV-16 and HPV-18 play a significant role in oropharyngeal carcinogenesis, HPV-6 and HPV-11 may play an analogous role in laryngeal papillomas [26]. Although more than one type of HPV can be found in tumor specimens, the low-risk types of HPV found in the majority of laryngeal papillomas differ from the high-risk HPVs in oropharyngeal SCCs. Similarly, the split between the types of HPV found in oropharyngeal and laryngeal SCCs is evidenced by the uneven distribution of HPV-16 and HPV-18 as previously mentioned. In addition, data collected from oropharyngeal SCC studies have shown that the tonsils are infected in particular more often than the rest of the oropharynx, though both contain HPV-16 as the dominant virus [34]. It seems that laryngeal papillomas and tonsillar SCC point toward a specific HPV tissue interaction, but further investigations are required to determine a more precise distribution of HPV types in various HNSCC locations. High-risk HPV subtypes may also possess more potent immune evasion capability, permitting malignant progression.

More than 20 different types of HPVs have been reported in HNSCC, and as many as 14 have been identified as high risk in cervical cancer [34]. The International Agency for Research on Cancer (IARC) concluded that there was sufficient evidence to implicate HPV-16 in causing carcinomas of the oral cavity, the oropharynx, and the tonsils, but limited evidence for HPV-18 in the oral cavity [38]. The IARC found inadequate evidence for other HPV types in the oral cavity and in the oropharynx, limited evidence for HPV-6, HPV-11, HPV-16, and HPV-18 in the larynx, and inadequate evidence for the carcinogenicity of HPV in the esophagus [32]. However, there is some evidence for a role of HPV-6 and HPV-11 in laryngeal papillomas which may occasionally turn malignant [38].

8.6 Detection of HPV and Diagnosis of HPV-Positive HNSCC

In the study of HPV in human cancers, many detection techniques of HPV DNA have been established. One of the primary concerns when performing molecular detection of HPV DNA is the sensitivity and reliability of the applied techniques. Compared to other HPV-positive SCCs, such as cervical carcinomas, HPV-positive HNSCCs and related dysplasia seem to have a relatively low level of HPV DNA present. For instance, studies involving polymerase chain reaction (PCR) assays of HPV-positive HNSCCs have produced weaker results when using samples from both oral mucosa and cancerous lesions in the head and neck as opposed to cervical carcinomas, potentially due to saliva clearance of the virus [35].

A wide variety of methods are currently being used to detect HPV in HNSCC, including PCR assays, in situ hybridization, Southern blot, and antibody detection, which in turn may provide for early diagnoses and treatment of HNSCC. PCR is utilized as one of the most sensitive methods of detecting HPV DNA in both cancerous and precancerous lesions. However, one of the drawbacks of using PCR is also one of its most pronounced strengths: its extreme sensitivity. As such, PCR is prone to contamination, and if contaminated, a sample of cancerous tissue analyzed using PCR may provide either an overestimation or underestimation of possible HPV positivity. Commonly, PCR detection of HPV relies on the amplification of the E6, E7, and L1 sequences of the viral genome. Compared to conventional PCR techniques, real-time quantitative PCR analysis is able to quantify the amount of HPV DNA in a tissue sample as well as greatly reduce the risk of contamination, thus providing more accurate results [22, 29, 39]. A "MassARRAY" assay based on coupling mass spectrometry with competitive PCR was described for measuring HPV DNA in serum and/or peripheral blood fraction of individuals with cervical, head/neck, or bladder cancers. The technique may be more sensitive than real-time quantitative PCR-based assays while specificity was maintained [40].

Before PCR was widely used, in situ hybridization (ISH) and Southern blot were prevalently used for detecting HPV DNA. In situ hybridization (ISH) involves the use of type-specific radioactively labeled DNA probes complementary to HPV sequences for detection. It is a clinically useful test to confirm the diagnosis of HPV and therefore has widespread applicability [10]. Southern blot, on the other hand, is known for its high specificity and low rate of contamination, even being able to distinguish between integrated and episomal HPV DNA [6].

Aside from the more classical methods of HPV detection, screening individuals for the presence of HPV antibodies or related proteins provides yet another way to detect the virus. HPV infections are in fact very commonplace among adults, and as a result, anticapsid antibodies are produced during the infection. Those exposed to harmless HPV infections and those exposed to high-risk carcinogenic HPVs, however, differ in the type of antibodies that the body produces. Serum antibodies to the viral capsid proteins, E6 and E7, are most frequently detected in individuals with HPV-positive cancer, as opposed to the anticapsid (L1) protein antibodies found in normal indi-

viduals. The detection of such specific immunologic biomarkers may provide evidence for the presence of the viral genome in patients as well as indicating a higher risk of developing HPV-mediated carcinoma. Similarly, immunohistochemical analyses of the expression of p16 may provide an important method of detecting productive HPV infection [37, 41, 42]. In many types of SCCs, the functional loss of p16 has been observed. In contrast, HPV-positive SCCs, including those of the head and neck, have shown a strong overexpression of p16, probably due to the impairment of the negative feedback control of pRb by the viral oncogene E7 among other mechanisms [35, 37, 41]. Further investigation of p16 may support its potential application as a biomarker in standard screenings, reflecting HPV status in early dysplastic lesions [37].

Early diagnosis of HNSCC is critical for reducing the rate of mortality of the disease and is the focus of much research in the field. As such, the molecular detection of HPV serves a vital purpose. Oftentimes, it may be difficult to appropriately diagnose HPV-positive HNSCC, since there are such a wide variety of molecular assays, sampling methods, and oral specimens available that standardization of methods is a difficult task [35]. Oral rinses have been suggested as another method of detection, but most oral HPV infections are cleared too quickly to be utilized for screening purposes [43]. Nevertheless, a positive detection of HPV infection does not necessarily indicate the development of head and neck cancer. In this regard, it is also important to develop molecular biomarkers (in addition to HPV DNA and proteins) for an improved diagnosis of HPV-positive HNSCC. Recently, expression of p16 has been recognized as a prognostic marker in cancer of oropharynx, as well as of the oral cavity, hypopharynx, or larynx, where HPV infection is not as common. Patients with p16-negative HNSCCs, of the oropharynx or non-oropharynx, have a poorer prognosis than p16-positive cancers [44].

8.7 Prognosis of HPV-Positive HNSCC and Therapeutic Treatment

Prospective clinical trials and large retrospective studies have shown that patients diagnosed with HPV-positive HNSCC have a more favorable prognosis than patients who have HPV-negative HNSCC [41, 45–48]. It has been estimated that HPV-positive tumors may reduce the risk of death by nearly 60–80 % in HNSCC patients when compared to HPV-negative tumors [10]. Since HPV-positive HNSCCs are molecularly and clinically distinct from HPV-negative cases, many hypothesize that there are factors specific to HPV-positive tumors that can explain the reduced rate of mortality and that cause them to respond differently to treatment [41]. Other cofactors need also be considered: tobacco use negatively affects the prognosis of HPV-positive HNSCC, and the female gender and black race also negatively impact prognosis of HNSCC in general, though the relationship is less clear with HPV-positive HNSCC specifically [49]. In oropharyngeal SCC specifically, HPV status, pack-years of tobacco smoking, tumor stage, and nodal stage have been shown to be strong prognostic factors for patient survival [50]. The United States has seen increases in both incidence and survival of oropharyngeal cancers, attributable to HPV infection [51]. This phenomenon certainly warrants further molecular analysis of HPV-positive HNSCC to understand the molecular mechanism responsible for favorable prognosis.

Most prominently, vaccines have come to the forefront of the battle against virus-associated cancers. A vaccine that could potentially prevent HPV infection, suppress its viral effects, or both would prove effective in treating HPV-positive HNSCC. Theoretically, a prophylactic vaccine should prevent HPV from infecting a host epithelium by completely neutralizing the virus upon exposure. Several prophylactic vaccines are already on the market (e.g., Gardasil and Cervarix) [7]. Such vaccines have the potential to prevent a significant number of anogenital carcinomas, most notably cervical cancer, but their effectiveness in preventing HNSCCs still remains to be evaluated [25]. In addition, the duration of protection that the vaccine offers is unknown, they do not guard against all types of HPV that could potentially result in carcinogenesis, and they are not therapeutic against existing infections [7, 52]. Gardasil is a quadrivalent vaccine developed by Merck that protects against HPV-6, HPV-11, HPV-16, and HPV-18, and Cervarix, developed by GlaxoSmithKline, is effective against HPV-16 and HPV-18 [52].

If a patient has already been infected with the virus, a therapeutic vaccine should instead induce a cellular immunity in which mainly T cells are primed against HPV antigen epitopes expressed by oncogenes E6 and E7 [11]. It may also be possible to develop a vaccine that provides both types of protection from HPV: prophylactic and therapeutic. Chemotherapeutic vaccines targeting the viral oncogenes E6 and E7 are still under development.

Similar to the idea of a therapeutic vaccine targeting E6 and E7, gene therapy for HPV-positive carcinomas provides another possible tool in combating HPV-mediated carcinogenesis. While not ready for clinical use in humans, the potential implementation of gene therapy might entail the use of E6 short interfering RNA, antisense RNA to E6 and E7, and a mutated E2 protein that would induce apoptosis in cancer cells [11, 12, 35]. Other studies have even suggested that altering the metabolism of estrogen in the body could prevent some laryngeal papillomas and laryngeal cancers, since estrogen levels can affect the risk of cancer in some tissues sensitive to hormones [12].

Radiation therapy has proven to be rather effective in treating HPV-positive HNSCCs with significantly improved survival rates of HPV-positive carcinomas in the head and neck [53, 54]. Cidofovir is an antiviral drug used to treat HPV-induced laryngeal papillomatosis and other viral infections, with initial reports

suggesting activity in cervical carcinoma cells. In the presence of cidofovir, HPV-16-transformed HNSCC cells exhibit a pronounced sensitivity to irradiation, perhaps due to the induction of p53 expression by cidofovir. Because p53 mediates proapoptotic effects of XRT, this provides a mechanistic explanation for cidofovir as a radiation-sensitizing agent [55].

Immunotherapy (e.g., targeting p53-derived or E7-derived peptides) may provide a potential approach to combating HPV-associated HNSCC [56, 57]. Wild-type sequence (wt) p53 peptides are attractive candidates because elevated levels of p53 protein occur in a high proportion of human carcinomas, including HNSCC. However, in HPV-associated HNSCC, increased proteasomal degradation of p53 may result in appreciable presentation of p53-derived peptides, despite low p53 expression. The requirement of p53 overexpression would visually exclude these individuals from wt p53-based immunotherapy. In fact, both wt and mutant p53 molecules were found sensitive to E6-mediated degradation in HPV-associated HNSCC and this HPV-induced p53 degradation was correlated with increased T-cell recognition of the tumor cells in vitro and in vivo. These findings suggest that p53 peptides may be useful tumor antigens for HNSCC immunotherapy and T-cell-mediated immunotherapy against wt p53 should not be restricted to tumors overexpressing p53 [57]. HPV-encoded oncogenic proteins, such as E7, are also promising tumor-specific antigens. T-cell frequencies against E7-derived peptides (HPV-16 $E7_{11–20}$ and $E7_{86–93}$) were found significantly elevated in HPV-16-positive HNSCC patients compared with HPV-16-negative patients or healthy volunteers. In addition to the presence of HPV-specific effector T cells, successful tumor elimination requires that HPV-infected tumor cells function as appropriate targets for cytotoxic T-lymphocyte (CTL) recognition and elimination. The study also suggested endogenous E7-specific immunity exists even in the presence of ongoing virus-associated malignancy, perhaps due to immune escape of tumor cells from CTL recognition by downregulation of some antigen-processing machinery component expression. These findings support that E7-derived peptides are potentially useful targets to facilitate HPV-specific immunotherapy of HNSCC [56].

8.8 EBV and Its Life Cycle

EBV was first discovered in 1964 from a patient with African Burkitt lymphoma (BL) [58]. As one of the most common human viruses, EBV is known today around the globe, infecting adults and children alike. Spread from person to person through close contact, EBV infection usually goes unnoticed by most, occurring as a subclinical illness or simple childhood sickness. The age at which a person becomes infected with the virus, however, depends on several factors, including living conditions, hygiene, and sexual behavior. By adulthood, over 90 % of the population has been infected by EBV at some point in their lives [59].

EBV itself is a γ(gamma)-herpes virus and a member of the *Herpesviridae* family. The herpesviruses consist of generally large, complex DNA viruses, are able to encode about 100 different proteins, and are one of the largest virus groups that significantly infects the pediatric population. After a primary infection, herpesviruses typically establish permanence in their host, in the form of a lifelong infection. In the case of EBV, the virus perpetuates its existence by latently infecting circulating B cells, which are subsequently shed into genital and salivary secretions. Instead of damaging or destroying the B cells that it infects, EBV increases the number of B cells in the host and extends their survival, causing a sudden growth of infected cells and ensuring the virus' permanence [59, 60].

The life cycle of EBV consists of two separate phases, which include an active, lytic form of infection and a latent state of infection. Most often, EBV resides in its host in a state of dormancy, infecting B lymphocytes in the blood. In this state, EBV expresses very few viral proteins and remains undetectable by the host immune system. Each B-cell carrier would contain around 2–5 copies of intact, circular viral DNA. But, as a highly infectious virus, EBV is capable of periodically reactivating and commencing the lytic phase of its life cycle. The lytic cycle then produces new progeny virions, infects more B cells, and eventually returns to a state of latency. Since the life cycle of EBV so closely resembles the natural differentiation pathway of antigen-activated B cells, the virus is able to guide infected B cells through its various stages of differentiation, essentially dictating whether EBV will exist in its latent or active form. It is in its ability to alter the various stages of B-cell differentiation and to permanently affect its growth transformation that EBV has its pathogenic capacity, which in turn results in the numerous lymphomas and carcinomas for which EBV is responsible [60–62].

8.9 Mechanisms of EBV-Mediated Carcinogenesis

While it may seem counterintuitive, EBV poses the larger risk of becoming tumorigenic when in its latent state, rather than in its active state. When EBV induces growth transformation in its host cell, the production of progeny virions is ceased, and the virus undertakes a tumorigenic pathway of replication. The host B cells propagate EBV's DNA by replicating it as an extrachromosomal episome, utilizing the host's own DNA polymerase. The tumorigenic properties of this type of latent infection largely come from a small set of latent genes, which include the latent membrane proteins (LMP1, LMP2A, and LMP2B) [63, 64], the EBV nuclear antigens (EBNA1, EBNA2, and EBNA3) [65, 66], and the EBV-encoded noncoding RNAs (EBERs) [62, 67, 68] (Fig. 8.2).

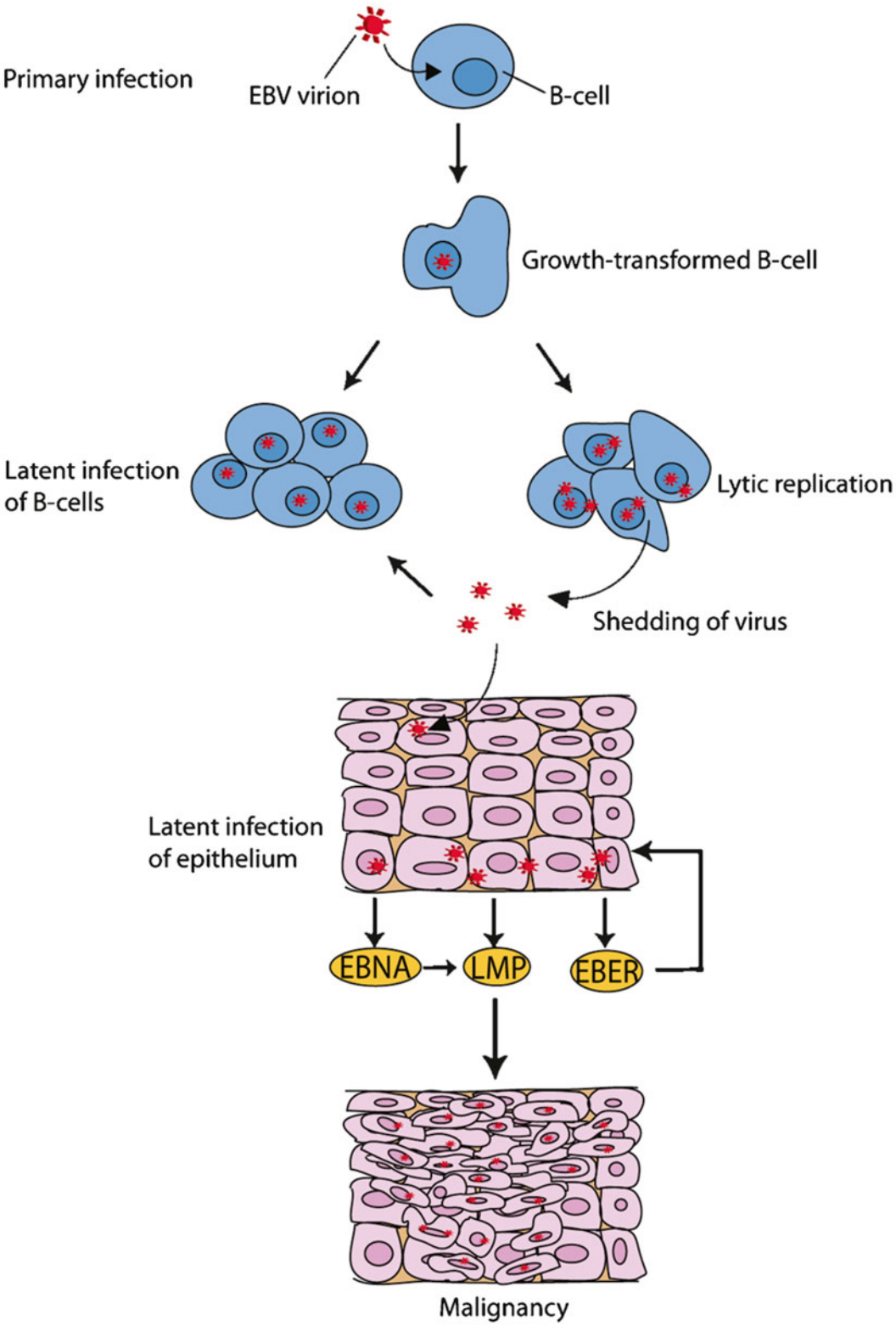

Fig. 8.2 Possible carcinogenic mechanisms of EBV in NPC. After the primary infection of a B cell by EBV, the growth-transformed B cell may undergo two different pathways. Usually, EBV will establish a latent infection in the B cells, lying in a state of dormancy. On occasion, however, the lytic phase of its life cycle may commence, and EBV will replicate in the B cells, shedding EBV virions which can then latently infect either more B cells or the epithelium of the nasopharynx. As the EBERs maintain viral latency, the EBNAs upregulate the LMPs—namely, LMP1, the principal oncoprotein responsible for inhibiting cell differentiation and promoting malignancy

EBNAs play a major role in promoting the activities of the other proteins, primarily oncogenic LMPs. In particular, EBNA1 holds a great deal of significance since it is found universally in all EBV-associated tumors and the presence of EBNA1 enables the EBV genome to be replicated and passed along to the daughter cells of an activated, dividing host. In addition to EBNA1, EBNA2 is produced during an infection and acts as the major transcriptional regulator of both cellular and viral expression. It has been shown, by deletion of the gene encoding EBNA2, that the protein is crucial in the transformation of infected B cells [62, 69, 70]. Functionally, EBNA2 upregulates the expression of several B-cell antigens, such as CD21 and CD23, plus the viral membrane proteins LMP1 and LMP2. Lastly, the EBNA3 family—which includes EBNA3A, EBNA3B, and EBNA3C—encodes hydrophilic nuclear proteins. The EBNA3s, with the exception of EBNA3B, have been demonstrated to be indispensable in B-cell transformation in vitro [59, 62, 69, 70].

As the principal EBV oncogene, LMP1 is necessary for cell immortalization and has demonstrated transforming ability. This viral protein has a significant effect on epithelial cell growth and inhibits cell differentiation, often inducing growth transformation. LMP1-positive cells have increased mobility, which in turn leads to greater tumorigenic potential and faster disease progression. In addition, LMP1 is also involved in suppressing immunogenic responses through its capacity to downregulate T-cell response genes related to tumor antigen presentation. On the other hand, less is known about LMP2A and LMP2B. Studies in rodent populations have suggested that LMP2A is a driving force behind the proliferation and survival of B cells, thus maintaining EBV latency and preventing the activation of the EBV lytic cycle. Reports have also shown that LMP2A can transform epithelial cells. The role of LMP2B is less complex, and it is thought to regulate LMP2A function [59, 62, 70]. Overall, the EBV LMPs may target multiple signaling pathways and sites that are important in controlling cell proliferation [71].

Lastly, the presence of EBERs is a characteristic of latent EBV infection, although they are not necessary for B-cell transformation. The EBERs are small, nuclear RNAs that are the most abundant RNAs in EBV-infected cells. They are present in all forms of latency and are thought to contribute to malignancy by maintaining viral latency. In some EBV-associated malignancies, such as BL, EBERs seem to play a more critical part in contributing to pathogenesis, especially in initiating B-cell growth transformation [62, 69].

The EBNAs, LMPs, and EBERs have been identified as the molecules of most interest in EBV-associated tumorigenesis. However, to some extent, EBV infection appears to be necessary but not sufficient for tumorigenesis in NPC. Although there are many aberrations that contribute to tumorigenesis, the critical signals in NPC development are the Wnt pathway and transcription factors NF-kappa B and beta-catenin. Most NPC tumors exhibit Wnt pathway protein dysregulation and overexpression of beta-catenin and NF-kappa B [59]. Another possible mechanism of EBV carcinogenesis includes interaction of these EBV proteins with telomerase activity through regulation of the *hTERT* gene. It is speculated that in EBV-associated cell immortalization, LMP2A may inhibit telomerase activity to suppress B-cell activation and maintain viral latency [71].

As with any carcinoma, the loss of tumor suppressors is to be expected. In EBV-mediated tumorigenesis, however, levels of tumor suppressors are less predictable. While p16 and p27 activity is decreased in EBV-associated carcinoma, high levels of p53 are found. It is unclear whether increased p53 levels contribute to EBV malignancy or whether it is merely a natural response to infection. Another oncogene that may play a role in EBV-associated carcinomas is the *BARF1* gene, which has been demonstrated to play an important role in growth promotion. Since the BARF1 protein exists in serum, it may also prove to be a useful diagnostic biomarker in some patients with EBV-associated carcinoma [59, 72, 73].

8.10 EBV in Nasopharyngeal Precancer

NPC is an EBV-related malignancy found mainly in parts of Southeast Asia. Tumorigenic activities of EBV in NPC have been well studied and documented, but there is a lack of evidence regarding the interaction of EBV and precancerous lesions of NPC. EBV infection has been well studied in B cells but not in nasopharyngeal epithelial cells [74]. In contrast to many cancers, early manifestations of malignancy such as dysplasia or carcinoma in situ are rare in the development of NPC. In one study, screening for dysplasia and carcinoma in situ, only 11 out of over 5000 nasopharyngeal biopsy samples displayed early malignant changes without adjacent invasive carcinoma. These 11 samples were then analyzed for the presence of EBV, and in all cases, the expression of EBV DNA, EBERs, and LMP1 were detectable. These results imply that the preinvasive lesions serve as a focal point of EBV-induced cellular proliferation and that EBV infection precedes the development of malignancy [75]. Additional studies support this notion that EBV infection is an early event in precancerous lesions and that EBV infection may confer enhanced survival ability to infected tumor cells [74]. Cell-to-cell contact, between EBV-infected B cells and nasopharyngeal epithelial cells, has also been identified as a possible route of EBV entry and oncogenesis [74].

However, in other reports, EBV DNA was detected in only a portion of the cells of tissue samples with carcinoma in situ, as opposed to all of the cells [76]. This suggests that EBV infection occurred after the initial neoplastic event and

that some preceding genetic change may affect viral infection, allowing for a latent EBV infection to establish and express oncogenic proteins. Another study highlights the loss of the p16 tumor suppressor as a potential contributor to the progression toward invasive malignancy. A more recent study suggested that chromosomal losses, which affect the chromosome 3p, occur at a preinvasive stage, early in the development of tumorigenesis. Early dysplastic lesions examined in this study supported the evidence that EBV infection in fact occurs after genetic alterations in the cell, allowing a latent EBV infection to develop [77]. Of course, these controversial results warrant further studies to investigate the role of EBV in precancerous lesions of the nasopharynx. Other cofactors in addition to EBV infection, including genetic modifications in tumor suppressors such as p53 and pRb or in *ras* genes, as well as environmental factors, may need to be considered as possible sources of preinvasive malignancy.

8.11 EBV in Nasopharyngeal Cancer

The association of EBV with NPC can be dated back to the early 1970s [78–80]. While NPC is often simply thought of as an EBV-related malignancy, it can be defined more precisely as a squamous cell carcinoma (SCC) that develops around the ostium of the Eustachian tube in the lateral wall of the nasopharynx. NPC tumors are comprised of malignant, EBV-infected epithelial cells that are surrounded by reactive lymphocytes [81]. The World Health Organization (WHO) classifies NPC into three categories, based on its histology. Type 1—keratinizing SCC—is characterized by well-differentiated cells that produce keratin. Type 2—nonkeratinizing SCC—is more varied in cell differentiation and does not produce keratin. Lastly, type 3—also nonkeratinizing SCC—is undifferentiated with highly variable cell types. In NPC, types 2 and 3 are EBV associated and have an overall better prognosis than type 1, which is typically EBV absent [59, 81]. Some studies suggest that regardless of subtype, all NPC shows strong evidence of EBV as an etiological factor in the onset of the disease, whereas others maintain that the association of EBV with more than type 3 NPC is controversial at best [59, 82, 83].

EBV episomes and viral proteins are consistently detected in all cells of most tumors associated with the virus, implying the necessary nature of EBV in the development of these malignancies. Since a ubiquitous EBV virion can lead to a wide range of cancers, it is clear that other factors aside from EBV must influence the development of these cancers as well. As such, EBV is recognized as a necessary, but insufficient, cause for NPC. EBV strain variation may play a part in determining the type of cancer that will arise, implying specificity in EBV strain and malignancy. Potential cofactors, including epidemiological patterns, genetic susceptibility, and environmental factors such as salted or pickled foods and exposure to fumes and chemicals from the occupational environment, have also been associated with the development of NPC [80, 82, 83]. In areas with high incidence, NPC clusters in families, suggesting that both geography and genetics may influence disease risk. A genome-wide scan for familial NPC revealed evidence of a major susceptibility locus for NPC on chromosome 4 [84].

In type 3 NPC, EBV infects the epithelial cells of the posterior nasopharynx. To explain the infection of these specific cells by NPC, two mechanisms have been proposed. First, while an EBV-compatible receptor on epithelial cells has not been found, the CD21 receptor, which is a surface protein antigenically related to B cells, could potentially be used as a point of virion entry. Alternatively, it has been suggested that EBV may gain entry into the nasopharyngeal epithelial cells through IgA-mediated endocytosis [85, 86]. In either case, the EBV genomes present in the epithelial cells are of clonal origin, and EBV is distinctly absent from surrounding tissues and invading T lymphocytes.

Another point to consider when discussing the causality of EBV in NPC is the way in which EBV-infected cells can evade the immune response. EBV-infected epithelial cells in the nasopharynx possess normal antigen processing and are recognized by EBV-specific cytotoxic T lymphocytes, but they are not destroyed [60, 82, 87]. One possible explanation involves the increased production of IL-1α(alpha) and IL-1β(beta) by the infected epithelial cells, which control the levels of lymphocytes and contribute to the growth of the tumor [88]. In addition, the overexpression of bcl-2 allows the infected cells to bypass apoptosis and this contributes to oncogenesis [89].

Overall, it has been well established that EBV contributes to the development of NPC, although to which specific WHO classification is less clear. EBV has been consistently linked to the disease in epidemiological studies, serological analyses, and the expression of malignant viral products by EBV, implying an etiological role for the virus in NPC.

8.12 Detection of EBV and Diagnosis of EBV-Positive NPC

The detection methods for EBV mainly rely on the presence of EBV DNA and its gene products [90, 91]. Depending on the type of latent infection present, different EBV-associated proteins may be detected in EBV-infected patients. Typically in NPC, type 1 and type 2 latency are observed [62, 92]. Namely, EBER transcripts, as well as ENBA1 and LMP2A proteins, characterize type 1 latency, while type 2 latency additionally expresses LMP1 and LMP2B [91]. Lab testing of EBV can be accomplished in several ways, including in

situ hybridization, Southern blot analysis, EBV DNA amplification with PCR, and serological analysis, all of which may contribute to early detection and diagnosis of EBV-positive NPC [91].

EBER in situ hybridization is considered the gold standard for detecting and localizing latent EBV in tissue samples. EBER transcripts are expressed in virtually all EBV-related NPC tumor cells yet are notably absent in adjacent normal tissue. This localization appears to occur in the early stages of infection and, as such, becomes a valuable diagnostic tool. The main advantage of using in situ hybridization is its ability to localize EBV in the context of cytological and histopathological features of the tissue [73, 91]. EBER in situ hybridization has been established as the most sensitive and practical means of detecting EBV [93]. Southern blot analysis is based on the variable number of terminal repeats at the ends of each EBV DNA molecule. Since any cell is only infected once with EBV, each infected cell may contain up to 20 terminal repeats from the infecting genome of the virus. EBV-related NPCs harbor monoclonal EBV DNA that can be detected with a clonality assay. After lesional EBV DNA is subjected to *BAM*HI restriction enzyme, electrophoresis, and transfer, monoclonal patterns can be distinguished and the amount of linear EBV DNA present can give some indication of active viral replication [91, 94].

EBV DNA amplification with PCR provides yet another method for the detection of EBV DNA in blood, fluid, or tissue samples [91, 95]. Since EBV DNA is present to some degree even in healthy virus carriers, this detection method lacks the specificity of EBER in situ hybridization. The use of EBV DNA amplification with real-time quantitative PCR, however, leads to the possibility of EBV viral load measurement. The assays are relatively quick, can be used as a screening method based on body fluid testing, and therefore appear to have advantages over other methods of viral detection [91, 96]. Since quantitative PCR permits precise measurement of EBV DNA levels in clinical samples, EBV viral load assays might be able to distinguish low-level infection in carriers from higher levels associated with EBV disease. Serology remains the most accurate detection method for confirming acute versus remote EBV-related infections. EBV-specific serological assays through enzyme-linked immunosorbent assay or immunofluorescent assay are used for more precise indication of acute or recurring EBV infection [91, 97]. Since other diseases can present biomarkers similar to those associated with EBV-related NPC, additional detection methods are commonly used to confirm the presence of EBV, most notably quantitative DNA amplification assays.

The early detection of EBV in NPC is absolutely critical concerning the prognosis of a patient, since NPC exhibits an extraordinarily high cure rate for early-stage disease. The detection of NPC is based on the clinical history of the patient and a physical examination, but a definitive diagnosis requires a biopsy of the lesion. However, it has been shown that noninvasive brushings of NP lesions to detect *BARF1* and *EBNA1* mRNA loads can be highly specific. Such an approach may be useful as a screening tool to reduce the number of NPC biopsies and as a means to monitor patients after therapy [98]. A combination of radiologic assessments, including CT and MRI scans of the head and neck, is used to assess the tumor and stage of the disease. Although there are mixed reviews of the usefulness of serology in predicting and diagnosing NPC, it is often a common technique to determine the status of EBV infection and site of the primary tumor [99].

8.13 Prognosis of EBV-Positive NPC and Therapeutic Treatment

Early diagnosis of NPC is vital in combating the disease, as it is much more effective when the tumors are treated at early stage. With traditional radiotherapy or chemotherapy, early-stage NPC treatment has proven to be highly effective, while later stage treatment using the same therapies, targeting NPC that is already metastatic or recurrent, provides much less favorable results [100]. The prognosis for individuals with NPC recurrence or progression remains very dim, as about 85 % of patients die within 1 year and, virtually, all die within 3 years [101].

Considering the poor prognosis of individuals diagnosed with late-stage NPC, it is important to screen patients regularly for the presence of the disease in order to provide effective treatment. Similar to other carcinomas, the prognosis of NPC depends on the size of the tumor, lymph node involvement, and distant metastasis [59]. Several studies have attempted to characterize the prognoses of patients with EBV-positive NPC in relation to the presence of several different diagnostic biomarkers [102, 103]. One study has demonstrated that the presence of EBNA1 DNA in peripheral blood cells is an important risk factor for patients with NPC, indicating a significantly higher risk of developing distant metastasis and an overall lowered survival rate [103]. Another study has suggested that the quantitative analysis of plasma EBV DNA levels is a useful tool in screening and monitoring potential NPC patients [104]. EBER in situ hybridization signals is an additional diagnostic marker of prognosis, as patients with EBER in situ hybridization positive signals received a much better prognosis, which may alter treatment considerations [93].

Aside from detection of biomarkers in screening for early disease, various imaging modalities may be useful in detection of NPC. Computerized tomography (CT) and magnetic resonance imaging (MRI) both can be used for detection of

early lesions, though generally MRI is considered superior in detecting soft tissue anomalies. Positron emission tomography (PET) use is not justified or suitable for early diagnosis of NPC, but it may be useful in detecting recurrent NPC regions when MRI is unsuccessful. Narrow-band imaging (NBI) is a novel technique to enhance the sensitivity of endoscopes and can be useful in detecting early mucosal lesions [105].

The standard treatment for NPC is radiotherapy, but better prognoses are obtained when utilized in combination with adjuvant chemotherapy [59, 105]. Since EBV infection in tumor cells is generally restricted to a latent form, switching from the latent form of viral infection into the lytic form may induce tumor cell apoptosis [106]. One potential tool for accomplishing this is the use of valproic acid (VPA), an antiseizure drug that also has strong histone deacetylase inhibitory activity, for activating lytic viral gene expression in EBV-positive tumors [107]. Another line of study involves the use of a variety of chemotherapeutic agents, including *cis*-platinum, 5-fluorouracil (5-FU), and taxol to induce the switch from the latent to lytic form of EBV infection in tumor cells. Because the lytic form of EBV infection converts the cytotoxic prodrug, ganciclovir (GCV), into its active form, the combination of GCV and chemotherapy has been shown to be much more effective in the treatment of EBV-positive NPC than either agent alone [108]. A follow-up study of the metastatic NPC patients with chemotherapy indicates that a high percentage of the patients (~70 %) can attain complete responses and long-term survival (disease-free for at least 36 months). The data confirms the promising potential of chemotherapy in treating NPC [102].

Cell therapy is another model that holds great promise for a specific treatment against EBV-positive NPC, targeting the viral aspect of the disease. EBV is present in virtually all poorly differentiated and undifferentiated nonkeratinizing NPCs, which makes it a reliable target in cell therapy. EBV expresses a restricted set of viral antigens, namely, LMP1 and LMP2, in addition to EBNA1, all of which are immunogens that are capable of inducing a T-lymphocyte response. Because it has been shown that NPC cells are capable of immunologic processing for cytotoxic T-lymphocyte recognition, studies have been conducted to explore the possibilities of pulsing dendritic cells with EBV peptides to enhance T-lymphocyte immunity. Generally, clinical responses to cell therapy have been well tolerated, although it does have its limitations in tumor specificity and targeting tumors with poorly expressed EBV antigens [100, 101].

Due to the involvement of EBV in NPC, there is also the potential for the use of prophylactic and therapeutic vaccines for treatment. However, considering the diversity of EBV-pathogenic mechanisms and EBV-related diseases, vaccines can only be designed for one disease entity, rather than all EBV-related malignancies [109]. Despite this shortcoming, a polyepitope-based vaccine has been developed for NPC that has numerous advantages over traditionally proposed vaccines that target EBV LMP antigens [110].

8.14 Proteomics of HPV- and EBV-Associated Cancers

Proteomics is a powerful approach for biomedical research because it aims for a comprehensive, quantitative analysis of protein expression and its changes under biological perturbations such as disease or drug treatment. Recent studies on stably transfected cancer (cervical and colon) cell lines have indicated that proteomics is powerful to identify the target proteins of E6 or E7 modulation as well as the E7-interacting proteins [111–113]. Analysis of the protein alterations and E7 binding partners in the transfected cells suggested that HPV-16 E7-infected epithelial cells could evade immune surveillance or resist against apoptosis by inducing or binding to chaperones, cell signaling, and cell cycle regulatory proteins [111, 112]. Similar proteomic studies can be performed to unveil the target proteins and binding partners of E6 and E7 in HNSCC, which can provide further insight on the mechanistic understanding of HPVs in head and neck oncogenesis and facilitate the development of antiviral or anticancer drugs based on these target molecules and protein–protein interactions. The best-known cellular targets of the HPV-16 E7 oncoprotein are the retinoblastoma tumor suppressor protein pRB and the related pocket proteins p107 and p130. However, there is ample evidence that E7 has additional cellular targets that contribute to its transforming potential. To identify cellular targets of HPV-16 E7, tandem affinity purification can be used to pull down HPV-16 E7-associated cellular protein complexes, and subsequently, mass spectrometry (MS) can allow for the identification of cellular targets of E7. Using this approach, a 600-kDa retinoblastoma protein associated factor, p600, has been identified as a cellular target of E7. The protein regulates cellular pathways contributing to anchorage-independent growth and cellular transformation [114].

When applied to studying HPV-positive and HPV-negative cancers, proteomics could reveal target proteins that have diagnostic or therapeutic implication in the diseases [115–117]. For example, proteomics has been successfully used to identify a novel target protein, retinoblastoma-binding protein 48 (RbAp48), as an important mediator controlling the transforming activity of HPV-16 in cervical cancer. The protein was found differentially expressed between HPV-positive and HPV-negative cell lines and cancer tissues based on 2-D gel electrophoresis and MS. Suppression of RbAp48 using small interfering RNA in cervical epithelial cells significantly stimulated cell proliferation and colony formation. Conversely, overexpression of RbAp48 signifi-

cantly inhibited cell growth and tumor formation [117]. Another target protein identified by proteomics to be central in HPV-related HNSCC is interleukin-6 (IL-6). Comparing HPV-positive and HPV-negative tumors via Western blot, immunocytochemistry, and ELISA analysis, one study found 36 proteins to be differentially expressed in HPV-16-related tumors. IL-6 in particular was suggested to play a central role in the survival and proliferation of cancer cells [118].

In oropharyngeal SCC, proteomic analysis of tumors by HPV status similarly revealed differentially expressed proteins. HPV-negative tumors showed enrichment of proteins associated with epithelial cell development, keratinization, and extracellular matrix organization, while HPV-positive tumors upregulated proteins associated with DNA replication and cell cycle control. Overexpression of argininosuccinate synthase 1 in HPV-positive oropharyngeal SCC was also noted, suggesting a dependence on arginine, an essential amino acid [119]. These results suggest that proteomics profiling followed by molecular biology validation is a powerful approach to elucidate signaling molecules in HPV-associated cancers and may reveal novel-driving molecular pathways between HPV-positive and HPV-negative cancers.

Likewise, proteomics may have promising applications in EBV-positive NPC toward the mechanistic understanding of the disease and discovery of diagnostic/therapeutic targets [120]. Using proteomics and a phosphoprotein enrichment method, LMP1 was found to increase the quantity of total phosphoproteins by ~18 %, and many proteins (e.g., annexin A2) showed significant changes in the degree of phosphorylation when LMP1 was expressed [121]. LMP1 increased the serine, but not tyrosine, phosphorylation of annexin A2 by activating the protein kinase C (PKC) signaling pathway [122].

EBV is able to efficiently immortalize primary B lymphocytes in vitro. The growth program of EBV-infected B cells is initiated and maintained by the viral transcription factor EBNA2, which regulates viral and cellular genes, including the proto-oncogene c-Myc. Proteomic analysis has proven to be a powerful approach to profile the target proteins of EBNA2, including both c-Myc-dependent and c-Myc-independent ones [123]. EBV nuclear antigen leader protein (EBNA-LP) is a phosphoprotein suggested to play important roles in EBV-induced immortalization of B cells. One of the potential functions of EBNA-LP is a cooperative induction with EBNA-2 of viral and cellular gene expression, including that of the genes for viral LMP-1 and cellular cyclin D2. Based on MS analysis, the major phosphorylation sites of EBNA-LP were identified to be at serine residue of position 35 in the W2 repeat domain. These modification sites are critical for the protein to cooperate with EBNA-2 in upregulating the expression of LMP-1 in B-lymphoma cells [124]. Functional proteomic analysis has also revealed tumor necrosis factor Nck-interacting kinase (TNIK) as an interaction partner of the LMP1 signalosome in EBV-positive B cells. TNIK was proven to play a critical role in canonical NF-κB and c-Jun N-terminal kinase (JNK) activation by LMP1 and CD40. TNIK orchestrates the formation of the LMP1 signalosome and the binding of critical signaling mediators TRAF6, TAK1/TAB2, and IKKβ. Ultimately, TNIK is mandatory for proliferation and survival of EBV-transformed B cells [125].

In addition to the traditional proteomic approaches to discover novel biomarkers and proteins, much focus has shifted to the analysis of easily accessible biofluids, such as saliva. In HNSCC, exosomes and microvesicles, which are nanometer-scale, membranous vesicles secreted from cells into their extracellular space and biofluids, are being described as a means of biomarker discovery. Cancer cells, including virally infected ones, can regulate their microenvironment through exosomes and microvesicles by transferring molecules such as proteins, lipids, and nucleic acids. Particularly in EBV-associated NPC and OSCC, exosomes and microvesicles are being studied as a useful source and alternative model for HNSCC detection and discovery of novel biomarkers [126].

8.15 Summary and Future Perspective

HPV infection has been recognized as an important risk factor for a subset of HNSCC, particularly those arising from the oropharynx (base of tongue and tonsils). HPV-16 and HPV-18 represent the most prevalent viral types, and they show specific virus–tissue interactions in HNSCC. In addition, patients with HPV-positive HNSCC seem to have a better overall and disease-specific survival, as compared with the HPV-negative group. On the other hand, EBV has critical viral transforming functions in epithelial cells that may lead to the development of NPC, as evidenced by the consistent expression of EBV viral genes and latent membrane proteins in NPC. The tumorigenic activities of HPV in HNSCC and EBV in NPC have been well studied and documented, but there is a large lack of evidence regarding the interaction of HPV or EBV with precancerous lesions.

Early diagnosis of virus-associated cancers is vital in combating the diseases, as it is much more effective when the tumors are treated at the early stage before metastatic spread. However, a positive detection of viral infection does not necessarily mean the development of cancer. In this regard, it is also important to develop new molecular biomarkers, in addition to viral DNA and proteins, for a more precise diagnosis of HPV- or EBV-associated HNSCC. Prophylactic vaccines have the potential to prevent and treat virus-associated HNC. However, it is equally important to develop molecular targeted therapies for patients with the cancers so as to slow down the progression of transformed cells and improve the survival.

The mechanism of virus-associated tumorigenesis is complex, involving the aberrations of many signaling pathways and the alteration in expression of numerous proteins leading to immune escape by malignant cells. Although clinical studies have shown strong association between HPV/EBV and subsets of HNCs, the molecular mechanism regarding how these viruses facilitate the development of HNC remains a topic of research. Previous molecular studies on HPV-associated HNCs have focused on DNA and chromosomal levels, but few on transcriptomic and proteomic profiles [39, 127]. An improved mechanistic understanding of the virologic basis for HNCs would require profound analysis of these tumors using high-content molecular analysis technologies such as proteomics [128], metabolomics [129, 130], and next-generation sequencing. This would facilitate the development of targeted therapies for treatment of these cancers if immune escape can be reversed. Meanwhile, molecular classification of tumors is likely to provide important translational information that will allow a better estimate of prognosis and may well influence treatment decisions if future HPV-stratified clinical trials support this approach.

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Head and Neck Cancer Staging and Prognosis: Perspectives of the UICC and the AJCC

9

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Abstract

The prognosis of head and neck cancer is determined by numerous factors related to the patient, tumor, and health-care system. For many measures of outcomes, especially the key endpoints of organ preservation, locoregional control, occurrence of distant metastases, and survival, anatomic extent of disease remains one of the most powerful prognostic factors. This is embodied in the tumor–node–metastasis (TNM) classification, which historically has provided a very effective enabling tool to facilitate many elements of prognostication and cancer control. Traditionally, its contribution has been a codified classification and language to describe anatomic stage of disease for use in the clinic, determining eligibility and stratification for clinical trials and treatment protocols, and for comparison and surveillance of treatment results among centers and jurisdictions. More recently, momentum to include nonanatomic factors has grown, partly because it is recognized that anatomic extent of disease does not embrace all dimensions of prognosis. In particular, this relates to the quest to understand the biological dimensions of cancer, the deterministic effects of patient health, and the systems within which treatment is delivered that are needed to achieve more personalized and/or biologically driven therapies. Increasingly, there is a need in head and neck cancer to exploit new biological discoveries to permit modification of treatment and interventions in the clinic for this heterogeneous group of tumors. Because of this, the TNM staging has been criticized due to a perception that it has not been adapted sufficiently to modern needs despite its worldwide adoption. This may stem from the fact that there is no alternative uniform functional framework available to classify nonanatomic predictive and prognostic factors. The prevailing view is to regard TNM as the optimal receptacle for these factors due to its uniform appeal and success. As the field evolves, both anatomic disease extent and other factors, especially those addressing biological behavior of disease, need to be studied in their component domains as well as in combination using an agreed upon enabling taxonomy. An important strategy is to move toward constructing prognostic mod-

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els to modify the current classification, which will not only include the TNM staging information but will also include other parameters of prognosis including comorbidities, lifestyle, and biochemical or genetic markers. In addition, experts in one area (e.g., translational science or clinical trial methodology perhaps) who may rely on TNM may not always consider that the classification provides very different needs for others (e.g., health services research or screening and cancer control initiatives, etc.) and vice versa. Ignoring or dismissing one dimension of prognosis compared to another will not be fruitful and the true contribution of each will remain unappreciated, and the goals of the prognostic factor effort in head and neck cancer may be left unfulfilled.

Keywords
Head and neck cancer • Staging • Prognosis • Prognostic models

9.1 Introduction

In oncology, "to stage" a patient implies two intentions. The first uses clinical examination and investigations to describe the extent of disease to permit a rational treatment strategy to be formulated. The second employs an agreed classification system to categorize the extent of disease within risk hierarchies that predict the outcome following conventional treatment strategies. For the latter, the foremost priority is given to the risk of death and is provided by the joint primary tumor–node–metastasis (TNM) classification of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC), a discussion about which will comprise much of this chapter. A challenge is to also consider new methods to enhance prognostic information and determine if these can be incorporated into or complement the traditional anatomically based classification. A variety of candidate areas exist and include features relevant to the host (or patient), the environment of the patient's treatment setting, and, finally, the assessment of the tumor itself, which has tended to receive the most emphasis. For the latter, of particular emphasis is the biological character of an individual tumor or groups of tumors. In this chapter, we discuss the importance of anatomic staging in the management of head and neck cancer and provide some perspective on the scope and application of the TNM classification and how it continues to evolve since its inception in the middle of the last century. A second component will briefly summarize the changes that were introduced in the seventh edition TNM [1, 2]. The final sections of the chapter address newer concepts including the evolving tension between anatomic staging in its current form and the value of nonanatomic methods of prognostication that need to be considered and a discussion of key issues being addressed for development of the eighth edition (see Sect. 9.9).

9.2 Achievements, Challenges/Limitations, and Opportunities of the TNM Staging System

1. Anatomic extent of disease remains one of the most powerful prognostic factors and is embodied in the TNM classification. The hegemony of the TNM results from its ability to stratify disease prognosis and provide a universally applicable and easily reproduced methodology and thus has facilitated many elements of cancer control on a global basis. Anatomic features of locoregional tumor extension are especially important in the head and neck since these underpin the management of these tumors. The static nature of TNM staging (determined at initial diagnosis) is a problem for future prognostication, for example, after several years of recurrence-free survival.
2. A major dilemma in TNM staging is the tension between the notions that frequent revisions would undermine the value conferred by the stability and universality of TNM, but a static formulation of TNM risks falling behind the state of the art in diagnostic techniques, biological concepts, biomarkers, and nonanatomic factors impacting on outcome.
3. Dimensions of prognosis are not uniform and the settings where some factors are useful to consider may not apply to other situations (e.g., early vs. advanced stage, or recurrence vs. first presentation, or important endpoint in head and neck cancer such as survival vs. organ preservation).
4. The TNM remains essential so that newer biological findings can be evaluated in the context of its existing structure. Although it has significant limitations in the era of molecular oncology, it is also needed to provide the framework for advances in biological discoveries when cohorts of patients are evaluated for prognostic or predictive outcomes.

5. Future research should focus on the evolution of biology with advancing stage since this could open the door to the potential for a true molecular-based "staging system." A major achievement of this type could override or complement traditional anatomic staging in some diseases or situations.
6. In considering prognosis in cancer, the UICC and AJCC are also focusing on *host* and *environmental* factors that may be as important as *tumor*-based prognostic factors in some settings.
7. The UICC and AJCC recognize an urgent need to achieve agreement on a new taxonomy and methodology to permit nonanatomic factors to be combined with traditional anatomic classifications while allowing the full impact of both to be explored, adopted, and used without compromise to the other. One future aim to achieve personalization and fluency over time is to move toward a prognostic nomogram, where the TNM anatomic staging will remain an important component. An intermediate step is the creation of prognostic groupings that use validated nonanatomic factors to modify the stage grouping.
8. TNM serves many purposes in cancer care, research, and control, and dismissing one dimension compared to another will not be fruitful since the true contribution of each will remain unappreciated and the goals of the prognostic factor effort in head and neck cancer may be left unfulfilled.

9.3 The Principles of Staging in Head and Neck Cancer

9.3.1 The Importance of Anatomic Staging in Head and Neck Cancer

The challenge for oncologists who manage head and neck cancers is to achieve tumor control while maximizing the opportunities for preservation or restoration of form and function. A dominant pattern of treatment failure of head and neck tumors is locoregional recurrence, making it important to have a clinical staging system that acknowledges this biological behavior and emphasizes the anatomic features of local tumor extension that underpin the management of these tumors. Clinical evaluation is a fundamental part of the assessment (i.e., palpation and visual observation of the head and neck that are almost unique to these sites because of their relative accessibility compared to other disease areas) and together with imaging studies informs a user-friendly language for the extent of disease that can be applied uniformly and consistently on a worldwide basis [3]. This traditional need to classify the extent of disease remains a paramount component of the assessment of patients with head and neck cancer and the basis for many comparisons between groups of patients and the means to develop initial treatment approaches.

As cancer approaches the concept of a chronic disease with survival extending months and years beyond the date of recurrence in selected patients, salvage of initial treatment failure also requires unique attention and diligence. Therefore, disease description at recurrence is important so that the goals of treatment are achieved and includes the ability to plan treatment and compile results that can be compared among centers and jurisdictions separately from the description of the initial treatment. Here again, a codified language to describe treatment and protocol guidelines and permit orderly reporting of results of this adverse setting is needed and is provided by an anatomic stage classification that is tailored to the recurrent scenario which in the TNM system uses the "r" prefix described later.

The TNM staging for head and neck cancer is unusual in that it encompasses multiple sites and disease types with differing etiologies, pathophysiology, and outcomes. Amalgamating all of these heterogeneous diseases into a single staging system is complicated.

9.3.2 The Evolution of the TNM Classification in Head and Neck Cancer

The TNM staging system was first proposed in 1944 by Pierre Denoix at Institut Gustave-Roussy, Paris, France [4]. The first formalization of the classification was developed by the Union for International Cancer Control (UICC) when it published the first of its brochures on cancer of the breast and larynx in 1958, to be followed by that on cancer of the buccal cavity and pharynx in 1963. This led to the classification of additional anatomic sites and their eventual compilation in 1968 as a single booklet, referred to as the *Livre de Poche*, which contained 22 body site classifications and represented the first edition of the TNM staging system [5]. Of central importance in the first edition of TNM were the classifications of head and neck cancer. These originally included buccal cavity, nasopharynx, hypopharynx, and larynx. All contained a common, though now outdated, regional lymph node classification that focused on whether lymph nodes in the neck were palpable or not and used fixity as the criterion for N3. The buccal cavity was subdivided into seven regions and a number of subsites such as "lips (red borders)" with divisions into upper and lower components. Of interest also, the oropharynx was initially allocated as a region within the buccal cavity site and did not achieve independence as a region within the head and neck until the 1974 second edition [6]. Another interesting element was that fixation of the vocal cord was classified as T2 in the first edition and only became T3 in the 1974 second edition classification following a trial period of a new proposal. Also the first edition contained only a limited attempt to combine the three different anatomic components (T–N–M) into groups that might

provide prognostic strata as stage groups. This process was confined to breast and cervix cancer as it was deemed "…in the opinion of the Union an attempt to stage group all sites would at present be immature" [5]. Importantly, this was also modified in the second edition thereby representing the first formal international attempt to prognosticate in head and neck cancer using different elements of extent of disease grouped together.

The American Joint Committee (AJC) was founded in 1959 to complement this work in the USA. Joint classifications were prepared by both organizations and distributed for trial periods before their formal adoption into the TNM classification. In 1977, the AJC introduced a TNM classification of its own [1] which had the potential for two separate classifications. This was recognized early on, and a strong collaboration between both organizations (the AJCC renamed in 1980 and UICC) has continued since, so that both classifications resemble each other as closely as possible. Nowhere is this more apparent than in the classification of the head and neck sites stewarded by the authors of this chapter representing the UICC and the AJCC.

From the outset, the TNM was intended to be an anatomic stage classification describing the anatomic extent of the primary tumor as well as the involvement and extent of regional lymph nodes and distant metastasis. It describes the anatomic extent of cancer and is based on the hypothesis that the probability of survival and the choice of treatment are related to the anatomical extent of the tumor at the primary site (T), the presence or absence of tumor in regional lymph nodes (N), and the presence or absence of metastasis beyond the regional lymph nodes (M). At present, in the head and neck sites, T is almost always divided into four major categories (T1–T4), with a further subdivision into moderately advanced local disease (T4a) or very advanced local disease (T4b). The genesis of subcategorization of T4 into "a" and "b" categories began during the development of the sixth edition of the staging manual, where category "a" was assigned to "resectable" and category "b" was assigned to "unresectable" disease based on the local extension of disease to vital structures. However, with increasing use of "nonsurgical" treatment approaches, the terms "resectable" and "unresectable" were felt to be inappropriate, and the terms "moderately advanced local disease" and "very advanced local disease" were assigned to the "a" and "b" subcategories of T4 tumors. However, the descriptions of the local extent of disease in each subcategory remained the same. A common lymph node classification represented by four categories (N0–N3) with some subcategories is used in almost all the head and neck sites. The T and N categories are also combined with the M categories that indicate the presence or absence of distant metastases to form groups representing stages and that confer prognostic guidance. As noted earlier and continues to be the case, TNM has always needed to evolve with the availability of additional information about outcome, new treatments, or novel ways to evaluate disease and anatomy, including developments in imaging or emerging biological insights about disease behavior or etiology. Almost all clinical trials use anatomic extent, generally represented by the TNM or its elements, to define entry criteria or to control for prognostic imbalance between arms of randomized trials by employing stratification based on anatomic stage [7]. It is also a critical pathway to developing clinical practice guidelines such as those of the National Comprehensive Cancer Network (NCCN) [8] and is a key determinant in identifying patients to be treated by guidelines and for monitoring compliance to guidelines [7].

9.3.3 The Place of Nonanatomic Prognostic Factors and Staging

It is important to recognize that the TNM classification was never intended to capture all elements that are important in determining prognosis or guiding treatment and that a variety of tumor-, host-, and treatment-related external factors are also important and are becoming increasingly so today. One of the ironies of the TNM classification is that it has been immeasurably successful in its goals and has enjoyed worldwide adoption but in recent times has become a target for criticism because of assertions that it has not adapted itself to modern needs [9]. This may stem from the fact that there is no uniform functional framework that can be used to classify nonanatomic predictive and prognostic factors. The tendency seems to have evolved to consider the TNM as the optimal receptacle for these factors presumably due to its uniform appeal and success. This needs to be considered carefully since the problem is not straightforward. Dimensions of the elements of prognosis are not uniform, and the settings where some factors are appropriate to consider may not apply to other situations of the disease. These concepts will be discussed later.

9.3.4 How TNM Is Modified

As discussed already, changes continually take place in the TNM classification because of the need to maintain relevance with current management approaches and to respond to the availability of new data that may be considered in revisions to the classifications. This generally requires evidence of the need for modification and for the most part relies on published data in the literature. Thus, for example, the AJCC and UICC meticulously reviewed the overall TNM classification for all diseases for the seventh edition. This process is being followed in preparation to create the eighth edition as well. In considering change, it is important to reflect on the

fact that any classification or staging system is a "compromise" between the "ideal" and the "practical." The more accurate and, thus by design, the more complex the system is, the less compliance we will observe. One of the basic tenets of the staging system is that it should be applicable and available worldwide, it should be user-friendly, and it should have the ease to have maximum compliance from all parts of the world [10].

The process of revision involves collaboration between both organizations, and that is partly accomplished by a series of disease-specific task forces. A number of resources are available to the task forces, which include a structured process for introducing changes to the TNM classification. The elements of the TNM process include the development of unambiguous criteria for the information and documentation required to consider changes in the classification, establishment of a well-defined process for the annual review of relevant literature, formation of site-specific expert panels, and the participation of experts from all over the world in the TNM review process [11]. For perspective, changes in the seventh edition will be briefly summarized later (see Sects. 9.8.1 and 9.8.2).

In addition some domains, including anatomically based issues, may seem relevant but are not included in the modifications. This may arise because the data supporting the change are not sufficiently strong, or may lack the practicalities to permit its inclusion in a general way, or may not fit into the established structure of the TNM. In order to address the need for awareness of other elements that are not included in the formal classification, the UICC and the AJCC have initiated separate processes with different but complementary goals.

The UICC approach includes a separate publication, entitled the *TNM Supplement, A Commentary on Uniform Use* [12]. The "Supplement" now appears following each revision of TNM. Its purpose is to provide explanations and examples to answer the numerous questions that arise during the daily use of TNM, particularly in unusual cases. It enumerates the recommended criteria for pathological classification (pT and pN). One example in the head and neck is a description of the superior and inferior boundaries of the glottis, since these are not elaborated in the UICC *Livre de Poche* though such items are included in the more expansive AJCC Cancer Staging Manual. Another example concerns the reminder that pathological classification also uses clinical information. Thus, in considering impaired mobility or fixation in the glottis, this information that is evaluated in the clinical T category is also used to define the pathologic TNM (see Table 9.1) [12]. The "Supplement" also contains proposed classifications for new tumor sites and types not yet part of the official UICC and AJCC TNM system and that can be tested by interested investigators with a view to encouraging publication that may result in their subsequent inclusion in the formal classification if the data prove robust. Optional expansions of existing TNM categories are also included in the "Supplement" for those needing to record more detail. An added feature is the "Frequently Asked Questions" chapter, derived from the UICC and AJCC TNM web sites' help desks.

The AJCC has taken a different approach. First, the AJCC staging manual is a more expansive text. Consequently, it is less portable for consultation in the clinic by clinicians, though it provides the reference foundation for the work of cancer registrars in North America. A more compact version is available though is still not as brief and synoptic in presentation as the UICC *Livre de Poche*. In addition, the AJCC has implemented the "Collaborative Staging System" (CS), which acts as a repository of all available prognostic information for current and future use. This process commenced in 2004 and comprises a data collection tool across all US hospital and population registries for cancer staging information [13]. It uses a standardized data dictionary to collect information on T, N, M, and site-specific prognostic and predictive factors. The CS system is built into all cancer registry software systems in the USA. Areas identified for data collection in the head and neck sites include such factors as the actual size of lymph nodes, the location of lymph nodes (e.g., upper or lower neck involvement), the presence of extracapsular spread (ECS), human papillomavirus (HPV) status, and tumor thickness in oral cancers. Many of these are not reliably available by clinical evaluation, but their strength is apparent on pathological examination where they may influence clinical care in significant ways. For example, the presence of ECS is a singularly adverse factor [14] and drives the need for chemotherapy in addition to radiotherapy in the postoperative adjuvant management of cervical lymph node metastases [15]. However, the role of ECS in HPV-positive patients appears to be of less significance [16]. Tumor thickness in oral cavity primary sites is one of the strongest predictors for the risk of lymph node involvement in the neck beyond the formal T staging system [17], thereby influencing the approach to neck management. Other important pathological issues that are not part of the TNM at present include the character of the tumor (e.g., endophytic vs. exophytic) and the nature of the host tumor interface (pushing vs. infiltrating) and the presence of perineural or lymphovascular invasion (LVI) that also impact on the treatment and outcome of patients. In addition to being implemented in some other jurisdictions beyond the USA, ongoing efforts involving the College of American Pathologists (CAP) and the Centers for Disease Control and Prevention (CDC) are revising the CAP Cancer Templates for reporting pathology on cancer specimens to collect core elements on tumor size, extension, nodal involvement, and metastases in the format needed for recording in the CS system. It is also expected that the CS system will be incorporated in the NCI's Cancer Bioinformatics Grid (caBIG) as the accepted standard for

recording data on the extent of disease and stage [13]. In this way, the future potential exists for important elements that influence treatment and prognosis to be analyzed in order to develop prognostic groups that may be able to enhance the existing TNM stage classification.

9.3.4.1 The Unique Case of HPV

The emergence of our understanding of oropharyngeal disease is explosive. The developing evidence suggests that p16-positive cancers of the palatine and lingual tonsils have a significantly better prognosis and behavior that defies our current staging system to quantitate. Later in this chapter, we will address the question of whether HPV-positive oropharyngeal carcinoma is a variation with a better prognosis or a completely separate disease entity.

9.3.5 Specific Designations and Rules in TNM

The staging of head and neck cancer requires the clinician and the cancer registrar to be familiar with an extensive assortment of anatomic sites and subsites. Practitioners and statisticians interested in how results from clinical trials are interpreted and received need to be familiar with the fundamental rules of the TNM classification. The same holds true for everyone involved in interpreting and applying the general results of treatment or in maintaining and addressing consistency in how treatment guidelines are developed, used, and assessed. Depending on an individual's or a group's focus, some of these may seem arbitrary, cumbersome, or even unnecessary. Nonetheless, they embody a uniformity that is applicable to all oncologic disease sites, health professionals, and jurisdictions around the world [3].

A detailed discussion of the rules of TNM is not intended in this chapter. Some basic issues will be known to practitioners such as the fact that the TNM for most mucosal sites is designed for squamous cell carcinoma and minor salivary gland cancer. It is also acknowledged that head and neck oncologists are very familiar with the TNM system though they may not be aware of some of the recent changes described below and may be interested in the current ongoing discussions regarding further modifications to come in the eighth edition. In addition, even experts may not be aware of all of the "fine print" that exists, and a summary of some of the questions and problems that arise in day-to-day usage is provided (see Table 9.1). This is not intended to be exhaustive, and the interested specialist should also consult additional sources mentioned earlier as well as the actual TNM classification publications [1, 2, 12]. Several broader issues merit comment, however. These concern the areas of clinical vs. pathological staging, some additional descriptors within the classification, and the use of grouping of elements to define prognosis.

9.4 Clinical Versus Pathological Staging

All cases should be confirmed microscopically through tissue biopsy of the primary tumor or metastatic lymph node. All cases should receive a *clinical classification* (the TNM or cTNM) based on evidence acquired before treatment through physical examination supplemented by endoscopic and imaging evaluation essential to select and evaluate therapy. Physical examination, radiographs, CT or MRI, PET scan, endoscopy, biopsy, and other relevant examinations including surgical exploration comprise the majority of this evidence. In contrast, *pathological classification* (pTNM) is based on postsurgical histopathological classification and is used to guide adjuvant therapy and provides additional data to estimate prognosis and to calculate end results in those patients that have surgery as part of their treatment regimen. Both should be recorded when available and should not be mixed or considered equivalent since different selection criteria apply to each. In addition, they should contain the same elements.

9.5 Additional Descriptors Used in TNM

The clinical TNM and pTNM classification also contain specific terms to facilitate clinical situations faced by clinicians in the contemporary management of head and neck cancer. Thus, several symbols may be used to facilitate including the m, y, r, and R identifiers (see Table 9.2).

The suffix m, in parentheses, is used to indicate the presence of multiple primary tumors in a single site, whereby the tumor with the highest T category should be classified and the multiplicity or the number of tumors should be indicated in parenthesis, e.g., T2(m) or T2(2) in the case of two tumors (see Table 9.1).

The y symbol is available to classify cases during or following multimodality therapy by identifying the clinical TNM or pTNM category identified by a "y" prefix that designates that the classification refers to the extent of tumor actually present at the time of that examination. Therefore, the y categorization is not an estimate of the extent of tumor prior to multimodality therapy, but is useful for description of TNM during concurrent chemoradiation therapy or after the completion of neoadjuvant regimens [18].

The lowercase "r" symbol is available to describe recurrent tumors and needs to be applied after a disease-free interval (usually in the order of 6 months). Such tumors are identified by the prefix "r" as rTNM or rpTNM and need to be distinguished from the uppercase "R" designation used to describe residual disease following surgical resection as R0 for microscopically clear resections, R1 for microscopic residual disease, and R2 for macroscopic residuum. In some cases, confusion could arise between the uppercase "R2"

Table 9.1 Application of selected rules relevant to the TNM head and neck classification

General issues
For each disease, there should be a clinical (obtained without resection) and a pathological (obtained after surgery) classification that contain equivalent descriptors
Pathological classification (pTNM) is based on evidence acquired before treatment, supplemented or modified by additional evidence acquired from surgery and from pathological examination
Because the designation is based on evidence acquired before treatment, a glottic cancer with a fixed vocal cord will remain a T3 lesion after surgery unless additional evidence of extension of disease is present, such as invasion of thyroid cartilage, to raise the category to the next (i.e., more advanced) level
The pathological assessment of pT and pN requires a resection adequate to evaluate the highest pT or pN category
If there is doubt about whether a tumor should be classified with a higher T or N category, it should be allotted to the lower category (i.e., less advanced) where the available criteria for that case can be reliably applied
The designation X is used for the T or the N categories, if there is inadequate information available to classify the lowest category when disease has been known to be present in that location. The term X is not used for the M category since a clinical exam alone cannot permit assessment of distant metastases. It is also not used for the designation of unknown primary where T0 is the correct convention
T-category issues
Tumors overlapping adjacent areas should be classified according to the site where the bulk of the lesion (epicenter) is located
In the case of multiple primary tumors in one organ, the tumor with the highest T category should be classified and the multiplicity or the number of tumors should be indicated in parenthesis, e.g., T2(m) or T2(5)
In simultaneous bilateral primary cancers of paired sites (e.g., tonsillar carcinomas), each tumor should be classified independently
In unknown primary cancer classification, the designation T0 should be used for the T category. T0 is also used at the time of recurrence of a previous known head and neck cancer (e.g., regional lymph node or distant failure) if there is no evidence of disease recurrence at the primary site, preceded by the descriptor "r"
N-category issues
The regional lymph nodes are the cervical nodes. Midline nodes are considered ipsilateral nodes
The definitions of the N categories for all head and neck sites except the nasopharynx and mucosal melanoma are the same
In oral cavity, larynx, and pharynx cancers, metastases at level VII (those in the anterior superior mediastinum, cephalad to the innominate artery) are considered regional lymph node metastases. The remaining mediastinal lymph node metastases are considered distant metastases
Histological examination of a selective neck dissection specimen will ordinarily include six or more lymph nodes
Histological examination of a radical neck dissection or a comprehensive modified radical neck dissection specimen will ordinarily include ten or more lymph nodes
If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0
When size is a criterion for pN classification, measurement is made of the metastasis, not of the entire lymph node
In unknown primary cancer classification, the designation T0 and the N classification should use that of the site most likely to represent the origin of the tumor

Table 9.2 Selected additional descriptors encountered in the TNM or pTNM of head and neck cancer

m symbol	The suffix m, in parentheses, is used to indicate the presence of multiple primary tumors at a single site. See commentary in Table 9.1
y symbol	In those cases in which classification is performed during or following multimodality therapy, the cTNM or pTNM category is identified by a y prefix
	The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The y categorization is not an estimate of the extent of tumor prior to multimodality therapy
	This convention should typically be used following neoadjuvant therapies and may be most applicable to induction chemotherapy
r symbol	Recurrent tumors, when classified after a disease-free interval, are identified by the prefix r
R classification	The absence or presence of residual tumor after treatment is described by the symbol R as follows
	RX: presence of residual tumor cannot be assessed
	R0: no residual tumor
	R1: microscopic residual tumor
	R2: macroscopic residual tumor
	Typically, these designations are used in surgical resections where microscopic residual tumor (R1) or gross residual tumor (R2) is left behind
	In some situations, the R2 designation may interact with the "r symbol" if macroscopic (gross) residual represents recurrence of previous tumor (see text)

designation for gross residual disease and the lowercase "r" designation that designates recurrent disease since one may eventually merge into the other if sufficient time evolves. This is especially prone during the time to referral to a cancer center for definitive treatment following an initially incomplete excision.

9.6 Lymph Node Classification for Micrometastasis and Sentinel Node Assessment

The regional lymph node classification has recently also been adapted to address subclinical disease. This is particularly relevant in the head and neck to sentinel lymph node assessment where the designation "Sn" has been introduced in the TNM classification (Table 9.3). Therefore, the following designations are applicable when sentinel lymph node assessment is attempted: pNX(sn), sentinel lymph node could not be assessed; pN0(sn), no sentinel lymph node metastasis; and pN1(sn), sentinel lymph node metastasis. Cases with morphological evidence of micrometastasis only, i.e., no metastasis larger than 0.2 cm, can be identified by the addition of "(mi)," e.g., pN1(mi) (see Fig. 9.1). A designation of morphologically evident isolated tumor cells (ITC) can also be used to designate single tumor cells or small clusters of cells not more than 0.2 mm in greatest extent that can be detected by routine H and E stains or immunohistochemistry and is designated as (i+) (see Table 9.3). This overall approach has been validated recently by experts in sentinel lymph node assessment [19].

The approach has been similarly adapted to the situation where no morphological evidence of disease is apparent, but evaluation is based on a molecular assessment of the presence of disease by techniques such as flow cytometry or DNA analysis (see Table 9.3). The term "mol" is used to indicate that such a technique has been employed in the assessment; e.g., pN0(mol−) indicates that no regional lymph node metastasis is present histologically, and there is a negative assessment for nonmorphological findings for ITC. In contrast, pN0(mol+) indicates that no regional lymph node metastasis is identifiable histologically, but there is a positive assessment for nonmorphological findings for ITC. Also, in the situation where these characteristics have been assessed but confined to a sentinel lymph node assessment, the term "Sn" may be used as follows: pN0(mol+)(sn), no sentinel lymph node metastasis histologically, but there are positive nonmorphological findings for ITC. In general, these terms are not commonly used in practice, but are available in the event that these assessments become more uniformly used in the future. It is apparent that the designations (i+) and (mol+) are considered N0 at this time.

Table 9.3 Refinement in description of subclinical disease (most applicable to regional lymph node evaluation using sentinel node biopsy) assessment

Cases with micrometastasis only, i.e., no metastasis larger than 0.2 cm, can be identified by the addition of (mi), e.g., pN1 (mi)	
Isolated tumor cells (ITC) are single tumor cells or small clusters of cells not more than 0.2 mm in greatest extent are designated by the term "i+"	
Molecular detection (nonmorphological findings for ITC) of tumor presence is designated by the term "mol+"	
Sentinel node assessment is described by the use of the suffix "sn" at the end of the classification of a given tumor as depicted below	
The classifications for ITC and molecular detection of tumor should be used and designated as follows	
pN0	No regional lymph node metastasis histologically; no examination for ITC
pN0(i−)	No regional lymph node metastasis histologically; negative morphological findings for ITC
pN0(i+)	No regional lymph node metastasis histologically; positive morphological findings for ITC
pN0(mol−)	No regional lymph node metastasis histologically; negative nonmorphological findings for ITC
pN0(mol+)	No regional lymph node metastasis histologically; positive nonmorphological findings for ITC
When sentinel lymph node assessment is attempted	
pNX(sn)	Sentinel lymph node could not be assessed
pN0(sn)	No sentinel lymph node metastasis
pN1(sn)	Sentinel lymph node metastasis
Cases with or examined for ITC in sentinel lymph nodes can be classified as follows	
pN0(i−)(sn)	No sentinel lymph node metastasis histologically, negative morphological findings for ITC
pN0(i+)(sn)	No sentinel lymph node metastasis histologically, positive morphological findings for ITC
pN0(mol−)(sn)	No sentinel lymph node metastasis histologically, negative nonmorphological findings for ITC
pN0(mol+)(sn)	No sentinel lymph node metastasis histologically, positive nonmorphological findings for ITC

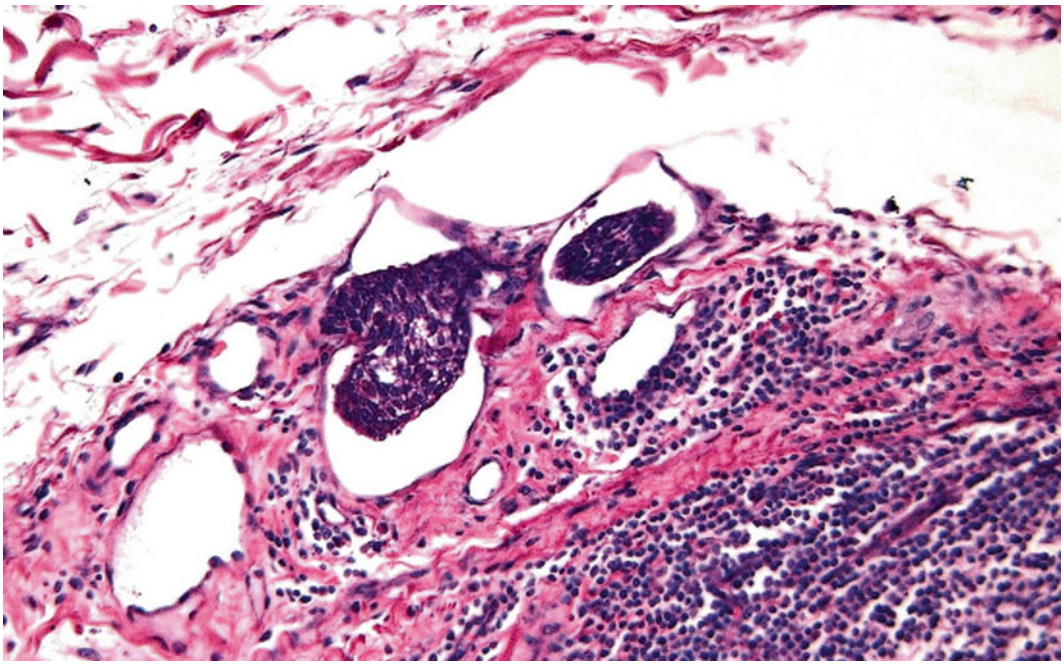

Fig. 9.1 Micrometastasis evident by small clusters of cells not more than 0.2 mm in greatest extent can be detected by routine H and E stains and is designated by the addition of "mi," e.g., pN1(mi) for detection in a single lymph node. Single tumor cell can also be classified using the term isolated tumor cells (ITC) and designated by the use of (i+) (see Table 9.3)

9.7 Stage Grouping

For purposes of tabulation and analysis, it is useful to condense the T, N, and M categories into stage groups. In general, in the TNM system, the groups are based on a hierarchy governed by the degrees of modification of prognosis. For most tumor sites in the body, carcinoma in situ is categorized as Stage 0, tumors localized to the organ of origin as Stages I and II, locally extensive disease and especially spread to regional lymph nodes as Stage III, and those with distant metastasis as Stage IV. In the classification of head and neck tumors, some unique differences exist and will be outlined in the sections that address specific anatomic sites in the head and neck region, most notably in the area of mucosal melanoma, where a new classification was introduced for the first time in the seventh edition, in anaplastic thyroid cancer and in the general head and neck classification where advanced local disease (T4a or b) and extensive regional adenopathy (N2c and N3) will place the case at the highest level of adverse prognosis (Stage IV). The HPV-positive patient will be handled in a unique way, akin to nasopharyngeal carcinoma.

The stage groups are intended, as far as possible, to provide homogeneous groups with distinctive survival rates for the different cancer sites. In addition, there are pathological stage groups if sufficient tissue has been removed for pathological examination to evaluate the highest T and N categories. As discussed earlier, the stage groups have also evolved over time. Originally, in the first edition of the TNM classification, they did not exist, and in the most recent edition, the AJCC and the UICC have introduced separate modified approaches in order to acknowledge the potential importance of nonanatomic factors (see Sect. 9.12.3 later).

9.8 Seventh Edition Modifications to "TNM"

The seventh edition of the TNM staging system became available for wide usage in 2010 [1, 2]. In the head and neck classifications, the most significant changes were the creation of a staging system for mucosal melanoma and fine-tuning of the relatively substantial modifications previously introduced in the sixth edition [20, 21]. Broadly speaking, the changes were intended to reflect current practices of treatment, clinical relevance, and contemporary data as well as providing the opportunity for data to be collected with a uniform classification in situations where this may have been problematic previously.

9.8.1 Recent Modifications to the T Classification

9.8.1.1 Very Advanced Local Disease (T4)

In the seventh edition, the terms "resectable" (T4a) and "unresectable" (T4b) introduced by the AJCC in the sixth

edition [20] were replaced by the words "moderately advanced" (T4a) and "very advanced" (T4b). These changes were made since a significant proportion of advanced-stage epithelial malignancies of the head and neck are being treated nonsurgically, and of those that are surgically treated, criteria for resectability may be subjective and are often dependent on the quality of available imaging studies [22, 23]. The anatomic criteria for the definitions of T4a and T4b, however, remained unchanged. Importantly for our discussion of the eighth edition, the nasopharynx was felt to have insufficient data to permit a subdivision of the T4 category. In particular, there is evidence that minimal invasion of the skull base or minimal cranial nerve involvement is not uniformly prognostically detrimental when determined by imaging assessments [24], further emphasizing the rationale for the importance of clinical evaluation in staging assessments (e.g., of cranial nerves in this instance). This remains an area of significant work in the development of the eighth edition to explore this heterogeneous and unique disease.

9.8.1.2 Nasopharynx T Category

The most apparent changes in T categories in the seventh edition occurred in the nasopharynx (see Table 9.4), a site that underwent no substantive change in the sixth edition TNM. Data over the past decade has demonstrated the relatively consistent finding of the absence of a difference in outcome between T1 and T2a tumors leading to a recommendation for reclassification of patients with soft tissue disease involvement of the oropharynx and nasal fossa to the T1 category [25, 26]. Thus, T2a lesions are now designated T1 and Stage IIA is now Stage I (see Table 9.4).

9.8.2 Recent Modifications to the N Classification

Traditionally, the N classification for cervical lymph node metastasis has been uniform for all sites except the thyroid, nasopharynx, and skin. The N classification for thyroid and nasopharynx is unique to those sites and is based on tumor behavior and prognosis.

An important change for nonmelanoma skin cancer in the seventh edition was the introduction of the N classification used in the remaining head and neck sites and is justified based on a variety of studies that indicate that increasing extent of neck disease is associated with adverse outcome [27]. Indeed this compelling argument has influenced the complete nonmelanoma skin cancer classification to a degree that the head and neck N classification was also used for axillary and inguinal lymph nodes in the seventh edition TNM. For metastatic squamous cell carcinoma, from mucosal primary sites, no major changes were made in the N staging for any site, except that a descriptor has been added. As noted earlier, ECS of disease has been added as ECS+ or ECS− as a descriptor for capture in the CS of the AJCC. These descriptors did not influence the nodal staging system but will likely provide data to permit future revisions of the N classification.

A final point concerning the neck is that the new classification for mucosal melanoma (see below) uses a limited schema restricted to only designating absence (N0) or presence of regional lymph node involvement (N1) without additional categories (see Table 9.5).

9.8.3 The New Classification for Mucosal Melanoma of the Head and Neck

Mucosal melanoma of the head and neck warrants separate consideration, and the approach to these lesions is outlined in a new chapter that introduces a TNM classification for the first time (see Table 9.5). Even small cancers behave aggressively with high rates of recurrence and death [28]. To reflect this aggressive behavior, even the smallest mucosal melanomas confined to the mucosa alone are designated as T3 and those with moderately advanced lesions (involving underlying cartilage or bone) are staged T4a. Very advanced primary tumors are staged T4b. In situ mucosal melanomas are excluded from staging, as they are extremely rare. There is also no T1 or T2 category. It is intended that the availability of a stage classification for this rare, unfavorable, and perplexing disease may facilitate research addressing its etiology, biology, and treatment. In fact, recent work has demonstrated the successful stratification of this system [29, 30].

9.9 The Future of TNM in Head and Neck Cancer

As implied and discussed earlier, the anatomic extent of disease remains one of the strongest and most consistent prognostic factors, especially in head and neck cancer. Multiple reasons for this exist and have been described. As also mentioned, however, its very success seems to have rendered it vulnerable since no alternative overarching strategy has emerged to amalgamate, administer, and process multiple prognostic elements for a given cancer. A major dilemma in TNM staging is that frequent revisions to include new biomarkers, for example, would undermine the value conferred by the stability and universality of TNM, but a static formulation of TNM risks falling behind the state of the art in diagnostic techniques, biological concepts, and biomarkers [31]. In fact, other techniques do exist and should be considered, but a shift in attitude is probably needed to embrace other methods of classification in addition to the TNM system.

Table 9.4 Nasopharyngeal TNM clinical classification (revision in seventh edition)

T – primary tumor			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
T1	Tumor confined to nasopharynx or extends to oropharynx and/or nasal cavity		
T2	Tumor with parapharyngeal extension[a]		
T3	Tumor invades bony structures of skull base and/or paranasal sinuses		
T4	Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, and orbit or with extension to the infratemporal fossa/masticator space		
N – regional lymph nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Unilateral metastasis, in cervical lymph node(s), and/or unilateral or bilateral metastasis in retropharyngeal lymph nodes, 6 cm or less in greatest dimension, above the supraclavicular fossa		
N2	Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa		
N3	Metastasis in lymph node(s) greater than 6 cm in dimension or in the supraclavicular fossa N3a greater than 6 cm dimension N3b in the supraclavicular fossa		
M – distant metastasis			
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping (nasopharynx)			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T1	N1	M0
	T2	N0, N1	M0
Stage III	T1, T2	N2	M0
	T3	N0, N1, N2	M0
Stage IVA	T4	N0, N1, N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Note: The term "Stage Grouping" is termed "Anatomic Stage/Prognostic Groups" in the AJCC version of the classification [1]
Adapted from Sobin LH, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumors. 7th ed. New York: Wiley; 2010. With kind permission from Wiley
[a]Parapharyngeal extension denotes posterolateral infiltration of tumor

Biological staging for head and neck cancer has been discussed for over two decades. The idea is that the natural history of cancer within an individual is varied and dependent upon many factors related to the tumor itself and the environment- or host-related factors [32]. This concept has gained widespread adoption conceptually, but as a practical matter, it remains to be properly structured for worldwide adoption.

In addition to the area of biomarker discovery, other areas of prognostic importance also exist and in many situations have the capability of equaling or even overcoming effects embodied by traditional areas of cancer classification in terms of disease biology and anatomic disease extent. For example, many nonanatomic factors address issues relevant to the host (i.e., patient) or the environment or setting where the patient is treated and particularly in the context of the availability of treatment or diagnostic assessments, but receive scant attention in the voluminous literature on prognosis that has emerged recently. The role of the health system and treatment factors such as patient volume, expertise of the treating team, distance from treatment facilities, socioeconomic status of the patient, and other factors are also known to influence prognosis. Some of these issues will be discussed to introduce these concepts while recognizing that this field is evolving and immediate solutions have not yet been developed or universally adopted. Broadly, prognostication in cancer can be classified into three domains that address the dimensions of the *tumor*, the *host*, and the *environment*. This traditional classification has been used by the UICC in its publication *Prognostic Factors in Cancer* now in its third edition [33]. In addition, this text has also introduced a tabular format

Table 9.5 TNM classification for mucosal melanoma of the head and neck (a new classification in the seventh edition TNM)

Primary tumor			
T3	Mucosal disease		
T4a	Moderately advanced disease		
	Tumor involving deep soft tissue, cartilage, bone, or overlying skin		
T4b	Very advanced disease		
	Tumor involving the brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, or mediastinal structures		
Regional lymph nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastases		
N1	Regional lymph node metastases present		
Distant metastasis			
M0	No distant metastasis		
M1	Distant metastasis present		
Stage grouping			
Stage III	T3	N0	M0
Stage IVA	T4a	N0	M0
	T3–T4a	N1	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Note: The term "Stage Grouping" is termed "Anatomic Stage/Prognostic Groups" in the AJCC version of the classification [1]
Adapted from Sobin LH, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumors. 7th ed. New York: Wiley; 2010. with kind permission from Wiley

for each disease site throughout the body to address these three dimensions but, additionally, has allocated them into three hierarchy tiers to address whether these factors influence treatment of the disease at the present time (based on recommendations in published practice guidelines), whether they add valuable additional information to understand the disease setting without influencing treatment decisions, or finally whether they represent new and promising discoveries that have not yet found a place to put it in the assessment of the disease in the clinic. A modified example of one of the head and neck tabulations is shown in Table 9.6 [33].

Some of these areas will be discussed briefly in addition to some of the challenges in grouping data and using them to prognosticate for the individual patient or in groups of patients. In addition, statistical assessments need ongoing understanding of concepts that address validation in particular. Development of the eighth edition has begun by a careful collection of literature that addresses each of these factors. The task before the committee is to develop a working framework within which these can best be detailed and statistically integrated. As of the writing of this chapter, each of the major issues is being researched by task forces designed to provide meaningful insight and modifications to the current system while respecting the important practical and historical role of TNM anatomic staging.

9.9.1 The Importance of "Nonanatomic" Tumor Factors

9.9.1.1 Introduction of Biologic Prognostic Markers

An interesting editorial [34] noted that the power of the TNM staging system is largely derived from the observation that tumors demonstrating locoregional or distant spread carry a worse prognosis than their less advanced counterparts. The problem is that, while this is true, and it is possible to predict survival based on a particular clinicopathological stage, there are clearly some patients that beat the odds [34]. Unfortunately, the authors also point out that there is also evidence that small tumors can metastasize early in their course and that a surgically resected primary tumor may in fact harbor cells demonstrating metastatic potential. This suggests the possibility to differentiate virulent tumor cells capable of metastasis from nonvirulent tumor cells based on molecular profiling. Molecular evidence may then be used to predict the outcome and treatment needs for an individual patient better than TNM staging. This speaks to the inherent clinical and molecular heterogeneity of cancer we now know that exists and to our inability to predict the behavior of any particular tumor. And so the question can be legitimately posed: will TNM survive the molecular revolution [34]?

We feel that it is unlikely to change for the foreseeable future. In large part, the place of TNM remains secure if only

Table 9.6 Prognostic factors in oral cavity, pharynx, and larynx cancer

Prognostic factors	Tumor related	Host related	Environment related
Essential	T category	Performance status	
	N category	Lifestyle – tobacco/alcohol	
	M category		
	Anatomic subsite		
Additional	Resection margin	Comorbidities	Radiation dose
	Number of involved nodes	Age	Overall treatment time
	Extracapsular nodal extension		Quality of surgery and radiotherapy
	Perineural, lymphovascular invasion		Response to therapy
	Tumor hypoxia		
	HPV status		
New and promising	EGFR expression		
	Surgical molecular margins		
	Osteopontin DNA profiling		

Based on data from: ESMO guidelines for management of SCC of the head and neck 2005 http://oncologypro.esmo.org/Guidelines-Prac...al-Practice-Guidelines/Head-and-Neck-Cancers; National Cancer Institute: Lip and Oral Cavity (PDQ®): Treatment Guidelines 2005 http://www.cancer.gov/types/head-and-neck/hp/lip-mouth-treatment-pdq; Clinical Practice Guidelines in Oncology: Head and Neck Cancer 2005 http://www.nccn.org/professionals/physician_gls/PDF/head-and-neck.pdf; Bourhis J. Oral cavity, pharynx, and larynx cancer. In: Gospodarowicz MK, O'Sullivan B, Sobin LH, eds. *Prognostic Factors in Cancer*. 3rd ed. New York: Wiley; 2006:99–104

for the fact that newer biological findings will need to be evaluated and validated in the context of an existing robust structure such as that provided by TNM, even if it remains imperfect. In addition, TNM is also a worldwide language, at least in head and neck cancer, and it is not possible to replace it in many areas of the world where complex molecular assays are unavailable. It also represents the basis for entry and stratification in many clinical trials [7] to permit the evaluation of new treatments and biomarkers in a manner that reduces the influence of treatment selection bias.

In head and neck cancer, as in all other regions, we are confronted by a large group of potential factors, but their precise place in the management of the disease remains uncertain. Articles are appearing that address a bewildering multitude of potential molecular characterizations of head and neck cancers, often in studies containing only modest patient numbers [35–38]. It is not the purpose of this chapter to discuss these in detail, but broad comments may be useful as we continue to search for the best use of potential biomarkers and explore how to incorporate these important elements that have the potential to profile these tumors in methods that take us beyond pure extent of disease. In the paragraphs that follow, for squamous cell carcinoma of mucosal origin, we have chosen two relatively well-recognized biomarkers, specifically the expression of the epidermal growth factor receptor (EGFR) and of HPV, that could be readily available if needed for clinical management of patients with head and neck cancer in the developed world. Both are being discussed by the head and neck task forces in the process of preparation of the eighth edition TNM. The situations surrounding both biomarkers will be discussed in relation to the proposition that they could replace or enhance the TNM or other prognostic models in the near future.

For some time, it has been recognized that EGFR expression is an independent determinant of survival and a robust independent predictor of locoregional relapse, although not for distant metastasis that is capable of withstanding the scrutiny of rigorous multivariate analysis. However, in one of the original landmark correlative studies of a large series of patients treated with radiotherapy alone, EGFR expression varied considerably among head and neck squamous cell carcinomas, and the study was restricted to the investigation of higher-stage patients (i.e., in excess of 95 % of patients had UICC/AJCC Stage III or IV disease) [39]. A recent meta-analysis of 68 studies suggests that copy number and overall expression of EGFR can predict survival although the magnitude was not dramatic. This suggests that early excitement is slightly dampened and illustrates the need for ongoing assessments and an ability to use selected biomarkers as modifiers of known existing information such as anatomic staging [40].

Thus, the precise impact of this biomarker in the continuum of the different degrees of head and neck cancer disease extension remains unclear. This problem in fact exists in much of the prognostic factor literature, where different factors or prognostic models may be important in subsets of a disease that address issues such as advanced stage as compared to early disease or in different scenarios (e.g., primary vs. recurrent presentations), but it becomes problematic when one wishes to apply them universally across the entire disease spectrum. An additional problem relating to

EGFR expression concerns its true value in the clinic as matters stand today. The initial data suggested that EGFR expression might be considered for selecting patients for more aggressive combined therapies or enrollment into trials targeting EGFR signaling pathways [39]. Strong claims have persisted that it is a promising therapeutic target in head and neck cancer based on the proven efficacy of cetuximab, a monoclonal antibody against EGFR, when combined with radiotherapy in locally advanced cancer (Stages III and IV) [41]. This observation had led to the approval of the drug for this indication on a worldwide basis. However, the role of EGFR-targeting agents in other therapeutic modalities, such as combined chemoradiotherapy or induction chemotherapy, remains to be defined [42]. In addition, and perhaps more disheartening, is the knowledge that the useful effects of cetuximab appear to be divorced from the degree of EGFR expression [42, 43]. The reality is that the majority of squamous cell carcinomas in the head and neck overexpress EGFR, but the clinical responses to EGFR-targeting agents have been modest, and molecular predictors for response to EGFR-targeted therapies have not been identified in the head and neck. Molecular marker studies have shown that mutations in the EGFR gene such as the L858R mutation in the tyrosine kinase portion of the receptor confer sensitivity to EGFR tyrosine kinase inhibitors in non-small cell lung cancer, but positive similar and additional studies in head and neck cancer have proven elusive to this point [42]. Recent data suggests that a negative regulator, the multiadaptor protein mitogen-inducible gene-6 (Mig6), plays an important role in signal attenuation of the EGFR network [44]. Thus, Mig6 may be important in understanding the complex relationship between EGFR and tyrosine kinase inhibition. Although the study is primarily based in cell lines, it is supported by a small clinical cohort as well. Another opportunity is that emerging data suggest that cetuximab may have the ability to elicit immune responses such as antibody-dependent cell toxicity (ADCC), and the search for predictive biomarkers for cetuximab therapy may need to be redefined to include elements of the immune system. Certainly, the response to cetuximab appears to be multifaceted and involves more than a simple inhibition of the EGFR pathway [42], and until the situation becomes clearer and its role more certain, the incorporation of this potentially important biomarker with elements of the TNM remains unresolved. It does seem clear, however, that its place in the prediction of prognosis in head and neck cancer should continue to be evaluated within the established framework of anatomic disease extent, and failure to do so may lead to spurious findings.

In contrast, the AJCC has recently recommended that HPV status in tumor should be assessed in mucosal squamous cell carcinoma of head and neck sites because of the impact it has on the prognosis of some head and neck cancers [1]. These data, together with other factors not included in TNM, have been compiled in the CS for analysis in particular as it relates to prognostic models that take into account various factors. This is an encouraging opportunity since the HPV status has emerged as a major predictor of survival that determines eligibility in multiple randomized trials currently underway investigating various treatment regimens. It is clear that HPV-mediated oropharyngeal cancer is an active field of investigation [44–46]. These tumors seem to have significantly more favorable outcome compared to HPV-negative squamous cell cancer in these locations [47]. These findings have led to HPV being widely accepted as a prognostic biomarker for oropharyngeal carcinomas.

An alternative interpretation is to regard this as an entirely different disease compared to non-HPV-related oropharynx cancer. In essence, it remains unresolved whether it should be considered separately from traditional smoking-related oropharyngeal cancer, and the clinical trials discussed above are designed specifically with this in mind to tailor treatment strategies to these more favorable, and presumably different, cancers. This potentially implies that a different TNM classification could be considered in this disease akin to the way a disease such as NPC is approached where its different etiology, also predominantly viral, and case profile set it aside from other head and neck cancer. Apart from their different etiology, other evidence for considering HPV-related oropharyngeal cancers uniquely includes the characteristic histological description of these tumors as poorly differentiated, often exhibiting minimal keratinization, basaloid features, and clinical features that include noninvasive submucosal primary lesions and lymph nodes with palpable features that resemble those found in lymphoma patients and that appear cystic on computerized tomography (CT) [48]. Recently, it has even been suggested that lymph node involvement carries dramatically less prognostic importance compared to traditional head and neck cancers emphasizing again that it is difficult to evaluate the influence of these important biomarkers unless the evaluation is undertaken within some framework that addresses the extent of disease. Indeed the evidence appears to be that, in this group of patients, a substantial percentage of whom have metastasis to cervical lymph nodes in less advanced primary tumors, the N status, is an unreliable prognostic indicator [49–52]. Again this is reminiscent of the NPC situation where different consideration to N classification has been needed, although the direction of the effect was the opposite due to higher risk of distant metastases in NPC with advanced neck disease.

Additional complexity also exists in relation to racial differences in outcomes for oropharyngeal cancer and that is related to molecular basis of these tumors. Recent data suggests that the adverse outcome of black patients compared to white patients may be explained by the paucity of association with HPV expression in tumors among the black

population [53]. The precise reason for the disparity in HPV expression remains unresolved, but its absence appears strongly associated with significantly less favorable outcome of oropharyngeal cancer in blacks compared to patients where HPV is associated.

Finally, in considering the HPV situation, patients who have HPV-related oropharyngeal cancers but who are smokers appear to retain some of the adverse profile of more traditional head and neck cancer and do not fare as well as *never-smoker* patients [38, 54]. Such "hybrid etiology" cancers appear to be complex, and in this situation, the concept of a biomarker within the spectrum of regular and traditional oropharyngeal cancer may indeed apply. Complicated interplays exist, including additional adverse expression of EGFR that appears to be expressed, possibly through increased hypoxia in the tumor tissues in smokers' cancers [38]. In addition, in their modest cohort of 66 patients, Kumar et al. identified other unexplained variables including an adverse effect of female gender (although only 12 were female) and additional adverse biomarkers. The authors advised additional validation to understand the role of these findings in predicting and guiding therapies. This would also apply to how these findings could be incorporated with TNM staging. Again most of the patients had presented with relatively advanced regional node involvement or with fairly advanced T-category disease rendering it difficult to address the whole spectrum of the disease [38]. To add to this complexity, the interrelationships of these biomarkers further complicate the picture. Just using these two markers, data suggests that the effect of EGFR may be only in those patients that do not harbor HPV. This suggests a relativism that evades the use of hard and fast categories [55].

9.10 Serum Markers

Among mucosal head and neck cancers, NPC has additional uniqueness in possessing a robust circulating tumor marker that can be expected to be employed clinically. One of the uses is the correlation of circulating EBV DNA with disease staging using quantitative real-time polymerase chain reaction (PCR) technology [56]. By means of its production by NPC cells, EBV DNA level has been shown to be more powerful than existing staging system in predicting outcomes by providing an index of disease burden in the individual patient and has been investigated now by numerous authors [57]. In particular, Leung et al. showed that pretherapy circulating EBV DNA load is an independent prognostic factor for overall survival in NPC. Thus, patients with early-stage disease can be segregated by EBV DNA levels into a poor-risk subgroup with survival similar to that of Stage III disease and a good-risk subgroup with survival similar to Stage I disease [58]. Pretreatment serologic antienzyme rate (AER) of Epstein–Barr virus has also been shown as a compliment to TNM staging and may also serve as a serum biomarker worthy of investigation [59]. While this provides an attractive concept, it also faces challenges in whether it can be applied universally at this time, especially in regions where the disease is most prevalent and resources to make it universally available are not as plentiful as in the developed world. A possibility may be to use it presently as an additional tool within clinical trials to augment prognostic assessment and disease monitoring. Also importantly, while it is attractive to consider it as a molecular marker that provides characterization of disease for prognostication, it falls somewhat short of this. As is the case for prostate-specific antigen in prostate cancer staging and in the case of serum markers for testis cancer, both of which are incorporated in the TNM classification [1, 2], these blood assays are considered indicators of disease burden and, in reality, represent surrogates for disease bulk. The same probably applies in NPC since the influence of the circulating marker correlates with the full spectrum of disease extent and the disparity noted above from Leung et al. could be explained by imprecision in estimating the extent of disease in these complex tumors in the region of the skull base.

9.11 Volume as a Predictor

Classification based on tumor volume instead of strict anatomic extent alone has been reported as a significant prognostic factor in the management of head and neck cancer. In turn, this has prompted investigators to suggest the incorporation of tumor volume into the TNM staging system. Indeed an extensive literature has now emerged that addresses this topic, but will not be discussed exhaustively. Much of this knowledge emanates from the treatment of NPC but has also been reported for other head and neck cancers [60, 61]. Nonetheless, if tumor volume is to be used as an independent prognostic factor, the methods for volume measurement need to be standardized [62]. Unfortunately, the technical challenges to routinely implement this in the clinical setting need to be resolved if it is to be used to classify patients using a TNM system. Not only is the measurement of tumor volume a tedious process requiring the tumor to be outlined digitally on cross-sectional imaging, but also the results are prone to difficulties created by both intra- and interobserver discrepancy and the quality of the imaging study. To overcome this problem, several investigators have developed semiautomated systems to reduce interoperator as well as intraoperator variability [62]. In order to overcome the technical and manpower considerations, alternative simpler methods have also been suggested including standard bidimensional measurements [63, 64]. While there seems to be no doubt that tumor volume provides a robust predictor of

outcome in many head and neck cancers, including claims of superiority to TNM in the contemporary era of head and neck cancer treatment, problems with implementing this approach remain. Manpower issues and other problems have not yet been resolved, including the determination of agreed potential cut points that might be used to create a classification that meets the needs of the clinician and scientists. This is also particularly relevant in regions of the world where NPC is most prevalent. In the end it must also be acknowledged that while volume assessment could provide utility if it was introduced, it remains fundamentally a measure of the extent of disease. In addition, the tumor volume of a totally exophytic cauliflower-like cancer does not have the same prognostic implications, as a tumor of the same volume, which is nearly all endophytic. It has been a long-standing observation that exophytic tumors are quite radiosensitive, in contrast to endophytic tumors. Thus, tumor volume, such as assessment of serum markers, is not strictly divorced from the anatomic stage paradigm and does not address many of the problems discussed earlier and that seem to lie at the heart of many of the criticisms of TNM [34].

9.12 Evolution of Biology with Advancing Stage

Another complex problem involving interplay between anatomic disease extent and molecular characterization of disease concerns the potential that disease could evolve in its character as it progresses from early to more advanced stage. While undesirable for patients, and implying the need for more intensive treatment as disease evolves, investigators might readily embrace this concept. Thus, intensified treatment, while often used for anatomically more extensive tumors, could additionally be needed because the disease character has evolved to a more aggressive phenotype. In turn, this also could open the door to the potential for a true molecular-based "staging system." Unfortunately, while the proposal is attractive in concept, few useful examples are available in the head and neck region. Investigation into this important area will need robust translational science activities, grounded in the laboratory and the clinic, where the anatomic stage classification and clinical parameters provide the framework for this evaluation. An example, in laryngeal cancer, is a study intended to address shortcomings in cancer prognostication and treatment due to a lack of methods to adequately address the complexity and diversity of disease. The authors of this study used multiparametric methods to identify specific patterns of disease progression. They investigated, on an exploratory basis, whether genome-wide alterations of loss and gain, using a panel of 122 gene probes (112 unique genes), discriminated between early-stage (Stages I and II) and late-stage (Stages III and IV) laryngeal squamous cell carcinomas. Significant differences between early and advanced stage were apparent for the following genes: ERBB4, CASP2, RECQL4, and BCL7A. Loss of ERBB4 ($P=0.045$) and BCL7A ($P=0.019$) significantly discriminated between early and advanced stages. Gain of RECQL4 copy number ($P=0.043$) was associated with advanced stage; gain of CASP2 ($P=0.043$) characterized early disease, but loss was associated with advanced stage. Problems with this approach include not only the isolated nature of this study, but also the multiple significance testing makes it important to validate the findings independently. The potential that the number of statistical assessments used could result in spuriously significant observations by chance alone appears to have also been recognized by the authors who identified their study as "exploratory" [65].

A related issue with a different application exists within the domain of head and neck cancer staging that embodies the concept of tumor evolution over time. In essence, this, as in the previous example, relies on the fact that carcinogenesis is a multistep process at both the phenotypic and genetic levels. A malignant neoplasm has several phenotypic attributes which commences with the benign and acquires genetic events that carry it through sequential steps that ultimately lead to excessive growth, local invasion, and the ability to form regional or distant metastases [66]. An application of this evolution with some practical clinical consequence relates to the potential to temporally model some of the key genetic events of a cancer and to identify whether different areas of cancer in the same patient could be related to each other or could have descended from each other. A very practical use for this is the potential to identify if pulmonary squamous cell carcinoma in a patient with head and neck squamous cell carcinoma might represent metastatic disease or a second primary. Depending on the approach taken for these two scenarios, it may have profound implications for a patient who may be denied potentially curative treatment when this might be possible if such a lesion is incorrectly declared metastasis. For some time, the ability has been available to achieve this diagnostic distinction using molecular tools for an important element of cancer staging, but as yet it seems not to have been translated actively to the clinic [67, 68].

9.12.1 The Importance of Host Factors

It has been well recognized that features of the host have significant prognostic impact in head and neck cancer. However, with the exception of differentiated thyroid cancer, where patient age is an important factor, the head and neck TNM classification does not take into account any host characteristics.

A consistent feature of the management of laryngeal cancer has been the demonstration that female gender is a powerful and independent favorable factor in addition to other more traditional factors. In a large retrospective series ($n=1252$) from Aarhus University Hospital in Denmark, women had absolute improvements of approximately 10 % compared to men for all cancer-specific outcomes including local control, locoregional, disease-specific survival, and overall survival following curative radiotherapy [69]. Female gender seems to retain this favorable advantage in other sites as well, based on a very large series ($n=3821$) from Germany [70]. For this reason, reports of adverse outcome in HPV-related oropharyngeal cancer in women compared to men are unexpected [38, 71]. While these represent small studies, they raise the possibility of host interactions with the biological process underlying the pathogenesis of head and neck cancer and the subsequent response to treatment. Earlier we have also noted the discrepancy in outcome between black and white patients with oropharyngeal squamous cell carcinoma and the fact that there is a dramatic difference in the association of cancers in these two groups with HPV oncogenesis, and the precise reasons underlying this remain speculative [53]. It is not just a difference in HPV however but a complex interplay between mutational, treatment, and socioeconomic differences [72]. There is also evidence that the status of the host immune system may be relevant and may be an explanation for the unusually favorable outcome of HPV-related oropharyngeal cancer compared to non-HPV-related cancers in this location [73].

Another well-described host-related prognostic variable for outcome in head and neck cancer is comorbidity. Comorbidity is described as "the presence of one or more medical ailments, in addition to the primary tumor but not caused by the primary tumor" [74]. Risk factors for the development of head and neck squamous cell carcinoma, such as smoking and alcohol abuse, contribute to other diseases as well (e.g., cardiovascular, pulmonary, or hepatic diseases). Therefore, comorbidity is to be expected in these patient groups. This has been well established by early work from Piccirillo [75] to more recent reporting of the influence of comorbidity for the first time in hypopharyngeal cancer [76]. Depression has been demonstrated to negatively affect survival as well [77]. Several established validated instruments designed to code and quantify comorbidity are available. These include, in historic order, the cumulative illness rating scale (CIRS) [78], the Kaplan–Feinstein comorbidity index (KFI) [79], the Charlson comorbidity index (CCI) [80], and the index of coexistent disease (ICED) [81].

In a comparative study of these four instruments, the KFI was the most successful in stratifying patients with head and neck cancer [82] though the CIRS appeared to be uniquely robust in another report that addressed laryngeal cancer exclusively managed with surgery [83]. Whether this would apply to patients treated with organ preservation strategies is unclear and emphasizes the context-based nature of some of these analyses that are sometimes overlooked. Nevertheless, a very consistent finding throughout such literature of head and neck cancer is the observation that comorbidity, assessed in various ways, seems to have as significant effect as the stage in understanding the prognosis of patients with these cancers and needs to be considered in designing treatment approaches. These analyses may also provide a framework for amalgamation of the various elements of prognosis into usable prognostic models that may be applicable in a broader perspective. This is discussed in Sect. 9.12.3.

9.12.2 The Importance of Environmental Factors

The relationship between outcome and the environment where the patient with head and neck cancer is treated can be profound, and the reasons underpinning these can be complex. What sets these apart from other prognostic factors is that they exert influence external to the parameters of the host and tumor, but their value relates to their ability to explain reasons for differential outcomes for treatments that might otherwise be expected to be similar. A classification is available and includes factors related to the physician, the health-care system, and society [34]. Each can also be subdivided into treatment-related issues (e.g., expertise, access, and health-care delivery processes), educational issues (e.g., participation in continuing education, development of practice guidelines, and access to information), or quality issues (e.g., quality of treatment, quality of the health-care facility, and access to affordable health insurance). Interested readers should consult the original description for a more detailed review [34].

The problem of environment as a prognostic factor is well exemplified by the report of outcome in a large prospective randomized trial where the technical planning and radiotherapy parameters of almost 700 patients were evaluated by a team of expert head and neck radiation oncologists. This review was undertaken without knowledge of the outcome of the patient or of the arm of the trial on which the patient was treated. In patients who received at least 60 Gy, those with major deficiencies in their treatment plans had a markedly inferior outcome compared with those whose treatment was initially protocol compliant. The 2-year overall survival was 50 % vs. 70 % (hazard ratio 1.99; $P<0.001$), and the 2-year freedom from locoregional failure was 54 % vs. 78 % (hazard ratio 2.37; $P<0.001$) for deficient vs. compliant radiotherapy, respectively. A large variation in the percent of plans with major adverse impact was noted according to country. Even more striking was the correlation between the number of patients entered and the probability of receiving

unsatisfactory radiotherapy. In centers enrolling fewer than five patients, 29.8 % had a predicted major adverse impact compared with 5.4 % in centers enrolling more than 20 patients [84]. A Canadian study of outcomes related to surgeon and hospital volume showed significant relationships. After controlling for clustering and patient/treatment covariates, hospital volume continued to be significant as a predictor of mortality [85].

Another interesting example relates to the availability of modern radiotherapy facilities in the form of access to intensity-modulated radiotherapy (IMRT). The use of IMRT has rapidly become widespread for the delivery of radiotherapy for patients with head and neck cancer in the USA. However, significant geographic variations are apparent in the utilization of IMRT, and patients in census tracks comprising the lowest socioeconomic quartile were less likely to receive IMRT than their more affluent counterparts [86].

Other reports also point out disappointing examples of environmental health-care disparities associated with advanced head and neck presentations in the USA. These are much more likely to be evident in patients without adequate health-care insurance, or individuals, especially blacks, residing in regions with low educational accomplishments or with low median household incomes. Similar findings were seen in patients with laryngeal cancer [87] and oropharyngeal cancer [88]. The authors indicate that it is important to consider the impact of insurance coverage on disease stage at diagnosis and associated morbidity, mortality, and quality of life.

Similar findings on stratified analysis and logistic regression were applied to two million incident cancers (1997–2000) from 32 states representing 57 % of the US population. For a great many cancers, poverty as a factor independently predicts advanced-stage cancer suggesting that improved access and utilization of good medical care might facilitate earlier diagnosis and longer survival [89]. Consistent with these findings is the report of a large series ($n=1231$) of patients with primary squamous cell carcinoma of the oral cavity, pharynx, or larynx diagnosed or treated at the University of Pittsburgh by Kwok et al. [90]. They report that patients with Medicaid/uninsured and Medicare disability were at increased risk of death after a diagnosis of SCCHN when compared with patients with private insurance, after adjustment for age, gender, race, smoking, alcohol use, site, socioeconomic status, treatment, and cancer stage. Similarly, Molina and colleagues studied 20,915 patients with head and neck cancer in the Florida Cancer Data System and showed that African American and poor patients have a dramatically worse prognosis although the disparity is not entirely explained by demographics, comorbidity, or undertreatment [91].

While numerous other factors are also associated with adverse outcome, space does not permit a more detailed discussion of this very important and often overlooked area. Ironically, as implied by the examples shown above, these factors have the greatest potential for remediation with consequent improvement in outcome compared to other prognostic factors, but this can only be accomplished if resource inadequacies and process deficiencies are addressed.

9.12.3 Combining Variables and Validation

The science of prognostic factor assessment is a nascent area that needs to be considered in a broader context. We have seen that the dimensions of prognosis in head and neck cancer cover a wide field, yet there remains uncertainty about how to proceed in our goals of using the extent of this knowledge to its full capability. It does appear that critical dismissal of one dimension as being less useful than another is probably not the solution, nor is it helpful to dismantle a system that is being used successfully worldwide, for nearly half a century, to permit newer elements to be introduced if the framework was not designed to receive them. In general terms, some agreement on taxonomy and methodology is required. Perhaps the adoption of formal terms such as *staging* to describe the anatomic extent of disease and *profiling* to describe the qualitative characteristic of tumors may be a start. The use of the term *prognostic models* could then permit them to be combined in a rational way that allows their full impact to be exploited. These concepts are under active discussion by the UICC and AJCC. Different aspect of these will be discussed below under different rubrics that address the traditional TNM groupings, the use of prognostic indexes, the use of nomograms, and the area of validation and comparison of prognostic models.

9.13 Handling Prognostic Groups Within TNM

In addressing the need to combine different prognostic elements into groups, the UICC and the AJCC took slightly different approaches in the seventh edition TNM classification. The AJCC substituted the term "Anatomic Stage/Prognostic Groups" in place of what were previously termed "Stage Groups" when the elements of TNM are combined together within the TNM in the seventh edition [1]. However, the goal of the new terminology is the same as it was previously, i.e., to create a basic form of prognostic index. The UICC approached this slightly differently in the seventh edition although the intent is identical to the AJCC, namely, to permit the incorporation of validated nonanatomic prognostic factors at present or in the future. The UICC's approach is to use two forms of grouping of component elements [2].

The predominant one is termed "Stage Groups" and contains only anatomic factors for virtually all sites within TNM and represents the same "Stage Groups" as were used in the former sixth edition. Certain diseases that traditionally used some nonanatomic factors, e.g., thyroid cancer where age has been incorporated and sarcomas that included grade, are retained in the "Stage Groups" of the seventh edition to avoid disruption to a classification developed many years ago. However, the incorporation of newer nonanatomic factors is being addressed by the creation of a third dimension within the UICC's version of TNM in the form of "Prognostic Groups." In truth, these are identical to the AJCC's "Anatomic Stage/Prognostic Groups" in the few diseases where this applies, and for all other diseases, the UICC "Stage Groups" are analogous. At present only two diseases have the new "Prognostic Groups" in the UICC version, namely, prostate and esophageal cancer, in both of which pathological grade was recently introduced in the classification. There were no head and neck sites included in this process in the seventh editions. In time, it is possible that the UICC may also modify thyroid and sarcoma so that the anatomic and nonanatomic elements will only be aggregated together in the "Prognostic Groups," and the "Stage Groups" will only contain anatomic extent of disease variables throughout TNM. In this way, anatomic disease extent can be addressed independently in "Stage Groups" or in combination with nonanatomic factors in the "Prognostic Groups," the latter being analogous to the "Anatomic Stage/Prognostic Groups" of the AJCC. Currently discussions are underway as to how best to amalgamate these two ideas and whether to expand these "Prognostic Groups" to head and neck.

A final and more sobering dimension in the area of "Prognostic Groups" or "Stage Groups" is the fact that these are generally developed in a pragmatic rather than pure scientific way. Hence, the literature contains numerous examples of the theme that the TNM stage group classifications, while successful in creating statistically distinct groups, often do not perform as well as other stage grouping systems [92]. Potentially, the future will require some attention to this area of research as well if the groups formulated within the classification are to be considered seriously. Detailed discussion of alternative staging systems is reported in the literature [93].

9.14 Prognostic Indexes

The head and neck literature contains a growing body of reports devoted to combining different elements of prognosis together. Generally, the intention is to focus on a particular setting (e.g., previously untreated patients, patients with recurrent cancer, patients with metastatic disease, early-stage disease vs. more advanced disease, etc.). Usually, the intention is to facilitate decision-making in the management of patients, usually concerning some intervention. Behind most is the goal of generating a quantified prognosis in the form of a score that may be useful to the patient, guiding clinical decisions, or for guiding eligibility for clinical trials tailored to specific treatments and patient types.

Some of the dimensions are appropriate to combine together, but as we have discussed, this can be fluid and variables are highly interdependent. Some factors are not present at baseline. A typical example is the inclusion of the status of resection margins in a model where this variable only becomes available after the first and often most important treatment has been administered (namely, surgery). Thus, it is not only unavailable at baseline, but it also automatically selects out cases with different prognosis based on their likelihood of undergoing a successful resection with clear margins. Cases with positive resection margins can be expected to be already having adverse prognosis from the standpoint of the anatomic extent of disease, but such classifications may still be highly useful in guiding decision-making for the use of adjuvant treatments once the primary treatment has been undertaken. This further illustrates the theme that disease extent must be considered in applying prognostic models, and one cannot necessarily extrapolate to another setting whether it concerns different stages of disease, different anatomic sites, or different scenarios (e.g., primary vs. recurrent cancer).

There is insufficient opportunity to explore the different models that have been developed in the head and neck area, but these include, among others, attention to parotid cancer [94, 95], metastatic nasopharyngeal cancer [96], laryngeal cancer [83], hypopharyngeal cancer [76], and various combinations of cancers of the larynx, oral cavity, and pharynx [74]. Some of these studies were mentioned earlier in the context of comorbidity in Sect. 9.12.1 where many have included comorbidity assessed in various ways combined with the TNM and other elements of anatomic disease extent and included other factors such as age, gender, and some pathological features. An outstanding example of this demonstrates that both claims-based and chart-based reviews have significant predictive capabilities [97]. As yet there is no report that incorporates a robust model that combines molecular characterization of disease (or even host) with more traditional domains, and this type of work is very inviting for the future. As noted some studies have combined different prognostic factors that include biological markers with more traditional parameters such as gender and smoking, but they have not as yet been formulated into a prognostic index to guide decision-making for individual patients or even groups of patients [38, 53].

9.15 Nomograms

Nomograms are widely used for cancer prognosis, primarily because of their ability to reduce statistical predictive models into a single numerical estimate of the probability of an event that is tailored to the profile of an individual patient [93]. Often these use appealing graphical interfaces, commonly displayed by computer, that facilitate interaction with individual patients about their personal disease situation. While widely used in some areas of oncology, especially prostate cancer, there is a small but growing body of literature addressing various questions through the use of nomograms for head and neck cancer [98, 99]. Gross et al. developed a nomogram for guiding adjuvant treatment after surgery for oral cavity squamous cell carcinoma [100]. Notably, this was developed for relatively early-stage resected oral cancer, and this context must be remembered as it is easy to stray from the original basis of the nomogram when using it to discuss problems with patients. So far there is no evidence that this is happening in head and neck cancer, but there may be such instances in other diseases.

The AJCC, in particular, is exploring the use of nomograms to address the potential goal of creating a "continuous prognostic nomogram" for each site and each patient, where the anatomic TNM staging will remain as the fundamental factor, but other important features, such as biomarkers as well as comorbidities, will be included with a weighted score to arrive at a "prognostic score," at any given point throughout the patient's life [10]. In this concept, the prognostic score will be a dynamic "staging and prognostic" tool to accurately reflect each patient's prognosis at the point of inquiry. The beauty of this is that its dynamic nature throughout a patient's life gives an accurate assessment of prognosis, while retaining the static parameters of TNM staging in its construct. This would also be a perfect example of "personalized prognostic model," for each patient. The CS approach implemented by the AJCC will act as a repository of all available prognostic information for current and future use to support this approach. This ambitious project is potentially both welcome and problematic. Clearly, it is important to be able to encompass the multiple dimensions of prognosis in this way, and the concept is certainly meritorious. On the other hand, a limitation is that it largely relates to individual prognosis at this time, and additional development will be needed to address groups of patients since one of the goals of the stage classifications is to be able to compare results across groups, in trials, and among regions. Thus, there is the possibility that two systems of staging and prognostic modeling may be required. One would be an individualized nomogram, and the other would be stage groupings, to compare results and outcomes of groups and for protocol entry. Another challenge concerns the statistical underpinnings of these models that require careful scrutiny, including the degree of uncertainty surrounding the point estimates. This is thoroughly addressed in a review that includes cautionary language that the methodology underlying the construction of nomograms should be understood by clinical users so that prognostic estimates are appropriately communicated [101].

9.16 Validation and Comparison of Prognostic Models

An important aspect to the creation of prognostic indexes concerns the underlying statistical principles and the epidemiological basis for their creation. This area cannot be addressed here, but the reader should be aware of such principles as the generalizability of the index to patients outside the source population. It includes transportability of results beyond the domain where it was created such as transportability regarding geographic location, but also by time or era, which may be more difficult to address with different historical dimension to the data, its assembly, and its use. Other dimensions include clinical and statistical validation. The complex nature of these issues and the assumptions behind the models, including understanding their inherent weaknesses, require attention and are summarized more completely elsewhere [92, 93, 102, 103].

Other elements in understanding prognostic models, and especially when comparing models against each other, concern a variety of concepts in the evaluating process. These include hazard consistency (i.e., homogeneity within strata for the outcome of interest), hazard discrimination (i.e., each stratum chosen should have a statistically distinct prognosis compared to the stratum above and below it for the outcome), outcome prediction (i.e., maximizing prediction accuracy by techniques such as percent of variation in outcome explained by the scheme or by measuring the slope or degree of separation in the mean probability predictions), and balance (where different prognostic strata or groups are relatively even and balanced). These are detailed elsewhere for the interested reader [92, 104].

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Preclinical Models of Head and Neck Squamous Cell Carcinoma

10

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Abstract

HNSCCs are characterized by a broad genetic diversity, likely from prolonged carcinogen exposure and high levels of genetic instability. To date, this high genetic heterogeneity of HNSCC has hampered the development of targeted therapy, and routine use of molecular markers for treatment selection is not established. This chapter reviews preclinical models of HNSCC as a critical tool for exploring tumor initiation and progression, cancer genetics, novel therapeutic approaches, and predictors of clinical response. HNSCC model systems including cancer cell lines derived from human HNSCC, primary human fresh tumor cultures, animals exposed to oral carcinogens, genetically engineered mouse models (GEMMs), and various combinations of these systems are discussed.

Keywords

Preclinical model • Head and neck • SCC • Cell line • Mouse model • Fresh primary tumor culture

Head and neck squamous cell carcinoma (HNSCC) represents 3–5 % of newly diagnosed cancers and has a 5-year survival between 25 and 95 % depending on disease site and stage. This indicates both the need for novel treatment strategies as well as the variable response to treatment. Currently, therapy selection is based on data derived from a combination of randomized controlled trials, meta-analyses, and retrospective case series. Although in HNSCC the routine use of molecular markers for treatment selection is not established yet, in several other tumor types such as breast, colon, lung, and melanoma, this molecular knowledge has already been translated into important predictive assays used in treatment selection [1–4].

HNSCCs are characterized by a broad genetic diversity, likely from prolonged carcinogen exposure and high levels of genetic instability [5, 6]; however, several signaling pathways are commonly involved in HSNCC carcinogenesis, including p16, p53, CyclinD1, and PTEN [7–9]. The high genetic heterogeneity of HNSCC has hampered the development of targeted therapy, and to date only anti-EGFR therapy has demonstrated clinical efficacy in locally advanced HNSCC [10]. Nonetheless, targeting other pathways including PI3Kinase-AKT, insulin-like growth receptor, BCL2, and c-met has shown promise in preclinical models [11–16].

Human papillomavirus oncogenes E6 and E7 bind and inactivate tumor suppressors p53 and retinoblastoma (Rb) [17]. Although HPV has been thought to promote HNSCC development for decades [18], it has only more recently been appreciated that HPV-positive and HPV-negative HNSCC

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are biologically distinct. HPV-associated HNSCCs tend to occur at a younger age, are less related to smoking and alcohol exposure, and do not typically exhibit p53 mutations or p16 (INK4a) alterations. Moreover, HPV status predicts both responses to radiation therapy and improved outcome [19–21]. However, as stated above, at the moment we lack the knowledge and reliable trials to personalize treatment regimens in HNSCC.

Because studying cancer in humans poses ethical, financial, and practical hurdles, preclinical models are a critical tool for exploring tumor initiation and progression, cancer genetics, novel therapeutic approaches, and predictors of clinical response. HNSCC model systems include cancer cell lines derived from human HNSCC, primary human tumor cultures, animals exposed to oral carcinogens, genetically engineered mouse models (GEMMs), and various combinations of these systems. Each system has strengths and weaknesses that are important to interpreting data derived from these models. To maximize clinical relevance, model systems should resemble human HNSCC as closely as possible. For example, cell lines should harbor the genetic and epigenetic alterations common to HNSCC, and carcinogen exposures should mimic the routes and chemicals associated with human HNSCC. Similarly, GEMMs or primary tumor models should examine the genetic alterations observed in human HNSCC. To overcome the limitations of a given model, results should be validated by multiple approaches in different systems; however, ultimately, all results obtained in model systems must be validated in human samples or subjects.

10.1 HNSCC Cell Lines

Cultured HNSCC cells are a versatile model system that can be characterized by genetic mutation, anatomic site of origin, and in vitro behavior [22]. Genetic manipulation of cultured cells can be used to elucidate the role of specific molecules on behaviors relevant to cancer development and progression in view of clinical treatment response [23]. HPV 16 E6–E7-immortalized mouse tonsil epithelial cells (MTECs) have been used to define the viral genes required for immortalization, anchorage-independent growth, and, eventually, malignant growth in vivo [24]. In addition, differences in response were attributed to differences in the genetic makeup of HNSCC cell lines, being either HPV positive or negative [12, 25].

A major advantage of HNSCC lines is that the low cost permits high-throughput approaches that allow screening of novel compounds (alone or in combination), treatment modalities (e.g., drugs plus radiation therapy), and resistance to targeted treatment. For cell lines have been used to demonstrate that resistance to anti-EGFR therapy may be overcome through simultaneous targeting of EGFR and either Src kinase [26] or HER3 [27]. Similarly, cell lines have been used to demonstrate that hypoxia and DNA repair are important in radioresistance [28–30], and studying DNA repair after radiation treatment may facilitate the development of strategies that increase the therapeutic window of XRT in HNSCC patients [31].

However, cancer cell lines have critical limitations. They are a homogeneous clonal population capable of growing in vitro without the supporting tumor stroma (fibroblasts, immune cells, or vasculature) and typically fail to reflect the genetic heterogeneity of the native tumor from which they were derived. Although the majority of individual tumor cells are incapable of growing in culture, patients whose tumors can establish cell lines have worse clinical prognosis, suggesting that characteristics supporting in vitro growth are indicative of aggressive tumor behavior in vivo [32]. Furthermore, as cells are passaged, there is selective pressure for in vitro growth, and a lack of standardized tissue culture techniques can limit reproducibility [33–39]. Culture conditions can also influence the responses to cytotoxic therapies as cells grown as anchorage-independent spheroids can have different responses to cytotoxic agents than the same cells grown as monolayers [40]. Also, passaged lines may exhibit different chemosensitivity patterns over time [41–43]. Therefore, cell lines are poor predictors of treatment response in individual patients [44, 45]. Many of these issues may have been accentuated in HNSCC secondary to the relative paucity of well-characterized lines [32, 46].

Despite these limitations, much of our basic mechanistic understanding of the roles of specific molecules has been derived from cell culture experiments. Perhaps the most successful example of this is identification and subsequent inhibition of the bcr-abl fusion protein in chronic myelogenous leukemia [47, 48]. Unfortunately, like most solid tumors, HNSCC is not uniformly sensitive to inhibition of a single oncogenic driver [6], and combinations of inhibitors or targeting of specific tumor subsets will be required to improve disease control. Currently, inhibitors of EGFR, phosphoinositol-3-kinase-AKT pathway, insulin-like growth factor receptor (IGFR), BCL2, and c-MET are being studied in preclinical HNSCC models [11–16].

Although cell lines are the optimal system to study pathways and the role of specific genes, it has proven difficult to identify reliable markers of treatment response using cell lines. We generated a radiosensitivity profile using HNSCC cell lines [30, 45], but this profile was not predictive of clinical local control after radiotherapy in laryngeal cancer patients. Nevertheless, other profiles like the Chung high-risk profile and the Slebos negative HPV expression profile have been useful in predicting local recurrence in HPV-negative HNSCC after chemoradiotherapy [49–51].

10.2 Short-Term Primary Tumor Cultures

As cell lines are difficult to establish and are poor predictors of in vivo responsiveness, short-term cultures of primary HNSCC specimens have also been used to predict therapeutic responsiveness. Soft agar culture of primary digested HNSCC cells was first described over 40 years ago, [52] and colonies of 20–50 cells can be established from 33 to 74 % of HNSCC biopsies within a few weeks [53–56]. This system has been used to assess chemosensitivity [54] and radiosensitivity [53], both of which correlated with clinical tumor behavior. The approach is limited by a relatively small number of available tumor cells, low clonal growth (presumably secondary to a limited number of cells capable of forming colonies), and high contamination with non-epithelial cells. Intrinsic radiosensitivity of fresh HNSCC cell cultures has also been tested in a cell adhesive monolayer that better restores cell-cell contact and thus may better predict treatment response [57–59]. Contamination with stromal cells can impact both chemo- and radiosensitivity where drug- or radiation-resistant stromal cells can mask selective epithelial sensitivity patterns [60–63].

To overcome these limitations, the histoculture drug response assay was developed to improve the predictive ability of primary cultures [64]. In this technique, tumor fragments are cultured without digestion to maintain cell-cell adhesions and tumor heterogeneity and potentially protect a limited number of tumor stem cells. This markedly improves culture success as well as the ability of the culture to predict clinical responsiveness [65–68]. The improved predictive value may be related to the three-dimensional structure and relative inaccessibility of the hypoxic tumor interior to chemotherapeutic agents which better models the actual in vivo tumor environment. Several groups have also grown HNSCC "spheres" or "organoids" to better mimic the three-dimensional configuration of tumor cells in vivo [69–73]. When benign and malignant "spheres" were generated from HNSCC tumor fragments in agar-coated culture flasks, the importance of the immune system was illustrated as increased cytokine production stimulated by contact between monocytes and tumor cells was predictive of an unfavorable clinical prognosis [69, 70]. Unfortunately the low culture success rate (6 %) limits the clinical applicability of this technique [71]. To date, no phase II or III studies have demonstrated added predictive value of preclinical short-term fresh HNSCC chemosensitivity or radiosensitivity assays.

10.3 Xenograft Mouse Models

A variety of approaches are available to study HNSCC tumor behavior in vivo: one of the most common is xenografting of established human HNSCC cell lines into immunocompromised mice. Depending on the desired application, xenografts can be established heterotopically in the flank or orthotopically, in the buccal mucosa, floor of the mouth, or tongue. Xenografts can be used to assess the response to drug or radiation therapy [74–76] or to define the role of specific molecules during head and neck cancer development [77, 78]. In addition, these models can be used to study other processes critical for HNSCC development and progression, including lymphatic metastasis [79], bone invasion [80], interactions between cancer-associated fibroblasts and cancer epithelial cells [81], and tumor cell invasion [82]. The major limitations of this technique are inability to study tumor-immune interactions, the poor ability of xenografts to predict drug activity against human cancers [83], and the cost compared to in vitro cell culture experiments.

Murine HNSCC lines can also be grafted into syngeneic immunocompetent hosts, and although the number of murine-derived lines is limited, these models can facilitate the study of advanced tumor behavior and tumor-immune system interactions. The oral SCC VII/SF line was derived from C3H/HeJ mice [84] while the PAM-LY and B4B8 lines were derived from BALB/c mice [85–87]; these lines have been used to study bone invasion, metastasis, and tumor recurrence [88–92].

Xenografts of primary human HNSCCs can also be established in the flanks of immunocompromised animals either after a short-term passage in vitro or from primary human HNSCC samples [93, 94]. Direct patient xenografts can amplify tumor material for downstream molecular or cellular analysis and can provide a platform for in vivo testing of therapeutic compounds [95]. Direct xenografts are genetically stable over multiple passages in mice [95] and preserve some features that cultured cells irreversibly lose [96]. Moreover, these systems may be better suited for studying invasiveness and metastases than cell culture systems [97] secondary to the preservation of tumor stromal cells that are important for these processes [98]. Since this model implants developed human tumors into immunocompromised mice, it is unsuitable for studying tumor initiation, chemoprevention, or tumor immunology.

10.4 Chemical Carcinogenesis Models

Oral cancers can also be induced by exposing rodents to carcinogens. Because specific mutagens produce characteristic genetic lesions [99, 100], carcinogen-induced tumors tend to be more homogeneous than their human counterparts, but because these models have a long latency and exhibit premalignant lesions, they are useful for studying tumor initiation and chemoprevention.

One well-characterized approach is the hamster buccal pouch model in which HNSCC are induced by prolonged

oral application of the H-ras mutagen DMBA (7,12-dimethylbenz(a)anthracene) [99, 101]. This produces squamous cell carcinomas in the majority of animals, and animals develop lymph node metastases if observed long enough [102]. This model has been used to study the chemopreventive activity of a variety of natural compounds [103, 104] as well as inhibitors of epidermal growth factor receptor (EGFR) and cyclooxygenase-2 (COX2) signaling [105, 106]. However, the utility of this model is somewhat limited by the relative paucity of hamster-specific tools and reagents, especially compared to mice.

Similarly, prolonged oral exposure to another H-ras mutagen 4-NQO (4-nitroquinoline *N*-oxide) induces both oral and esophageal SCC in mice [100, 107, 108], and cervical lymph node metastasis can be observed with a more prolonged observation period [109]. This model has been used to test chemoprevention by inhibitors of mammalian target of rapamycin (mTOR), vascular endothelial growth factor (VEGF), and EGFR [110–112]. Although DMBA and 4-NQO are not tobacco-derived carcinogens, they provide a convenient way of inducing a clinically relevant tumor-initiating event [113].

10.5 Genetically Engineered Mouse Models

GEMMs have been an enormous step forward for cancer modeling and allow evaluation of discrete genetic alterations in specific organs in vivo in an immunocompetent animal. Additional benefits of GEMMs include the ability to evaluate how multiple genetic defects interact to promote or inhibit cancer and the opportunity to evaluate whether specific targeted therapies are active against tumors with a defined genetic composition. Drawbacks are that human cancers are more genetically complex and heterogeneous than tumors produced in mouse models, and differences in the human and mouse immune systems may complicate studies of tumor immunology.

Targeted mutagenesis of the mouse germ line by homologous recombination in embryonic stem cells can be used to create classic "knockout" mice, and if the genetic modification is not embryonic lethal, heterozygotes can be crossed to create mice homozygous for a particular gene deletion. While knockout mice can be used to study tumor suppressor loss if combined with HNSCC carcinogens [114–116], there are critical limitations to this approach. First, global deletion of putative tumor suppressors is frequently embryonic lethal; thus, it is difficult, if not impossible, to study combinations of genetic modifications using this technique [117]. In addition, because the genetic modification is present in all tissues, tumors can develop in multiple anatomic locations, and gene deletion in tumor stromal cells (fibroblasts, immune cells, and vasculature) can impact both animal phenotype and tumor behavior in unanticipated ways.

To overcome these issues and target genetic manipulations to specific tissue compartments, several approaches have been taken. One of the first strategies was to target oncogene overexpression with a promoter that restricts transgene expression to the oral epithelium. For example, when the Epstein–Barr virus ED-L2 promoter was used to target cyclin D1 to oral-esophageal epithelium, mice develop dysplasia that progresses to SCC when this transgene is crossed into a $p53^{-/-}$ background [118]. Second generation systems provided another layer of control of genetic manipulations through an ability to induce transgene expression. For example, when a keratin 5 (K5)-targeted, doxycycline-inducible system was used to induce expression of a tet-responsive $Kras^{G12D}$ oncogene, animals developed tumors of the oral mucosa and esophagus; however, because these animals also develop skin and urogenital lesions (secondary to broad K5 expression and systemic doxycycline treatment), the applicability of this system to HNSCC has been limited [119].

Most current GEMMs combine promoter-mediated tissue targeting and ligand induction to achieve organ specificity and temporal control of genetic alterations. In these systems, conditional genetic deletion is achieved by placing loxP restriction sites around a target gene; the target gene is excised upon Cre recombination activation [120]. By placing a loxP-flanked stop codon upstream of an oncogene (e.g., $Kras^{G12D}$), this approach can also be used to "knock-in" oncogenes [121]. Tissue specificity is achieved by placing Cre recombinase expression under the control of an epithelial-specific promoter (typically keratin 5 or keratin 14); however, an additional layer of control is required to restrict Cre recombinase expression to the oral epithelium as keratins are robustly expressed in other epithelial tissues including the skin and mammary gland. This control is achieved through a ligand-inducible Cre recombinase fusion protein; the two most common are the tamoxifen-inducible truncated estrogen receptor (ER) fusions ($K14CreER^{T}$ and $K5CreER^{T2}$) and RU486-inducible truncated progesterone receptor (PR) fusions (K14CrePR or K5Cre*PR) [122, 123]. The advantage of these systems is tissue-specific, spatial, and temporal control of recombination and the ability to introduce multiple genetic alterations simultaneously. Disadvantages of this system are that most inducible Cre recombinase systems have some level of background activity and there may be variability in recombination efficiency for different genes which may be related to the distance between LoxP sites [124, 125].

When the K5Cre*PR construct and oral RU486 are used to target oncogenic $K\text{-}ras^{G12D}$ expression, mice develop oral papillomas that progress to HNSCC with the simultaneous activation of mutant $p53^{R172F}$, but not with conditional p53

deletion [122, 126]. Similarly, deletion of transforming growth factor beta type II receptor (TGFβRII) in conjunction with $Kras^{G12D}$ activation causes full penetrance HNSCC with frequent metastases [127]. As deletion of TGFβRII alone does not cause tumor formation, it appears that $Kras^{G12D}$ functions as a tumor initiator while TGFβRII loss functions to promote tumor development and progression. In contrast to TGFβRII, Smad4 deletion in the oral epithelium targeted by K14CrePR or K5Cre*PR and oral RU486 causes HNSCC in the absence of Kras activation, perhaps secondary to the genomic instability that characterizes $Smad4^{-/-}$ HNSCC [128].

The $K14CreER^T$ construct and oral tamoxifen have been used to simultaneously target conditional deletion of TGFβ receptor type I (TGFβRI) and phosphate and tensin homolog (PTEN); this model exhibits full penetrance HNSCC and has been used to study chemoprevention by rapamycin and treatment with inhibitors of phosphoinositide 3-kinase (PI3K)/mTOR and interleukin-13 receptor [129–131].

Chemoprevention by rapamycin was also seen in a model that used $K14CreER^T$ to target $Kras^{G12D}$ and conditional p53 deletion to oral mucosa [132]; it is unclear why conditional p53 deletion promoted SCC development in this model but not when these same genetic alterations were targeted by K5Cre*PR [126]. In a more complex model, conditional p53 deletion targeted by $K14CreER^T$ caused malignant conversion of dysplasias produced by a K5-targeted constitutively active Akt construct [133]. Finally, $K14CreER^T$ targeting of TGFβRII and E-cadherin deletion results in both oral and esophageal SCC formation [134]. In sum, the current HNSCC GEMM models offer a wide array of options for both examining the role of a specific gene during HNSCC development and testing the efficacy of therapeutic interventions on genetically defined tumors.

Genetic and carcinogenesis models have also been combined to study the effects of oncogenes and tumor suppressors on HNSCC initiation, progression, and metastasis. For example, a single dose of oral DMBA produces HNSCC in 100 % of mice with K5-targeted TGFβRII deletion [127] and 45 % of mice with a K14-targeted TGFβRI deletion [135]. Interestingly, cervical lymph node metastases were observed in both models, but no tumors were observed without DMBA tumor initiation [127, 135]. A single submandibular DMBA injection has also been used to induce salivary gland sarcomas in $p53^{-/-}$ mice [114], while chronic oral DMBA treatment has been used to demonstrate that nude mice develop HNSCC more rapidly than immunocompetent C57BL6 animals [136]. Similarly, deletion or mutation of tumor suppressors such as p53 or xeroderma pigmentosum A renders mice more susceptible to 4NQO carcinogenesis [115, 116], while overexpression of oncogenes like human papillomavirus (HPV) proteins E6/E7 and cyclin D1 has a similar effect [137–139].

10.6 Imaging Techniques

A number of imaging techniques are also now being coupled with in vivo models. The most common is the stable introduction of the firefly luciferase gene into cancer cells prior to grafting; this allows in vivo serial imaging of tumor growth by bioluminescence (IVIS) [76, 140, 141]. Organs can also be imaged by bioluminescence ex vivo at the time of euthanasia to detect regional and distant metastases [142]. HPV-targeted luciferase reporters can also be combined with genetic models to track tumor response to treatment over time [143]. Cancer cells can also be engineered to express mCherry and then tumor growth and metastasis tracked by two-photon microscopy [144]. Other imaging techniques have also been used to improve the applicability of animal HNSCC models. Ultrasound can be used to monitor growth of cervical lymph node metastases as well as to guide fine-needle sampling of these nodes [145]. This approach may prove powerful for serially tracking lymph node metastases over time. Rigid confocal endoscopy has been used to monitor the growth of carcinogen-induced oral lesions [146]; this may be helpful in modeling the progression of mucosal lesions from dysplasia to cancer. These imaging techniques will likely improve the utility of many HNSCC mouse models by facilitating the monitoring of tumor growth and metastases as well as the response to therapy without needing to euthanize the animal.

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Translational Research in Head and Neck Oncology

11

David S. Yoo and David M. Brizel

Abstract

Translational research continues to shape the clinical practice of head and neck oncology. Ongoing discoveries in basic mechanisms of cancer biology and technological advances in diagnostic imaging and radiation delivery seek to improve treatment outcomes, maximizing therapeutic benefit and minimizing toxicity. Its ultimate goal is to offer an ever-expanding menu of options available for the care of individual patients.

Focusing on this goal has become more challenging, with socioeconomic and political pressures casting shadows across the health care landscape. As external financial concerns encroach on the translational process, it is imperative to recognize that the research itself is best positioned to remedy them—matching more efficacious treatments with reduced toxicity burdens in appropriately selected patient populations.

What should also not be lost in translation is the unpredictable and serendipitous nature of research. Decades of research with rational strategies based on tumor hypoxia in head and neck tumors have yet to penetrate widespread clinical practice. Meanwhile, two current mainstays of therapy, cisplatin and cetuximab, were developed with fortuitous levels of chance. However, even these two workhorses face new scrutiny with more recent publications. And perhaps, the long-heralded realm of cancer immunology may finally find its way to the table. To borrow a phrase from the fashion world, one day you're in, and the next day, you're out.

Since the last edition of this textbook, the practice of head and neck cancer has seen two significant translational trends—(1) the power of viruses to potentially dictate management and (2) the realization that doing more to patients does not necessarily translate into better outcomes for them.

This chapter will explore the meaning of translational research, identify potential pitfalls on the horizon, and highlight common themes and new avenues of research using specific examples from both the head and neck and general oncology literature.

Keywords

Translational research • Radiation therapy • Targeted therapy • Head and neck cancer • Chemoradiation • Human papillomavirus

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11.1 Introduction

Translational research continues to shape the clinical practice of head and neck oncology. Ongoing discoveries in basic mechanisms of cancer biology and technological advances in diagnostic imaging and radiation delivery seek to improve treatment outcomes, maximizing therapeutic benefit and minimizing toxicity. Its ultimate goal is to offer an ever-expanding menu of options available for the care of individual patients.

Focusing on this goal has become more challenging, with socioeconomic and political pressures casting shadows across the health care landscape. As external financial concerns encroach on the translational process, it is imperative to recognize that the research itself is best positioned to remedy them—matching more efficacious treatments with reduced toxicity burdens in appropriately selected patient populations.

What should also not be lost in translation is the unpredictable and serendipitous nature of research. Decades of research with rational strategies based on tumor hypoxia in head and neck tumors have yet to penetrate widespread clinical practice. Meanwhile, two current mainstays of therapy, cisplatin [1, 2] and cetuximab, were developed with fortuitous levels of chance. However, even these two workhorses face new scrutiny with more recent publications. And perhaps, the long-heralded realm of cancer immunology may finally find its way to the table [3]. To borrow a phrase from the fashion world, one day you're in, and the next day, you're out.

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11.2 Translational Research

The concept of translational research in oncology evokes images of a bridge, spanning and connecting the separate worlds of basic bench research and clinical bedside investigation and treatment [4]. Cellular and molecular discoveries in the laboratory yield clues to underlying mechanisms of disease, identifying novel targets for therapeutic intervention that, ultimately, improve cancer patient outcomes. The National Cancer Institute (NCI) defines translational research as "the process by which the results of research done in the laboratory are used to develop new ways to diagnose and treat disease" [5]. To facilitate this process, the NCI has established Specialized Programs of Research Excellence (SPOREs) throughout the USA to promote interdisciplinary collaboration in cancer research. There are currently six such programs devoted to head and neck cancer.

The discipline of head and neck oncology possesses a strong history of translational research and continues to expand and build upon its foundation of scientific discoveries. Several chapters in this textbook are singularly devoted to epidemiology, genetics, virology, proteomics, predictors and prognosticators, hypoxia, molecular targeted therapies, and functional imaging. Other chapters discuss preclinical models and phase I study methodology. Translational research then is not unlike the United Nations, gathering these topics together under one roof and forging a common ground that is beneficial to all. Ultimately, it is responsible for shaping and writing the current and future chapters on patient management and evidence-based practice.

11.3 Roadblocks

One of the ironic aspects of cancer research today is that the sheer avalanche of data and knowledge generated may overwhelm the ability to ask the most appropriate clinical questions. When the haystack is filled with needles, finding one gives way to the more challenging task of finding the right one. For example, at least 12 different agents target the epidermal growth factor receptor (EGFR) alone [6]. There are four downstream pathways associated with EGFR, and the number of potential therapeutic strategies to shepherd through from conception to daily practice expands geometrically along each signaling cascade [7]. The danger then becomes one of seeing a promising new treatment get lost in the translation.

The Clinical Research Roundtable at the Institute of Medicine (IOM) in their special communication to JAMA in 2003 highlighted an example of one of the dilemmas in translational research [8]. The IOM, comprised of individuals from the fields of nursing, medicine, basic science, public health, medical informatics, insurance companies, industry, and private foundations, described two translational roadblocks that "impede efforts to apply science to better human health in an expeditious fashion." The first exists when trying to convert basic in vitro and in vivo laboratory discoveries into novel interventions for human studies. The second occurs in the process of applying these novel agents into rigorous human studies and attempting to integrate them into everyday clinical practice and decision-making. The culprits deemed to be responsible for both blocks include insufficient funding, insufficient infrastructure, lack of qualified personnel, lack of career incentives, and a dearth of willing research subjects [9].

Much of the emphasis and funding in medical research to date had been placed on trying to overcome the first block. Now, novel therapeutics and new diagnostic modalities have exploded on the scene. Many are now concerned, however, that the second translational block constitutes the greatest bottleneck and is most detrimental to the health outcomes of everyday patients. More people, it has been argued, can be better served by focusing on the appropriate delivery of already proven treatment strategies rather than inventing new ones [10]. For example, the expenditure of effort to develop new and incrementally more efficacious statins or antiplatelet drugs contributes less to the overall societal health than using those same resources to ensure delivery of already available drugs to all eligible patients [11].

US health care expenditures in 2013 totaled $2.9 trillion, nearly 17.4 % of the gross domestic product (GDP) [12]. Current projections are for this sum to increase to 20 % of GDP by 2017. Historically, approximately 5 % of this spending has been related to cancer therapy, although this percentage is also expected to rise with the aging US population and the adoption of newer, more expensive technologies and therapies [13]. How much should be spent and what level of care it should buy will require national debate and political intervention, suggesting the probability of a rational solution is low.

A growing awareness of how new cancer treatments contribute to the escalating costs of health care has resulted in urgent calls to police within the oncology community before outside government agencies are mandated to do so. Such external intervention may result in more translational blocks, with decisions made by individuals with priorities focused beyond the clinic. Previously, the NIH reviewed four molecular targeted agents—cetuximab, bevacizumab, erlotinib, and sorafenib—pinnacles of the translational research effort and compared their "purported" benefits and estimated costs [14]. They highlighted the multinational phase III FLEX (First-Line ErbituX) study comparing platinum-based chemotherapy with or without cetuximab as first-line therapy in EGFR-overexpressing non-small cell lung cancer patients with either wet stage IIIB or stage IV disease [15]. Patients randomized to the cetuximab arm received a loading dose of 400 mg/m^2, followed by weekly doses of 250 mg/m^2 concurrent with up to six cycles of chemotherapy and continuing weekly until disease progression or unacceptable toxicity. The primary endpoint was achieved with a statistically significant increase in median survival from 10.1 to 11.3 months with the addition of cetuximab. Ten percent developed grade 3 acne-like skin toxicity.

The cost of adding cetuximab to the 18 weeks of chemotherapy (60 kg patient and $11.52 per mg of cetuximab) was $80,352 per patient [14]. Similarly, the addition of the small molecule tyrosine kinase inhibitor erlotinib to gemcitabine in advanced pancreatic cancer increased median survival by 10 days [16] for a cost of $15,752 [14]. Other examples were presented for the use of bevacizumab in metastatic breast cancer [17] and sorafenib in renal cell carcinoma [18], emphasizing the tension that exists reconciling the costs of these therapies and their limited impacts on overall survival and/or quality of life.

The ErbituX in first-line Treatment of REcurrent or MEtastatic head and neck cancer (EXTREME) trial had a very similar design to the FLEX study in lung cancer. In this trial, 442 patients with previously untreated recurrent or metastatic disease not amenable to local therapy were randomized to platinum and 5-FU-based chemotherapy alone versus chemotherapy with weekly cetuximab [19]. Those patients with stable disease on concurrent therapy continued with weekly cetuximab until disease progression or unacceptable toxicity. The addition of cetuximab improved median survival from 7.4 to 10.1 months, along with improvements in progression-free survival and response rates.

This increase represented a significant achievement in the recurrent/metastatic setting, the first intervention shown to improve survival in this population since cisplatin over 30 years ago [20]. However, this 2.7-month improvement in EXTREME may face further scrutiny, given the shot across the bow from the NIH regarding the results of FLEX. A typical patient in the USA with a body surface area of 2 mg/m^2 would have required 9300 mg of cetuximab in 18 weeks in the experimental arm of the EXTREME trial at a cost of $107,136 based on 2008 data. Weekly treatment for 12 months in the setting of stable disease would have received 26,300 mg, which would have cost $302,976. Neither a privately run nor a publicly administered health care system can sustain this level of expense. A potential doomsday scenario for translational research could result if insurance companies and/or governments decide to offer patients a fraction of that cost to NOT take therapy.

The American Society of Clinical Oncology published the initial deliberations of its Cost of Care Task Force focusing on the perspectives of the different stakeholders in the oncology community—patients, industry, payers, and physicians—and highlighted the need to "define the value of specific cancer interventions" [21]. Some advocate funding restraints on research studies which would place cost limits on experimental interventions depending on their potential survival advantages [14]. In the same vein, some industry stakeholders may decide that certain disease entities, including head and neck cancers, lack the necessary patient numbers and potential market share for allocation of their resources in support of clinical trials.

11.4 Common Themes

The story of ICI 46,474, more commonly known as tamoxifen, is an instructive case study. This compound was first developed in the 1970s by Imperial Chemical Industries Ltd. Pharmaceuticals Division (now AstraZeneca) as a postcoital contraceptive [22]. The initial research that established tamoxifen as an antiestrogen capable of controlling hormone-dependent tumors almost did not happen. At the time, the company did not see a financial incentive to market a drug used for a short period of time by a small number of metastatic breast cancer patients, most of whom were getting the latest and most promising therapy, cytotoxic chemotherapy combinations. It took the threatened resignation of the Head of Research, serendipity, and years of preclinical data before the antitumor activity of tamoxifen was established. Moreover, testing in humans was originally performed in patients with advanced metastatic disease. Although somewhat effective, it was not until tamoxifen was studied in the adjuvant setting that the large benefits in reducing recurrence and improving overall survival were seen in estrogen receptor-positive patients [23]. As stated by Dr. Jordan, the man who helped translate tamoxifen into clinical practice, "the key to success was targeting women with the right tumour with the correct duration of treatment at the right stage."

The right woman, the right tumor, at the right stage—parallels can be drawn from the tamoxifen story to the targeted agents of today. Cetuximab's origins can be traced back to a woman born in the late nineteenth century. At the age of 85, her squamous cell carcinoma of the vulva was harvested and transformed into the immortalized cell line A431 [24]. Eleven years later in 1984, her cell line provided the substrate for the creation of murine monoclonal antibodies against the EGF receptors overexpressed along the cell surface [25]. In 1991, one of these antibodies, mAb 225, was successfully injected and studied in human subjects [26]. By 1995, the chimeric antibody C225, aka cetuximab, was developed to overcome the human anti-mouse antibody phenomenon that limited the clinical utility of mAb 225 [27].

Head and neck cancer patients with overexpression of EGFR were noted to have a poorer prognosis, providing the rationale for targeted therapy with C225 [28, 29]. Cetuximab has been utilized in a variety of different clinical scenarios since—as a single agent in advanced chemorefractory disease [30], with chemotherapy in the recurrent/metastatic setting [19, 31], with radiation therapy alone in locally advanced but nonmetastatic patients [32], and with concurrent chemoradiation [33]. In refractory patients, single-agent cetuximab showed a median survival of 178 days [30]. The results of EXTREME in previously untreated recurrent/metastatic patients were outlined earlier, showing an increase in median survival from 7.4 to 10.1 months [19]. The pivotal phase III trial from Bonner et al., which compared radiation therapy alone in the definitive setting with or without cetuximab, showed significant improvements in both local control and survival, increasing median survival from 29.3 to 49 months and 3-year overall survival from 45 to 55 % [32]. As with tamoxifen, the earlier utilization of cetuximab in the non-metastatic and treatment-naïve setting demonstrated a more robust improvement in clinical outcomes.

The fate of cetuximab and other novel therapeutic agents as they progress through various phases of development highlights several important themes for current and future translational research efforts. As the specificity of these agents toward their molecular targets increases, so too should the process of patient selection in order to optimally use them in various clinical scenarios. The keys to success appear require several interrelated questions to be addressed: who gets therapy, what agent(s) gets tested, whether to give or not give therapy, scheduling and sequencing, where is the primary tumor located, and why did things work or not work? Limitations on resources and competition for study patients will prevent all of these questions from being asked. The head and neck oncology community will need to prioritize which ones are most important.

11.5 Who Gets Treated

The standard approach for new investigational agents that emerge from preclinical development is to first test them in patients that have failed all known conventional therapies, initially for dose-limiting toxicities and safety and then for efficacy. An exciting and challenging avenue for research is to ask whether improvements in outcomes in the recurrent and refractory setting translate in treatment-naïve patients. Are the additional months in median survival outback simply reshuffled upfront? Or are there true qualitative and quantitative improvements in survival, with more cures and less patients going on to require therapy for recurrent or metastatic disease? In head and neck cancer, the Bonner cetuximab/RT study suggested the latter.

This has not always been the case. In colorectal cancer, the addition of bevacizumab to irinotecan, bolus fluorouracil, and leucovorin in previously untreated metastatic patients resulted in a statistically significant improvement in survival (median duration 15.6 vs. 20.3 months HR 0.66 $p<0.001$) [34]. A similar benefit in overall survival was seen in a phase III ECOG study in patients with previously treated metastatic colorectal cancer. In this trial, the addition of bevacizumab to fluorouracil, leucovorin, and oxaliplatin (FOLFOX) improved median survival from 10.8 to 12.9 months compared to FOLFOX alone [35]. However, the survival benefits of adding bevacizumab to standard-of-care chemotherapy do

not appear to automatically translate in the nonmetastatic setting. Preliminary results from NSABP C-08 showed no statistically significant improvement in disease-free survival with the addition of bevacizumab to FOLFOX in resected stage II–III colon cancer patients [36].

Another more ominous example is a phase III SWOG adjuvant lung cancer study. Patients received definitive concurrent thoracic chemoradiation and consolidation docetaxel chemotherapy with or without the addition of gefitinib, a small molecule EGFR tyrosine kinase inhibitor. Patients receiving gefitinib had a significant decrease in median survival (23 vs. 35 months) [37]. These findings further emphasize the importance that promising preclinical and early phase data for targeted agents must be validated in a rigorous phase III setting before they can be incorporated into widespread clinical practice.

Even then, the translation of successful randomized phase III trials into the phase IV practice setting can encounter unexpected hazards. Cetuximab is associated with an approximate 3–4 % incidence of grade 3–4 infusion reactions in the USA. However, in certain geographic locations, the rate of severe anaphylactic hypersensitivity-type reactions approaches 20–25 % [38]. In an illustrative example of bedside-to-bench reverse translation, these reactions have been linked to preexisting IgE antibodies that cross-react to a galactose-alpha-1,3-galactose moiety that is tagged to the Fab portion of the mouse component of the cetuximab molecule during antibody production [39]. Moreover, preexisting IgE antibodies in the general population were found to be more prevalent in people from Tennessee, Arkansas, and North Carolina (20.8 %) as opposed to northern California (6.1 %) or Boston (0.6 %). The potential increased risk for these severe reactions has limited the enthusiasm for and restricted utilization of cetuximab in pockets of the Southeast USA. It was perhaps serendipitous that C225 was developed in a different part of the country.

Parallels may be drawn to trials examining the addition of concurrent chemotherapy to radiation in nasopharyngeal carcinoma (NPC), a tumor known for significant geographic variability with regard to histology and EBV status. Following the positive results of the Intergroup 0099 trial [40], studies were undertaken throughout Asia to determine whether the significant survival benefit seen in North American patients with a concurrent chemoradiation (CRT) strategy translated to the endemic form of NPC found more predominantly in that part of the world. Three phase III trials from Taiwan, Singapore, and Hong Kong confirmed a survival benefit with concurrent CRT versus radiation alone [41–43]. However, preliminary results from a fourth study with nonkeratinizing/undifferentiated histology patients from Hong Kong and Canada showed no statistically significant survival benefit but increased acute and late toxicity with concurrent CRT [44]. Whether regional or demographic differences in efficacy and/or toxicity will be discovered with other targeted therapies remains to be seen.

In nasopharyngeal cancer, more translational research is underway to select patients treated with definitive CRT for further adjuvant chemotherapy. NRG-HN001 is an ongoing combined phase II/III study that uses pretreatment plasma EBV DNA levels to randomize patients with undetectable levels to standard adjuvant chemotherapy (cisplatin/5FU) versus observation, while those patients with detectable EBV levels will receive standard therapy versus a hypothetically more intense regimen with gemcitabine and paclitaxel.

Another head and neck cancer story that has gone viral in recent years is the link between the human papillomavirus (HPV) and certain oropharyngeal cancers [45]. These double-stranded DNA viruses have survived millennia in the terminally differentiated epithelia of higher-level organisms, restarting their nondividing hosts' replication machinery by inactivating both the p53 and pRb tumor suppressors. The first suggestion of HPV involvement in head and neck cancer came in 1983 based on histopathologic findings seen in a subset of oral squamous cell carcinomas similar to those caused by HPV in the uterine cervix [46]. Detection of high-risk HPV16 DNA in tonsil cancer specimens came in 1990 [47].

Multiple retrospective series and a subsequent meta-analysis suggested that patients with HPV-positive oropharyngeal tumors had improved disease-free and overall survival, with a 28 % reduced risk of death compared to HPV-negative patients [48]. The prognostic significance of HPV status was demonstrated prospectively in 96 patients from a phase II ECOG study examining an induction chemotherapy regimen followed by CRT [49]. Patients with HPV-positive tumors had higher response rates to chemotherapy and CRT as well as a 2-year overall survival of 95 % (95 % CI = 87–100 %) versus 62 % (95 % CI = 49–74 %) for the HPV-negative patients. The prognostic significance of HPV status has since been confirmed in multiple phase III studies with various treatment regimens, including radiation alone (DAHANCA 5), sequential chemotherapy/radiation (TAX 324), and concurrent CRT (RTOG 0129) [50–53].

The improved outcomes and atypical presentations (younger age, lack of prior tobacco, and alcohol use) of HPV-positive head and neck cancer patients suggest these tumors represent a distinct clinical entity [54]. Their emergence has had significant implications for translational research. A clinical trial population enriched with HPV+ patients destined for an already excellent prognosis would make it difficult to detect any potential benefit from the experimental treatment. This phenomenon has been suggested as one rationale for the negative results seen in the phase III sequential CRT trials that examined the use of induction chemotherapy prior to definitive CRT [55, 56]. Both studies were already underpowered, terminating early prior to meeting accrual targets, but

the presence of a significant number of HPV+ patients also likely contributed to the statistical burden.

Moreover, the excellent prognosis of HPV-positive patients has further implications regarding the future direction of treatment strategies that incorporate novel translational therapies. The question arises whether intensive concurrent regimens using radiation, chemotherapy, and/or molecular targeted agents are necessary for optimal tumor control in HPV-positive patients or whether they are just more toxic [58, 59]. Therefore, strategies for de-intensification of therapy in this subset of patients, including radiation alone, radiation and/or chemotherapy dose reductions, or radiation combined with better-tolerated targeted agents in lieu of chemotherapy, are underway.

Current and future translational studies in head and neck cancer have begun enrolling patients based on HPV status [57]. RTOG 1016, now closed to accrual, is a randomized phase III trial for HPV+ oropharyngeal patients comparing standard of care CRT with cisplatin versus a potentially less toxic regimen of radiation therapy plus cetuximab. ECOG 3311 is a phase II study of transoral surgery in HPV+ patients, with subsequent adjuvant therapy based on pathologic risk factors. Patients considered low risk would undergo observation, while high-risk patients would receive postoperative CRT. Patients with intermediate risk factors are randomized to 50 Gy versus 60 Gy postoperative IMRT. For HPV− patients, RTOG 1221 is a phase II study that randomizes patients to definitive CRT versus potential treatment intensification with upfront transoral endoscopic surgery followed by risk-adapted postoperative radiation ± concurrent chemotherapy.

11.6 What

With more stratification and reclassification of HPV-positive disease into a separate disease entity, the already small pie of head and neck cancer patients eligible to participate in clinical trials could get sliced further, reducing the ability to definitively answer study questions. RTOG 9003, the largest trial in head and neck cancer, needed over 6 years to enroll 1113 patients [60]. Already, the increasing number of investigational agents has likely outgrown the number of people available for enrollment in clinical trials and the resources available to conduct them.

The study of one agent at a time is challenging enough, with or without radiation, with or without chemotherapy. Another area of increasing interest involves targeting multiple signaling pathways at once, either with multi-agent cocktails or more promiscuous inhibitors like vandetanib or lapatinib. The rationale for this approach has been the limited clinical utility seen with single targeted agents alone and the redundancy of signaling pathways. Despite the fact that a majority of head and neck tumors have EGFR overexpression, cetuximab with radiation therapy still showed a 50 % local recurrence rate in the Bonner trial [32].

This fact is not surprising, given the complexity of the molecular signaling pathways involved in the pathogenesis of head and neck cancers [61]. Preclinical studies have shown significant crosstalk, with both direct and indirect associations between the various signaling cascades, providing alternative routes to bypass inhibition of one pathway [62]. Already, the simultaneous inhibition of the EGFR and VEGF pathways with erlotinib and bevacizumab has been studied in the recurrent/metastatic setting, showing the combination was well tolerated and potentially more efficacious in a subset of patients with molecular evidence of activated pathways [63].

At Duke University, a phase I/II trial examining the use of erlotinib, bevacizumab, and concurrent cisplatin with hyperfractionated radiation therapy in treatment-naïve, locally advanced nonmetastatic patients has recently completed accrual. Median follow-up is 2 years, and the results have been promising, with only two of the 28 patients having had a local recurrence. The trial design has also incorporated companion studies with serial functional imaging scans and serum samples collected at time points before, during, and after completion therapy. The goal is to help identify potentially predictive and/or prognostic factors that correlate with treatment outcomes, improving the selection of patients for targeted therapies in the future.

However, more is not always better. The Dutch CAIRO2 study in metastatic colorectal cancer found that the addition of cetuximab to capecitabine, oxaliplatin, and bevacizumab leads to a decrease in progression-free survival and quality of life [64]. The search for molecular rationales, including mechanisms of resistance, will require more bench research to help translate these unexpected bedside findings.

11.7 When

Clearly, not every patient benefits from the administration of targeted therapies. Even with the potential for more dramatic clinical improvements in the definitive and nonmetastatic setting, it does not appear economically feasible to incorporate one or two (or more) targeted therapies into the treatment regimen of every patient that presents de novo with locally advanced head and neck cancer. Finding biomarkers and molecular assays that can reliably predict who might respond favorably to certain agents and when they should be utilized is a key emphasis of ongoing studies.

In colorectal cancer, patients with EGFR-expressing tumors and unresectable metastatic disease were randomized to FOLFIRI chemotherapy with or without cetuximab. Tumor KRAS gene mutation status was also examined. A

progression-free survival benefit for cetuximab was limited to those patients with wild-type KRAS [65]. In the previously mentioned phase I/II study examining erlotinib and bevacizumab in recurrent/metastatic head and neck cancer, patients with increased phosphorylation of VEGFR in tumors and EGFR in endothelial cells were more likely to have complete responses [63]. Another study examining cisplatin and erlotinib in recurrent/metastatic head and neck patients found a correlation between improved treatment response and high EGFR gene copy number [66]. More robust and clinically applicable prognostic and/or predictive tools will be identified and validated. In fact, given the current climate, research that results in the more judicious use of novel therapies is mission critical to the viability and support of future translational studies [67].

The ability to identify responders versus nonresponders to targeted therapy early on in the treatment course would further improve patient selection and efficacy, providing guidance on when changes in therapy should be made. Recent trials with targeted agents have incorporated correlative studies with functional imaging modalities to noninvasively and serially assess the tumor microenvironment and monitor any possible treatment-related changes. Tools such as dynamic contrast-enhanced MRI (DCE-MRI) and PET-based assays attempt to capture novel information based on the underlying tumor biology, yielding potentially prognostic and predictive information to augment the anatomically based TNM staging system. For example, many antiangiogenic targeted agents exert their effects on tumor perfusion and vascular permeability, physiologic processes that can be quantitatively measured with DCE-MRI [68]. In breast cancer, early changes in tumor microvessel functionality as monitored by changes in DCE-MRI signaling predicted final clinical and pathologic response to neoadjuvant chemotherapy [69]. Other DCE-MRI parameters have also correlated with local control and disease-free and overall survival in multiple tumor sites, including the lung, cervix, and head and neck [70–75].

11.8 How

The question of how to optimally incorporate novel therapeutic agents in radiation-based treatment regimens remains an active area of research. One limitation of the Bonner cetuximab trial was the use of a control arm that utilized radiation therapy alone instead of concurrent CRT in locally advanced patients. Based on the Meta-analysis of Chemotherapy in Head and Neck Cancer (MACH-NC), which examined updated patient data on 16,485 patients from 87 trials published between 1965 and 2000, the addition of chemotherapy to radiation provided an absolute benefit of 4.5 % at 5 years with a hazard ratio of 0.88 [76]. This benefit was more pronounced (6.5 % at 5 years, HR 0.81) with the concomitant use of chemotherapy and radiation as compared to induction or adjuvant strategies.

One hypothesis-generating result from Bonner's pivotal trial arises from the differences in survival seen between those patients who received cetuximab with altered fractionation versus conventional daily treatment schedules. Subset analyses showed that patients treated with concomitant boost regimens had a hazard ratio (HR) of 0.62 while the hyperfractionation group had an HR = 0.74. No difference in survival was seen in those patients who underwent conventional fractionation (HR = 1.01) [32]. This suggests that a trial design that happened to utilize only conventional radiation with cetuximab could have resulted in a negative study.

Radiation fractionation does not seem to matter when combined with conventional systemic agents. Results from MACH-NC suggested that the survival benefit seen with concurrent chemotherapy is similar irrespective of the radiation fractionation regimen utilized [conventional HR 0.83 (95 % CI 0.78–0.88) vs. altered HR 0.73 (95 % CI 0.65–0.82) $p = 0.14$] [76]. These findings have now been corroborated by the results of randomized phase III trials. RTOG 0129, which tested conventional fractionation RT with three cycles of cisplatin versus accelerated fractionation with two cycles of cisplatin, showed no differences in outcomes [77]. A GORTEC phase III study also showed no difference in progression-free survival at 3 years between accelerated versus conventional radiation therapy with concomitant carboplatin and 5-FU [78]. Therefore, determining the optimal radiation fractionation schedules to use with novel investigational agents may present an ongoing challenge.

The randomized phase III RTOG 0522 trial tested the addition of cetuximab to altered fractionation definitive CRT in locally advanced nonmetastatic head and neck cancer patients [79]. There were no statistically significant differences in 3-year progression-free survival (61.2 % CRT vs. 58.9 % CRT + cetuximab, $p = 0.76$) or overall survival (72.9 vs. 75.8 %, $p = 0.32$) between the two arms. Moreover, the addition of cetuximab had no benefit in patients with tumors that overexpressed EGFR (>80 % vs. <80 % tumor cell staining). If anything, there were potential trends in favor of CRT alone in stage III and HPV+ oropharynx patients.

Despite the apparent lack of success of cetuximab with platinum-based CRT, the addition of other novel agents to concurrent CRT may ultimately establish a new standard of care for patients with high-risk, poor prognosis disease. For example, the use of lapatinib with concurrent CRT is being evaluated in locally advanced head and neck patients [80]. In a randomized phase II trial with 67 patients, the addition of lapatinib to definitive CRT showed statistically nonsignificant improvements in complete response, PFS, and OS, especially in HPV− patients [81]. RTOG 3501, another randomized phase II study, is also examining the addition of

lapatinib to CRT in HPV− patients only. At the same time, others are examining lapatinib with radiation therapy alone in locally advanced patients who cannot tolerate CRT [82].

To further complicate matters, the efficacy of molecular targeted agents or other novel investigational drugs may differ depending on which systemic chemotherapy is used during CRT. In RTOG 0234, head and neck patients with high-risk pathologic features (positive margin, and/or extracapsular extension, and/or two or more involved lymph nodes) were treated with 60 Gy plus weekly cetuximab and randomized to either concurrent cisplatin or docetaxel [83]. When compared to the historical outcomes with concurrent cisplatin in RTOG 9501, this phase II study showed improved disease-free and overall survival with the docetaxel-containing arm. This regimen is now being tested in RTOG 1216, a phase II/III study of postoperative IMRT combined with the docetaxel plus cetuximab arm of RTOG 0234 versus docetaxel alone versus cisplatin.

How novel investigational agents are incorporated into current standard treatment regimens will be a critical area of ongoing research. Potential improvements in efficacy will need to be balanced against any increases seen in acute and late toxicity. In this context, tools to improve patient selection will play increasingly more important roles to optimally match treatment regimens of varying intensities to individual patients in order to optimize their therapeutic ratio.

11.9 Where

The location of the primary tumor site may also affect prognosis. A multivariate analysis of 492 patients showed better outcomes in patients treated for larynx and nasopharyngeal tumors compared to those with oropharynx, oral cavity, and hypopharyngeal primaries [84]. In another series of locally advanced patients treated with intra-arterial cisplatin and radiation (RADPLAT), those with hypopharyngeal primaries were more likely to develop distant metastases (odds ratio 2.8) compared to patients with oral cavity, oropharynx, or laryngeal tumors [85]. In the Bonner trial, 253 of the 424 patients in the study had oropharyngeal tumors. On subgroup analysis, these patients appeared to derive the greatest benefits in locoregional control and survival from the addition of cetuximab [32].

These findings further underscore the complexities facing the successful translation of targeted agents into clinical practice. Future prospective trials need to focus on specific head and neck cancer subsites with enriched patient populations most likely to benefit from the investigational therapy to avoid potential dilution of successful outcomes by the inclusion of possibly "nonresponding" patients. In the case of oropharyngeal tumors, trials have been further subdivided according to HPV status. At the same time, excessive stratification and selection of patients will severely cripple study power and applicability of results to the general head and neck cancer population.

11.10 Why

The need to confirm hypotheses in prospective trials is highlighted by several pitfalls in the translation of the very logical and rational hypoxia story into clinical practice. Since 1912, when Swartz observed less severe skin reactions when a radiation source compressed the surrounding blood flow, careful clinical and laboratory research has subsequently established the significant role hypoxia plays in cancer progression and increased resistance to radiation and chemotherapy [86, 87]. In head and neck cancer, studies directly measuring pretreatment intratumoral oxygenation levels in primary tumors and lymph node metastases using polarographic electrode techniques predicted for response to radiation therapy [88] and were prognostic for disease-free survival [89]. More recent studies have focused on less invasive methods such as hypoxia-related biomarkers and functional imaging studies to correlate tumor hypoxia with treatment-related outcomes [90]. Using tissue samples from RTOG 90-03 patients, expression of lysyl oxidase, a hypoxia-related protein, was shown to be strongly associated with increased metastases, disease progression, and death [91].

This rationale leads to the testing of therapeutic strategies designed to ameliorate or target hypoxia. Anemia, which contributes to tumor hypoxia, is associated with inferior outcomes following both radiotherapy alone and concurrent CRT [92–94]. However, correction of anemia has not improved treatment outcome in prospective trials. In one series of patients treated with sequential chemotherapy followed by CRT, the use of blood transfusions to maintain hemoglobin levels >12 g/dL was associated with worse survival [95]. Two randomized DAHANCA studies that incorporated blood transfusions for low hemoglobin levels showed no benefit [96, 97].

Both erythropoietin [98] and darbepoetin alfa [99] reversed the effects of anemia on radiation response in preclinical models. Moreover, in a retrospective study of patients treated with neoadjuvant CRT and surgery for oral cavity/oropharyngeal cancers, the use of recombinant human erythropoietin completely abrogated the negative prognostic impact associated with hemoglobin levels <14.5 g/dL [100]. However, two randomized phase III trials showed no benefit to the addition of erythropoietin in anemic HNC patients undergoing radiation therapy [101, 102]. In fact, the Henke study resulted in poorer disease control and survival in patients randomized to receive erythropoietin [101]. A randomized study in cervix cancer patients was closed prematurely due to concern for increased thromboembolic events with erythropoietin [103].

A Cochrane Review including 13,933 cancer patients in 53 trials showed that erythropoiesis-stimulating agents were associated with increases in on-study mortality and worse overall survival [104]. These unexpected clinical findings stimulated laboratory research that demonstrated expression of erythropoietin receptors on tumor cells in a variety of malignancies, including squamous cell carcinomas of the head and neck [105]. Potential erythropoietin-mediated signaling mechanisms responsible for increased cancer cell survival have been implicated [106, 107].

An alternate strategy of specifically targeting hypoxic cancer cells leads to the study of bioreductive agents such as tirapazamine [108]. Preclinical data showed preferential cytotoxicity to hypoxic tumor cells, and early phase I/II data demonstrated encouraging results when this agent was combined with chemotherapy and/or radiation [109–111]. However, two randomized phase III studies have shown no benefit from the addition of tirapazamine to radiation and chemotherapy. The HEADSTART trial showed no benefit in patients with locally advanced HNC treated to 70 Gy with three cycles of concurrent cisplatin [112]. The TRACE study, which used the same treatment scheme, was terminated early due to excessive mortality in the experimental tirapazamine arm [113]. Unfortunately, no systematic assessment of tumor hypoxia was performed in either of these trials. Studies using electrode and PET-based techniques suggest that approximately one third to one half of HNC patients do not have significant levels of tumor hypoxia [114, 115]. Therefore, it is possible that both of these trials were "biologically underpowered" to address the hypoxia question which was being investigated.

Translational studies using functional imaging modalities that correlate with tumor hypoxia may better identify candidates for hypoxia-targeted therapy [116]. A sub-study of TROG-98.02 using ^{18}F misonidazole-PET to image tumor hypoxia found a significantly higher risk of locoregional failure in hypoxic patients who received concurrent chemotherapy compared to those who also received tirapazamine [115]. The ability to image hypoxia-specific regions with PET and/or functional MRI may further allow for physical targeting and treatment intensification with radiation techniques such as intensity-modulated radiation therapy [117]. However, significant daily fluctuations in tumor hypoxia imaging have been seen in as many as 30 % of patients [118]. This suggests widespread clinical application will require further translational research into the dynamic nature of these processes studied by functional imaging modalities—vascular permeability, perfusion, and metabolism.

11.11 Conclusion

Successful translational research will help to define new standards of care by improving the therapeutic ratio between treatment efficacy and toxicity. Better prognostic tools and more robust predictive assays will help to improve patient selection, stratifying patients to appropriate intensifications or de-intensifications of therapy and identifying those most likely to benefit from various treatments. In future trials, enriching the study population with those most likely to need and respond to certain therapies will hopefully magnify any potential improvements in outcome, in turn lowering the number of subjects needed to detect statistically significant differences. This is especially critical for head and neck cancer where the eligible patient pool from which to draw is smaller than other disease sites.

New experimental therapies will need to be built on the foundation of prior successes, incorporating themselves into optimized standard of care regimens. Due to increasing economic constraints, leadership and guidance will likely need to come from the large umbrella cooperative groups such as the RTOG and EORTC regarding trial design and priorities. The design of trials should continue to combine treatment interventions with various correlative studies to identify and validate predictors that will help determine who benefits most from specific therapies. Strategic plans within RTOG have been discussed to improve the ability to perform more successful translational studies—tissue banking, seed grants, bioinformatics, and statistical support [119].

The war on cancer has seen decades of translational research creating a new generation of targeted weapons with increasing specificity and accuracy. The danger now lies in using these agents to carpet-bomb entire patient populations, failing to commit the same level of resources to identifying the correct human targets.

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Hypoxia in Head and Neck Cancers: Clinical Relevance and Treatment

12

Yungan Tao and Jean Bourhis

Abstract

Tumor hypoxia, or the condition of low oxygen, is a key factor for tumor progression and treatment resistance. Hypoxic areas arise as a result of an imbalance between the supply and consumption of oxygen. Cellular responses to hypoxia are orchestrated through activation of the hypoxia-inducible factor (HIF) family of transcription factors. There are several approaches for detecting tumor hypoxia in head and neck cancer (HNC). Recent studies have focused on molecular markers of hypoxia, such as HIF-1 and carbonic anhydrase isozyme IX (CA-IX), and on developing noninvasive imaging techniques such as positron emission tomography (PET) scan with 18F-FMISO and 18F-FAZA. Hypoxia gene signature is a promising strategy for characterizing the hypoxic status of tumor. Hypoxia appears to be prognostic for outcome in HNC. Several studies have shown that low PO_2 in tumor, HIF-1, Glut-1 and CA-IX expression, and serum level of osteopontin correlated with treatment outcomes in HNC patients treated with radiotherapy or chemoradiotherapy. The correlation of human papillomavirus and hypoxia needs to be further clarified.

Several strategies have been used to overcome hypoxia-induced treatment resistance in HNC, such as hyperbaric oxygen treatment, accelerated radiotherapy with carbogen and nicotinamide (ARCON), and hypoxic cell radiosensitizers—nitroimidazoles, erythropoietin manipulation, and hypoxic cell cytotoxin. More recently, new approaches such as vascular normalization, HIF-1 targeting or integrating FMISO-PET information for adaptive radiotherapy appeared also very promising.

Keywords

Hypoxia • Radiotherapy • Head and neck cancer • HIF-1

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Tumor hypoxia or the condition of low oxygen is a key factor for tumor progression and treatment resistance.

Hypoxia develops in solid tumors due to aberrant blood vessel formation, fluctuation in blood flow, and increasing oxygen demands for tumor growth. Because hypoxic tumor cells are more resistant to ionizing radiation (IR), tumor hypoxia has been recognized as a potential cause of failure when treating human solid tumors with IR, both in experimental models and in patients with several types of cancer including head and neck cancer (HNC). The potential importance of hypoxia as a potential mechanism limiting the probability of cure rate in patients with HNC treated with radiotherapy (RT) has been recognized [1].

12.1 Description of Factors Associated with Hypoxia and Potential Mechanisms of Resistance Related to Hypoxia

Hypoxic areas arise as a result of an imbalance between the supply and consumption of oxygen. In locally advanced solid tumors, the O_2 consumption rate of neoplastic cells may outweigh a restricted oxygen supply and results in the development of tissue areas with low or very low O_2 levels [2]. Other mechanisms are involved in the development of hypoxia in solid tumors: severe structural and functional abnormalities of tumor microvessels induce perfusion limited O_2 delivery; deterioration of diffusion geometry limits oxygen penetration; tumor-associated and/or therapy-induced anemia could lead to a reduced O_2 transport capacity [2].

As a consequence of these mechanisms, tumor hypoxia is associated with the production of fewer radiation-induced cytotoxic free radicals, less radiation-induced DNA damage, and decreased tumor cell kill. This is called as oxygen enhancement effect. Damage to DNA is mainly induced by interaction with oxygen-reacting free radicals formed by the ionization of water surrounding DNA [3]. Typically, DNA strand breaks that are not repaired can lead to fatal chromosomal aberrations. It has been shown that oxygenated cells are 2.5 to 3 times more radiosensitive than hypoxic cells [3]. Hypoxic cells are also considered to be resistant to most anticancer drugs for several reasons [4]: first, hypoxic cells are distant from blood vessels and, as a result, may not be adequately exposed to some types of anticancer drugs [5]; second, cellular proliferation decreases as a function of distance from blood vessels, an effect that is at least partially due to hypoxia; third, hypoxia can select for cells that have lost sensitivity to p53-mediated apoptosis, which might lessen sensitivity to some anticancer agents; fourth, hypoxia can upregulate genes involved in drug resistance, including genes encoding P-170 glycoprotein.

Hypoxia is not only an important cause of treatment resistance but also a powerful stimulus of several critical tumor phenotypes. These discoveries have prompted to question whether the link between hypoxia and radioresistance is completely explainable by the oxygen enhancement effect as described above or whether hypoxia also influences radiosensitivity through additional biological effects.

12.2 Molecular Pathways Involved in Hypoxia

Cellular responses to hypoxia are orchestrated through activation of the hypoxia-inducible factor (HIF) family of transcription factors [6]. HIF-1 is a heterodimer that consists of the hypoxic response factor HIF-1α and the constitutively expressed HIF-1β [7]. The level of HIF-1α expression is determined by the rates of protein synthesis and protein degradation. HIF-1α protein synthesis is regulated via O_2-independent mechanisms, by activation of phosphatidylinositol 3 kinase (PI3K)/Akt and extracellular-signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) pathways [8]. These pathways can be activated by signaling via receptor tyrosine kinases, non-receptor tyrosine kinases, or G-protein-coupled receptors.

HIF-1α protein degradation is regulated by O_2-dependent prolyl hydroxylation, which targets the protein for ubiquitylation by E3 ubiquitin-protein ligases. These ligases contain the Von Hippel–Lindau (VHL) tumor-suppressor protein, which binds specifically to hydroxylated HIF-1α. Ubiquitylated HIF-1α is rapidly degraded by the proteasome. In the absence of oxygen, HIF-1 binds to hypoxia-response elements (HREs), thereby activating the expression of numerous hypoxia-response genes, such as the pro-angiogenic growth factor—vascular endothelial growth factor (VEGF). The redox active apurinic/apyrimidinic endonuclease-1 has been shown to keep HIF-1α in a reduced state that is necessary for its transcriptional function. HIF-1 can affect several intracellular processes including glycolysis, cell proliferation, apoptosis, angiogenesis, and invasion/metastasis—which have been shown to influence the response to IR and might, therefore, serve as a link between HIF-1 activity and tumor radiosensitivity.

Recently, two other pathways that independently influence gene expression and processes of importance for tumor cell behavior have proved to be O_2 sensitive [9]. The first occurs through regulation of an important integrator of metabolic signals, the kinase mammalian target of rapamycin (mTOR), also known as FK506-binding protein 12-rapamycin-associated protein 1 (FRAP1), and its downstream effectors that orchestrate the initiation of protein synthesis, autophagy, and apoptosis sensitivity. The second is

through activation of the unfolded protein response (UPR), a program of transcriptional and translational changes that occurs as a consequence of endoplasmic reticulum (ER) stress. The UPR controls multiple downstream processes, including protein production, protein maturation and degradation, cell metabolism, and cell death. HIF-, mTOR-, and UPR-dependent responses to hypoxia act in an integrated way, influencing each other and common downstream pathways that affect gene expression, metabolism, cell survival, tumorigenesis, and tumor growth.

Increased HIF-1α protein synthesis was inhibited by treatment with rapamycin—a macrolide antibiotic that inhibits mTOR. However, it is not known whether phosphorylation of these proteins by mTOR is necessary or sufficient for increased HIF-1α synthesis. In addition to effects on HIF-1α synthesis, activation of the RAF-MEK-ERK signaling pathway has also been shown to stimulate HIF-1α transactivation domain function. This effect is due at least in part to phosphorylation by ERK of the co-activator p300.

A recently characterized hypoxia-induced protein, the regulated in development and DNA damage 1 (REDD1), could negatively control mTOR activity. In head and neck squamous cell carcinoma (HNSCC) cell lines, the expression of the phosphorylated forms of the mTOR downstream targets S6 kinase and S6 (pS6) decreased after hypoxia. These events were associated with REDD1 upregulation. Inhibition of AMP-activated protein kinase (AMPK) before prolonged hypoxia prevented REDD1 expression, thereby sustaining mTOR activity. Reduced mTOR activity in response to hypoxia through AMPK/REDD1 was deregulated, which hence might contribute to the persistent activation of the mTOR pathway in HNSCC cells [10].

12.3 How to Detect Hypoxia in the Tumors: Techniques to Measure Tumor Hypoxia

There are several approaches for detecting tumor hypoxia in HNC. In contrast with the general consensus to consider hypoxia as an important parameter of tumor physiology and response to treatment [11] there is a lack of simple and efficient methods to measure hypoxia that limit its clinical usefulness. There is no gold standard for measuring hypoxia. Briefly, techniques for measuring tumor oxygen can be categorized into two groups: direct invasive and indirect noninvasive methods. Direct oxygen measurements in tissues with Eppendorf PO_2 histography have been used, but this method is invasive. Recent studies have focused on molecular markers of hypoxia, such as HIF-1 and carbonic anhydrase isozyme IX (CA-IX), and on developing noninvasive imaging techniques. The workshop report also presented a comprehensive review of different approaches for measuring tumor hypoxia.

Electrode PO_2 measurements have been used in several normal tissues such as the brain, breast, and skeletal muscle, and these measurements have been used to develop profiles that can be illustrated by PO_2 histograms reflecting the oxygenation status of a given tissue. These PO_2 distribution profiles may reflect the efficacy of several oxygen supply determinants, such as blood flow rate, the blood's oxygen transport capacity, the availability of oxygen to the cells, rate of oxygen extraction from the blood, oxygen diffusion distances, microvascular density, and oxygen diffusion coefficients within the tissue, as well as the rate of oxygen consumption by the cells. Although the microelectrode technique directly measures tumor PO_2, it suffers from several drawbacks that make it difficult for general use. These include invasiveness, tumor inaccessibility, pressure dependence, interobserver variability, failure to distinguish necrosis from hypoxia, and the lack of spatial information [12].

Endogenous and secreted molecular markers for tumor hypoxia represent proteins and genes whose expressions are induced by hypoxic exposure. One of the most studied oxygen response pathways is HIF-1 pathway; HIF-1 and several of its downstream targets, including Glut-1 (glucose transporter-1), CA-IX, and VEGF, have been widely investigated as prognostic markers in HNC patients with mixed results. One advantage of endogenous markers is that levels of these proteins can be assessed on archival materials, thereby allowing possible correlation with treatment outcomes. In addition it requires neither the injection of a hypoxic marker drug used as an exogenous marker nor any additional invasive procedure except the need of a biopsy at diagnosis. A possible drawback of these approaches is that these proteins can be regulated by factors other than hypoxia. Another hypoxia-related marker, the serum level of osteopontin (OPN), has also been reported recently. Le et al. [13] investigated the relationship between OPN, tumor PO_2, and prognosis in patients with HNSCC, and it has been shown that plasma OPN levels appeared to correlate with tumor hypoxia in HNSCC patients and may serve as noninvasive tests to identify patients at high risk for tumor recurrence.

Other indirect approaches use injectable molecular reporters of oxygen (exogenous marker) which include 2-nitroimidazole compounds such as misonidazole (MISO), pimonidazole (1-[2-nitro-1-imidazolyl]-3-Npiperidino-2-propanolol) [14], and EF5 (2-[2-nitro-1H-imidazol-1-yl]-*N*-[2,2,3,3,3-pentafluoropropyl] acetamide) [15]. These compounds form stable adducts with intracellular macromolecules only in hypoxic regions ($PO_2 < 10$ mmHg) [16]. Detection of these adducts with antibodies can provide information on the relative oxygenation at the cellular level [17, 18]. In general, 2-nitroimidazole markers stain for areas of chronic hypoxia and are more sensitive at severe hypoxic conditions than the microelectrode [19]. This approach is limited by the requirement for exogenous drug administra-

tion, additional biopsies for staining, and quantification of staining [20].

MRI can provide a useful way to measure hypoxia. Absolute PO_2 can be measured on the basis of fluorocarbon reporter molecules. These may be introduced by direct intratumoral injection, and they provide measurements consistent with electrodes (interstitial PO_2). A major advantage over electrodes is that maps of regional PO_2 may be measured at 50–150 individual locations simultaneously. MRI methods for interrogating tumor oxygenation are attractive since they avoid the complication of short-lived radioactivity and MRI equipment is widely available. Blood oxygen level-dependant (BOLD) MRI is an imaging technique that distinguishes paramagnetic deoxy-Hb from O_2Hb. BOLD MRI signal is related to vascular oxygenation and may allow direct estimates of PO_2. However, the correlation becomes difficult for small blood vessels where partial volume effects combine vessel and tissue in individual voxels, and BOLD may also be confounded by flow effects [21]. Oxygen-sensitive MR reporter molecules have also been developed generally based on perfluorocarbons (PFCs). Other MRI-based methods such as fluorocarbon relaxometry using echo-planar imaging for dynamic oxygen mapping (FREDOM) and proton imaging of silanes for tissue oxygen levels (PISTOL) are also under investigation [21].

Positron emission tomography (PET)-based hypoxia imaging has also been widely evaluated over the past 15 years. 18F-fluoro-misonidazole (18F-FMISO) is the most widely used PET agent for mapping regional hypoxia [21]. Because 18F-FMISO partitions nearly equally between octanol and water, normoxic tissues have tissue-to-blood ratio (T/B) pixel values of almost 1.0. When the O_2 supply is adequate, most tissues have relatively similar levels of 18F as in the blood. The hypoxic part of a tumor can be characterized by the maximum T/B value or by the total number of pixels with T/B greater than the same threshold. 18F-FMISO PET could identify hypoxic tissue that is heterogeneously distributed within human tumors and can help to facilitate image-guided radiotherapy. 18F-FMISO imaging has also been used to identify post-radiotherapy tumor recurrence by differential uptake of tracer. A significant correlation was found between hypoxic tissue identified by 18F-FMISO and both pimonidazole and CA-IX, detected by immunohistochemical staining techniques. Recent study showed that the values for 18F-FMISO PET uptake and hypoxic volume in 11 head and neck tumors between two 18F-FMISO scans with a 48-h interval were highly reproducible [22]. A further study showed that 18F-FMISO PET uptake is correlated with HIF-1α expression in the primary site of oral squamous cell carcinoma (SCC) [23].

Although hypoxia imaging using 18F-FMISO PET is feasible and has prognostic value, there are also some disadvantages using this PET radiopharmaceutical [24]. One of the problems is the relatively short half-life time (110 min) of 18F-FMISO, which hampers late imaging that could enhance good contrast between hypoxia and normal tissues [24]. Several other components have also been evaluated as imaging agents [21]. 18F-fluoro-erythro-nitroimidazole (18F-FETNIM) has been evaluated in head and neck cancers [25]. A derivative that is more hydrophilic than 18F-FMISO, 18F-fluoro-azomycin-arabinofuranoside (18F-FAZA), has been shown to be promising for clinical use, and so as 18F-EF5 [26] and 18F-HX4 [27]. A recent Danish Head and Neck Cancer Group (DAHANCA) 24 trial investigated the hypoxia using 18F-FAZA PET before and during RT in 40 patients with HNSCC [28]. There were 25/40 hypoxic tumors before and 6/13 during treatment. For six patients with detectable hypoxia, the location of hypoxic volume (HV) remained stable in location during RT, though the size of the HV decreased. Significantly poorer prognosis was observed in patients with hypoxic tumors compared with nonhypoxic tumors. This study strengthened the idea that 18F-FAZA PET scan is a reliable method for hypoxia imaging with prognostic potential [24]. 18F-HX4, another new potential marker for hypoxia PET scan, has recently been described [27]. Preclinical studies showed advantageous bio-distribution and dosimetry properties, which make 18F-HX4 a promising hypoxia radiopharmaceutical candidate [24]. A pilot PET study on hypoxia imaging using 18F-HX4 as a radiopharmaceutical in 12 patients with HNC has recently been published [29]. The data showed that 18F-HX4 may have higher sensitivity, specificity, faster clearance, and shorter injection imaging time compared with 18F-FMISO.

An alternative PET agent for hypoxia is based on a metal complex of radioactive copper with ATSM, diacetyl-bis-(N4-methylthiosemicarbazone). Dithiosemicarbazones have antitumor properties that are enhanced when they are complexed with Cu(II). Because there are several advantageous imaging radionuclides of copper, this has led several laboratories to develop substituted ligands of dithiosemicarbazones as potential imaging agents. Cu-ATSM uptake is more rapid than 18F-FMISO uptake, and the reported hypoxic-to-normoxic ratio is greater. One concern is that, because of its lipophilicity, the early uptake and washout of Cu-ATSM is probably influenced by regional blood flow, which is a major confounder with hypoxia [21]. ^{62}Cu-ATSM was used to delineate hypoxic tissue, and its distribution was compared with that of 18F-FDG PET in 27 patients with HNSCC, and intratumoral distribution of Cu-ATSM has been shown a negative correlation with FDG in HNSCC [30]. The ^{64}Cu-ATSM has also been evaluated in a preliminary prospective study in HNC, and this Cu-ATSM scans showed high sensitivity but low specificity in predicting chemoradiotherapy (CRT) response [31].

Hypoxia gene expression signatures are a developing strategy for characterizing the hypoxic status of tumor based on quantifying the gene expressions of hypoxia-responsive

and hypoxia-specific genes within tumor biopsy [32]. This method has evolved along with the development of complementary DNA microarray analysis and classified tumors in accordance to the expression of specific hypoxia-responsive genes. Thus, tumors are classified and categorized in terms of the biological behavior to hypoxic conditions in the microenvironment [33]. A gene expression signature containing 15 genes has been evaluated in a set of 58 hypoxia-evaluated HNSCC [32]. This 15-gene hypoxia signature has been shown a potential to predict benefit from hypoxia-modifying therapy in DAHANCA 5 trial [34]. In 323 patients with HNSCC, 114 patients (35 %) were classified as having "more" hypoxic tumors. These patients had a significant benefit of hypoxic modification with nimorazole in combination with RT compared with placebo in terms of 5-year locoregional control (LRC, 49 vs. 18 %; $p=0.001$). "Less" hypoxic tumors had no significant effect of hypoxic modification. A recent study investigated the ability of a 26-gene hypoxia signature to predict benefit from hypoxia modification using 157 samples of T2–T4 laryngeal cancer from a phase III trial of accelerated radiotherapy with carbogen and nicotinamide (ARCON) [35]. Customized TaqMan low-density arrays (TLDA) were used to assess expression of this 26-gene signature using quantitative real-time PCR. The median expression of the 26 genes was used to derive a hypoxia score (HS). Patients were categorized as TLDA-HS low (≤median) or TLDA-HS high (>median, hypoxic tumor). The 26-gene hypoxia signature predicts benefit from hypoxia-modifying treatment in laryngeal cancer. Five-year regional control was 81 % (RT alone) versus 100 % (RT with hypoxia modification) for TLDA-HS high ($p=0.009$) patients. No significant difference has been shown for TLDA-HS low patients.

12.4 Hypoxia and Clinical Outcomes in Head and Neck Cancers

Hypoxia appears to be prognostic for outcome in HNC, with data suggesting that hypoxia is prognostic for survival and local control. Several studies have shown that low PO_2 in tumor, defined by either the median value or the hypoxic fraction, correlated with treatment outcomes in HNC patients treated with RT or chemoradiotherapy [36–38]. Brizel et al. [38] reported 63 HNC patients with pretreatment tumor oxygen assessment including primary site and lymph nodes. Hypoxia (median PO_2 in tumor, 10 mmHg) adversely affected 2-year LRC, disease-free survival (DFS), and overall survival (OS, 35 vs. 83 %). It was also found that tumor PO_2 predicted for pathologically persistent neck nodes in patients undergoing a neck dissection for clinical N2–3 necks after chemoradiation treatment [39]. In another study by Terris [40], only a small number of patients were assessed, and hypoxia did not appear to be a prognostic factor. A multicenter study by Nordsmark et al. [41] involving 397 patients with HNC provided further evidence that tumor PO_2 was an independent predictor for survival and tumor hypoxia was associated with a poor prognosis in patients with advanced HNC following primary radiotherapy. In HNC, hypoxia not only predicts for DFS and OS but also for local control, suggesting hypoxia-induced radiation resistance as an important factor for local failure.

The prognostic impact of HIF-1α and HIF-2α expression has been the subject of numerous studies [42–45]. High HIF-1 expression has been correlated with a poorer survival in HNC treated with radiation with or without chemotherapy [42, 46]. Similar trends are observed in nasopharyngeal tumors [47]. Koukourakis et al. [42] assessed the expression of HIF-1α and HIF-2α in 75 cancer specimens from patients with HNSCC treated with concurrent CRT. HIF-1α overexpression and HIF-2α overexpression were shown in 52 % and 33 % of cancer samples, respectively. Bone/cartilage involvement was more frequent in tumors with high HIF-1α expression. HIF-1α overexpression and HIF-2α overexpression were significantly associated with high microvessel density and with VEGF expression. High levels of HIF-1α and HIF-2α expression were associated with incomplete response to CRT, poor local relapse-free survival, and poor OS. HIF-2α expression was an independent prognostic factor in multivariate models. Aebersold et al. [46] explored the predictive potential of HIF-1α expression in 98 patients with oropharyngeal cancer treated by curative RT in which 94 % of primary tumors showed overexpression of HIF-1α. The degree of HIF-1α immunoreactivity correlated inversely with both the rate of complete remission of primary tumor and lymph node metastases as well as with local failure and OS. However, in another series of 233 patients with oropharyngeal SCC, the HIF-1α positivity rate was 58.8 %, and HIF-1α positivity was associated with higher T category (T3/T4 vs. T1/T2, 64.2 vs. 48.4 %, $p=0.001$) and lower grade. After adjustment for clinicopathological variables, HIF-1α has not been shown as a strong predictor of outcome [48]. Winter et al. [49] investigated the role of expression of HIF-1α and HIF-2α in a series of 151 patients who underwent surgery for HNSCC. High HIF-1α was expressed in 45 of 140 tumors (30 %) and HIF-2α was expressed in 21 of 139 tumors (14 %). High HIF-1α alone was associated with a worse DFS, and high HIF-1α/high HIF-2α expression was also an independent prognostic factors.

The immunohistochemical detection of the HIF-1α target gene Glut-1 is of particular interest [50]. High Glut-1 expression has been shown to correlate with a poorer survival in HNC. Oliver et al. [51] investigated the relationship between Glut-1 expression and clinical outcome of a retrospective series of 54 oral SCC. There was a significant relationship between tumors with Glut-1 overexpression and locore-

gional recurrence especially nodal recurrence. Kunkel et al. [52] analyzed retrospectively Glut-1 expression in 118 patients with oral SCC. The survival rate of patients with a low Glut-1 labeling index was significantly longer compared with patients with a high Glut-1 labeling index, and Glut-1 expression was found to be an independent prognostic marker. The prognostic relevance of co-expression of HIF-1α and GLUT-1 has been evaluated in 82 patients with oral SCC. Co-expression of HIF-1α and GLUT-1 was additively and significantly associated with adverse prognoses in patients with oral SCC. Patients with increased levels of expression of both HIF-1α and GLUT-1 in tumor were found to have a fivefold increased risk of tumor-related death [53].

The second target gene of HIF-1α which has been extensively studied with regard to its prognostic significance is CA-IX [54]. As with HIF-1α and Glut-1, most studies found a negative impact of high CA-IX expression in patient with HNC. In one study by Koukourakis et al. [55], HIF-2α and CA-IX were assessed in a series of patients treated with radiotherapy in the frame of the continuous hyperfractionated accelerated radiotherapy randomized trial (CHART, 54 Gy in only 12 days compared with conventional RT, 66 Gy in 6.5 weeks). Both high levels of HIF-2α and CA-IX were correlated with LRC and survival, suggesting the importance of tumor hypoxia in HNC. However, no benefit was found with the accelerated regimen in the group of hypoxic tumors. In another study [56], tumors with a nonhypoxic profile, defined as low HIF-1α and low CA-IX expression, had significantly better local control. In 382 patients with T1 and T2 SCC of the glottic larynx treated by RT (50–55 Gy, in 16 fractions), however, high CA-IX and HIF-1α expression did not show any prognostic significance, while the pretreatment hemoglobin <13.0 g/dl and T2 stage were adverse prognostic factors for locoregional recurrence [57].

A recent work by Overgaard et al. [58] used another hypoxia-related marker, the serum level of OPN, in a randomized trial that compared radiotherapy with and without a hypoxic sensitizer (nimorazole). The patients who benefited the most from the hypoxic modification were in the group with high levels of serum OPN, strongly suggesting that measuring tumor hypoxia before radiotherapy helps to individualize irradiation in a more rational way. In 578 patients with HNSCC (plasma sample available for OPN assay by ELISA and absence of major radiation therapy deviations) from the phase III randomized trial TROG 02.02, high OPN levels were not associated with worse OS or time to locoregional failure, and there was no interaction between OPN and treatment arm (tirapazamine and CRT) for survival or locoregional failure. Thus, there was no evidence that high plasma OPN levels were associated with an adverse prognosis in HNSCC or were predictive of benefit with hypoxia-targeting therapy [59].

A recent prospective study investigated the change of hypoxia using 18F-FMISO PET and its predictive value for survival during RT in patients with HNC. Each patient has been scanned before and three times during RT. The scan parameters performed at weeks 1 (8–10 Gy) and 2 (18–20 Gy) strongly correlated with the local progression-free survival, suggesting good prognostic value of 18F-FMISO PET at the time points during treatment [60]. An advantage of 18F-FMISO PET over FDG PET for predicting histological response to preoperative chemotherapy was observed in 22 patients with oral SCC [61]. A pilot study suggested that ^{62}Cu-ATSM uptake may be a predictive indicator of tumor response to CRT in patients with locally advanced HNC [62].

Hypoxia and Human Papillomavirus (HPV) One important recent advance in head and neck cancer especially oropharyngeal cancer has been the recognition of the prognostic significance of human papillomavirus (HPV). It has been demonstrated that HPV and/or p16-positive oropharyngeal cancer shows superior response to radiotherapy, compared with HPV and/or p16-negative cancer [63, 64]. In DAHANCA 5 trial, hypoxic modification with nimorazole improved LRC in HPV/p16-negative tumors but was of no significant benefit in HPV/p16-positive tumors, suggesting that hypoxic radioresistance may not be clinically relevant in HPV-positive cancer [64]. In TROG 02.02 trial, p16-positive patients had lower rates of locoregional failure, and there was a trend of improved LRC favoring the combination of CRT with hypoxic modification by tirapazamine in p16-negative patients [65]. A retrospective study on 233 oropharyngeal SCC showed that there was no significant association between HIF-1α expression and HPV status 48. The combination of HPV and HIF-1α was not a prognostic variable, but the worst outcomes were seen in those with HPV-negative and HIF-1α-positive cancers. The clinical observation that HPV-positive patients do not seem to benefit from nimorazole treatment is not due to inherent differences in hypoxia sensitivity or response to hypoxic modification. A recent preclinical study showed that the HPV-positive and HPV-negative cell lines exhibited similar patterns of upregulation of hypoxia-induced genes in response to hypoxia. HPV-positive cells displayed the same relative radioresistance under hypoxia and same relative sensitizer effect of nimorazole [66]. In the further assessment by 18F-FMISO PET, hypoxia was shown frequently present in both p16-positive and p16-negative HNC treated on phase I and II chemoradiation trials [67].

12.5 Strategies to Overcome Hypoxia-Induced Treatment Resistance in Head and Neck Cancers

There are several strategies to overcome hypoxia-related radiation resistance of head and neck cancers. The first approach has been to bring more oxygen to the hypoxic regions of the tumors, including hyperbaric oxygen, carbogen breathing, or increasing the hemoglobin levels. The second strategy consisted of using hypoxia as a partner and combining radiotherapy with drugs that are either active or cytotoxic in hypoxic conditions or to use drugs able to target tumor vasculature or angiogenic process. A third and more recent strategy consisted of using adaptive radiotherapy plans in order to adapt the dose according to hypoxia imaging or alternatively to use radiation beams that are not dependent on hypoxia such as carbon ions.

These three main approaches will be detailed below.

12.5.1 Hyperbaric Oxygen Treatment

The most straightforward strategy to overcome hypoxia is to administer oxygen at a pressure higher than room air (usually 3 atm.), i.e., hyperbaric oxygen treatment. The largest clinical trial with hyperbaric oxygen has been conducted by the British Medical Research Council, which randomized 1669 patients between radiotherapy with and without hyperbaric oxygen [68]. Hyperbaric oxygen significantly improved both survival and local controls after RT for HNC showed promising results in HNC patients. Some of the earliest work toward this end was done using hyperbaric oxygen to radiosensitize cervical [69] or head and neck cancers [70]. Though there was some initial success with this technique, recent studies have indicated that combining radiation with hyperbaric oxygen results in significant increase of normal tissue toxicities [71]. A meta-analysis of randomized trials suggests that the use of hyperbaric oxygen breathing during RT can improve local control by 10 % and also improve 5-year survival for irradiated HNC; however, it has not gained general acceptance for clinical use due to inconsistent responses, safety issues, and the high cost for implementation and especially due to the increased incidence of severe radiation toxicity [72].

12.5.2 Accelerated Radiotherapy with Carbogen and Nicotinamide

Another promising approach to decrease hypoxia in HNC is to combine radiotherapy with both a vasodilator nicotinamide and carbogen breathing (95 % O_2, 5 % CO_2) to increase tumor PO_2 [73]. This strategy, so-called ARCON, has produced excellent 3-year local control rates of >80 % for locally advanced stage T3–T4 laryngeal and oropharyngeal cancers in a phase II study [74]. A large randomized phase III clinical trial evaluated the efficacy of ARCON in 345 patients with cT2–cT4 laryngeal cancer. No overall benefit in 5-year local control nor in larynx preservation was observed with ARCON treatment compared to accelerated radiotherapy (AR). However, the interpretation of this trial is difficult since the total dose of radiotherapy was reduced in the ARCON arm, introducing a confounding factor to evaluate the primary end point. The results suggest the ARCON approach could compensate for the lower dose of radiation. Interestingly, the 5-year regional control (cervical nodes) was significantly better with ARCON (93 %) compared with AR (86 %, $p=0.04$). The improvement in regional control was specifically observed in patients with hypoxic tumors determined by a hypoxia marker pimonidazole (100 vs. 55 %, $p=0.01$) and not in patients with well-oxygenated tumors [75]. Further study showed that in patients with low pretreatment hemoglobin levels, ARCON significantly improved 5-year LRC (79 vs. 53 %; $p=0.03$) and DFS (68 vs. 45 %; $p=0.04$); however, this effect was not observed in patients with normal pretreatment hemoglobin levels [76]. No correlation between pretreatment hemoglobin levels and pimonidazole uptake was observed.

12.5.3 Improving Hemoglobin Levels with Erythropoietin

Early studies were also done using blood transfusion to increase oxygen transport and thereby increase tumor tissue PO_2. Despite some initial success with this method, transfusion failed to improve the local control in a randomized trial performed by the DAHANCA group [77]. Recently, blood transfusion has been supplanted by the administration of erythropoiesis-stimulating factors. Unfortunately, the combination of erythropoietin and radiotherapy was proved to be detrimental in several large randomized studies in head and neck cancer. Anemia is associated with a poorer outcome in patients treated with radiotherapy [78], possibly because it leads to low oxygen levels in tumors. Correction of anemia has been suggested to reverse this hemoglobin effect, thereby improving cancer control [79]. Recombinant human erythropoietin (EPO) can correct anemia and improve quality of life in anemic patients with cancer. A phase III trial (ENHANCE study, 351 patients) was conducted to address the question whether anemia correction with erythropoietin could improve outcome of curative radiotherapy among patients with HNSCC [80]. It showed that EPO corrected anemia, but tumor control, survival, and disease control rates were significantly worse when using EPO. This detrimental effect associated with EPO, when combined with RT in HNSCC, was confirmed by the results of other randomized trials such

as RTOG 99-03 [81] and DAHANCA 10 [82]. In the latter study, in a series of 515 patients eligible for analysis, a significantly poorer LRC rate was observed for the patients who received erythropoietin compared with the control group in HNSCC patients treated with radiotherapy. However, the target hemoglobin range in that study was 14.0–15.5 g/dl, which is beyond the optimal range for tumor oxygenation.

The reason of the observed negative effect of EPO on tumor control could be that tumor oxygenation is decreased by both anemia and inappropriately high hemoglobin levels. The latter are associated with an increased blood viscosity and a drop in nutritive perfusion. Hemoglobin concentrations between 12 and 14 g/dl could be optimal for maximum tumor oxygenation [79]. Thus, it is important to keep the hemoglobin concentrations within this range during radiotherapy. In addition, a retrospective analysis of a subset of patients from the ENHANCE study suggested that the expression of erythropoietin receptors on cancer cells can play an important role in HNSCC patients receiving erythropoietin during radiotherapy [83]. Locoregional progression-free survival was substantially poorer if erythropoietin was administered to patients positive for the receptor expression compared with placebo; however, erythropoietin did not impair outcome in receptor-negative patients. Given these results, the use of EPO in HNC patients should not be considered outside controlled clinical trials [84].

12.5.4 Hypoxic Cell Radiosensitizers: Nitroimidazoles

A widely investigated hypoxia-targeted strategy is to use electron-affinic drugs (nitroimidazoles) to sensitize tumors to the effect of radiation. Xenograft studies showed significant radiosensitization with nitroimidazole compounds in tumors without enhancing normal tissue toxicity. These encouraging results led to the realization of several clinical trials exploring the clinical radiosensitizing potential of misonidazole in the late 1970s. However, the results of these clinical trials have been generally disappointing. One of the possible factors to explain the failure of misonidazole to provide significant advantage is the low plasma concentrations achievable with the permitted dose of this neurotoxic drug. In the DAHANCA 2 trial [85], 626 patients with head and neck carcinoma were randomized to two different split-course radiation regimens and given either misonidazole or placebo during the initial 4 weeks of treatment. Overall, the misonidazole-treated group did not have a significantly better control rate than the placebo group. However, some benefit was found in patients with pharynx carcinomas. Misonidazole induced significant peripheral neuropathy in 26 % of the treated patients, whereas other drug-related side effects were minimal. In the DAHANCA 5 trial [86], a less toxic nitroimidazole compound, nimorazole, was used. Four hundred and twenty-two patients with carcinoma of the supraglottic larynx and pharynx were randomized to receive nimorazole or placebo, in association with conventional radiotherapy. With a median follow-up of 112 months, the nimorazole group showed a significantly better LRC rate than the placebo group and a lower cancer-related death rate, without increasing major side effects. A systematic review of 4805 patients with HNC treated in 32 randomized clinical trials, hypoxic modification of radiotherapy in HNC did result in a significant improved therapeutic benefit. This benefit was most dominantly observed in LRC with an odds ratio (OR) of 0.71 ($p<0.001$) and to a lesser extent in the OS (OR 0.87, $p=0.03$). The risk of distant metastases was not significantly influenced although it appears to be less in the tumors treated with hypoxic modification (OR 0.87, $p=0.22$). The improvement in LRC was found to be independent of the type of hypoxic modification [87].

Recently, a multicenter randomized phase III trial (EORTC-1219 ROG-HNCG) commenced recruiting patients to compare accelerated fractionated CRT with or without nimorazole in HPV/p16-negative HNSCC, with an objective of 640 patients. An additional aim is to investigate if patients that gain such a benefit can be predicted by the use of the 15-gene hypoxic signature. Another phase III trial NIMRAD has been designed to investigate the use of RT with nimorazole versus RT alone in patients with locally advanced HNSCC not suitable for concomitant chemotherapy or cetuximab in 18 UK centers aiming to recruit a total of 470 patients [88].

12.5.5 Hypoxic Cell Cytotoxin: Bioreductive Drugs

Bioreductive agents can selectively kill hypoxic cells. The first bioreductive drug used in clinical trials was mitomycin-C [89]. Haffty et al. [90] showed that the addition of mitomycin-C to RT resulted in statistically significant improvement in LRC and cause-specific survival in HNC. Another study by Dobrowsky et al. [91, 92] comparing conventional fractionated RT to the Vienna continuous hyperfractionated accelerated RT regimen (V-CHART) or to V-CHART plus mitomycin-C showed that the best survival and LRC rates were observed for the V-CHART and mitomycin-C group. However, the use of mitomycin-C is limited by its significant toxicity making it unlikely to be the ideal drug for exploiting tumor hypoxia.

Recently, a new approach to tumor hypoxia has been developed using drugs that are preferentially cytotoxic to hypoxic cells [4], such as tirapazamine (TPZ). Preclinical studies have demonstrated that TPZ results in potentiation of both radiation and CDDP cytotoxicity [93]. In a phase I trial

of TPZ, CDDP, and radiation (TPZ/CIS), impressive results were seen in locally advanced HNSCC [94]. This drug was then further evaluated in a randomized phase II trial Trans-Tasman Radiation Oncology Group (TROG) 98.02 [95]; 122 previously untreated advanced HNSCC patients were randomized to receive RT concurrently with either CDDP plus TPZ (TPZ/CIS) or CDDP and 5-FU. The striking observation of this study was that tumor control probability was strongly related to the pretreatment level of hypoxia, as measured by PET misonidazole. Hypoxic tumors treated with tirapazamine had an excellent control rate (>90 %), while hypoxic tumors receiving 5-FU instead of tirapazamine had a very poor control rate (<25 %) [96]. On the other hand, Rischin et al. reported recently the results of the phase III trial (TROG 02.02, HeadSTART) [97]. Eight hundred and sixty-one patients with previously untreated stage III or IV HNSCC were randomized to receive RT concurrently with either CDDP (100 mg/m^2 every 3 weeks) or CDDP (75 mg/m^2 every >3 weeks + tirapazamine). No benefit was found due to the addition of TPZ to CT-RT in the absence of selection for the presence of hypoxia. All together, these two randomized studies suggest that a key issue in this area is to detect hypoxia and adapt the treatment to the characteristics of each individual tumor.

In another phase II trial [98], 62 patients with lymph node-positive, resectable, stage IV HNSCC were randomized either to receive two cycles of induction chemotherapy (TPZ, cisplatin, and 5-FU) followed by simultaneous CRT (TPZ, cisplatin, and 5-FU) or to receive the same regimen without TPZ. Patients who did not achieve a complete response at 50 Gy underwent surgical treatment. The addition of TPZ increased hematologic toxicity but did not improve outcomes in this small series of patients with resectable HNSCC.

12.5.6 Microenvironment: Vascular Normalization

Jain [99] has proposed the concept of normalization of tumor vasculature through anti-angiogenesis- and anti-vasculature-targeted therapy [100]. Owing to high levels of pro-angiogenic molecules produced locally, such as VEGF, tumors become hypervascular, but the vessels are leaky, and the blood flow is spatially and temporally heterogeneous. This leads to increased interstitial fluid pressure (IFP) and focal hypoxia, creating barriers to delivery and efficacy of therapeutics. The proposed mechanism of action of the VEGF-specific inhibitors such as bevacizumab and sorafenib is inhibition of new vessel formation and killing of immature tumor vessels, transient normalization of the remaining vasculature by decrease in macromolecular permeability (and thus the IFP) and hypoxia, and improvement of blood perfusion. The lowered IFP can lead to improved delivery of chemotherapeutics and molecularly targeted agents; the improved oxygenation sensitizes cancer cells to cytotoxic therapeutics and reduces the selection of more malignant phenotype; and, finally, increased cellular proliferation around normalized vessels might increase the cytotoxicity of chemotherapeutics [101]. Normalization of the vasculature might also benefit the direct killing of cancer cells by bevacizumab, in synergy with the chemotherapeutics.

Combined effects of bevacizumab with erlotinib and irradiation have been observed using a preclinical study on a HNC orthotopic model [102]. A phase I dose-escalation study [103] has been conducted to evaluate the combination of bevacizumab with CRT (5-FU, hydroxyurea, radiation) in a series of 44 poor-prognosis HNC patients (including re-irradiation for recurrent tumors). Bevacizumab was integrated with CRT at a dosage of 10 mg/m^2 every 2 weeks. Some fistula formation/tissue necroses were observed and could be bevacizumab related. More recently, Fury et al. reported the outcomes of phase II trial of bevacizumab with cisplatin plus intensity-modulated radiotherapy (IMRT) in 42 previously untreated HNSCC. The addition of bevacizumab (15 mg/kg on days 1, 22, and 43) to high-dose cisplatin (50 mg/m^2 on days 1, 2, 22, 23, 43, and 44) plus IMRT did not appear to increase toxicity to unacceptable levels [104]. Another phase II trial RTOG 0615 evaluated the tolerability of combination of bevacizumab (15 mg/kg) with cisplatin (100 mg/m^2 on days 1, 22, and 43) and IMRT in nasopharyngeal carcinoma. No grade 3–4 hemorrhages or grade 5 adverse events were observed [105]. Erlotinib and bevacizumab combination has been investigated in 58 patients with recurrent or metastatic HNSCC in a phase I/II study [106]. The most common side effects of any grade were rash and diarrhea. A few patients could have benefit from this approach especially when the ratios of tumor cell phosphorylated VEGF receptor-2 (pVEGFR2) over total VEGFR2 and endothelial cell pEGFR over total EGFR in pretreatment biopsies were associated with complete response. A phase II trial of sorafenib has been conducted in a small series of 27 patients with recurrent or metastatic HNSCC or nasopharyngeal carcinoma. Sorafenib was well tolerated with few grade 3 and no grade 4 toxicities but had modest anticancer activity comparable to monotherapy with other targeted agents in this group of patients [107].

12.5.7 Targeting HIF-1

Given the role of HIF-1α in response to hypoxia, there is a major interest to develop specific HIF-1 inhibition. In xenograft assays, manipulation of HIF-1 activity by genetic or pharmacological means has marked effects on tumor growth along with some effects on angiogenesis, glucose metabolism, and/or cell survival [108].

Topotecan, a topoisomerase I poison that reversibly binds to and stabilizes the topoisomerase I enzyme, inhibited HIF-1 protein translation by a proteasome- and DNA damage-independent mechanism. Currently, topotecan is being tested in a clinical trial at the National Cancer Institute for its ability to inhibit HIF-1a protein expression and function in patients with advanced malignancies refractory to standard therapy [108].

Inhibitors of several upstream signaling pathways of HIF-1, such as EGFR and mTOR, have been extensively investigated in clinical trials these recent years [7]. The mTOR inhibitors (everolimus and temsirolimus) that can suppress mTOR-dependent HIF-1 translation and EGFR inhibitors (gefitinib, erlotinib) or antibodies (cetuximab, panitumumab) could inhibit HIF-1 induction by EGFR-dependent pathways [8]. Bonner et al. have shown that cetuximab plus radiotherapy significantly improved OS compared with RT alone in patient with locoregionally advanced HNSCC in a phase III trial [109]. A recent phase I trial showed that the inhibition of mTOR everolimus at therapeutic dosages (5 mg/day) was well tolerated when given concomitantly with weekly cisplatin and IMRT in HNC patients [110].

Hsp90 is a molecular chaperone associated with a number of proteins, which include transcription factors (AhR, glucocorticoid receptor, p53) and signaling kinases (Akt, ErbB2, Raf-1, v-Src), and ensures the proper conformation, localization, and function of these client proteins. Hsp90 inhibitors were found to induce ubiquitination- and proteasome-mediated degradation of HIF-1α in a VHL-independent fashion, under both normoxic and hypoxic conditions [108]. Histone deacetylase (HDAC) inhibitors have also been tested recently [108]. The dynamic process of reversible acetylation of the lysine residue of histone and nonhistone proteins is controlled by histone deacetylases (HDAC) and histone acetyltransferases. Acetylation of histone proteins is important for DNA chromatin conformation and regulation of gene expression. Acetylation of nonhistone proteins has been implicated in proteins' stability and function, and direct acetylation of HIF-1α has been suggested.

12.5.8 Positron Emission Tomography-Based Intensity-Modulated Radiotherapy

Image fusion techniques and the use of intensity-modulated and image-guided radiotherapy can allow to delineate hypoxic radioresistant sub-target volumes for delivering a partial tumor boost. PET could detect hypoxia in tumors and a higher dose could be given to the hypoxic areas using IMRT. The MSKCC experience with micro boosts on hypoxic areas up to 100 Gy. This approach requires that PET imaging be sensitive and specific enough to image hypoxia. In this framework, a validation of PET imaging used for adaptive radiotherapy (ART) was undertaken in animal models by comparing small-animal PET images (2.7 mm resolution) with autoradiography (AR) (100 μm resolution) in various tumors under various physiological situations [111]. Discrepancies were found between PET images and the underlying microscopic reality represented by AR images. These differences, attributed to the finite resolution of PET, were important when considering small regions of the tumors. Dose painting based on PET images should be carefully considered and should take these limitations into account.

The feasibility of a Cu-ATSM-guided IMRT approach through coregistering hypoxia ^{60}Cu-ATSM PET to the corresponding CT images for IMRT planning has been reported in head and neck cancer patients [112]. Radiation dose to the hypoxic tumor volume could be escalated without compromising normal tissue sparing (parotid glands and spinal cord). The plan delivered 80 Gy in 35 fractions to the ATSM-avid tumor sub-volume, and the gross tumor volume (GTV) simultaneously receives 70 Gy in 35 fractions, while more than one-half of the parotid glands were spared to less than 30 Gy.

18F-FMISO has been used for mapping regional hypoxia [113]. In a recent prospective study, Dirix et al. [114] suggested the added value of 18F-FDG PET and 18F-FMISO PET for RT planning of HNSCC and the potential of diffusion-weighted (DW) MRI for dose painting and early response assessment. Thorwarth et al. [115] investigated the feasibility of different hypoxia dose-painting strategies in radiotherapy of 13 HNC patients. For each patient, three different treatment plans were created: a conventional IMRT plan, an additional uniform dose escalation (uniDE) of 10 % to the FDG-positive volume, and a plan in which dose painting by numbers (DPBN) was implemented. DPBN was realized according to a map of dose-escalation factors calculated from dynamic 18F-FMISO PET data. For DPBN, the prescriptions could be fulfilled in larger regions of the target than for uniDE. DPBN seems to result in higher benefits for the patients regarding tumor control probability. A phase I trial was recently completed to investigate the feasibility of adaptive IMRT using DPBN for HNC with two dose prescription levels: a median dose of 80.9 Gy to the high-dose clinical target volume (CTV) (dose level I) and a median dose of 85.9 Gy to GTV (dose level II). Each patient's treatment used three separate treatment plans: fractions 1–10 used a DPBN (18F-FDG PET) voxel intensity-based IMRT plan based on a pretreatment 18F-FDG PET; fractions 11–20 used a DPBN plan based on 18F-FDG PET acquired after the 8th fraction; and fractions 21–32 used a conventional (uniform dose) IMRT plan. All patients (7 at dose level I and 14 at dose level II) finished treatment without a break, and no grade 4 acute toxicity was observed. Treatment adaptation (i.e., plans based on the second 18F-FDG PET) reduced the volumes for GTV (41 %, $p=0.01$) and high-dose CTV (18 %, $p=0.01$) [116]. Olteanu et al. showed that compared to RT, ART readjusts dose painting, increases minimum and decreases maximum doses in target volumes, and improves

dose/volume metrics of organs at risk. The results favored the adaptive strategy, but also revealed considerable heterogeneity in patient-specific benefit [117].

Hendrickson et al. investigated the utility of co-registered 18F-FMISO PET and CT images to develop clinically feasible radiation treatment planning with higher tumor control probabilities (TCPs). FMISO PET images were used to determine hypoxic sub-volumes for boost planning. An IMRT plan was created for each patient with a simultaneous integrated boost to the hypoxic sub-volumes. A significant improvement in TCP was predicted when the modest additional boost dose to the hypoxic sub-volume was included without increasing expected complications [118]. Lee et al. reported the results from a prospective study of pre-/mid-treatment 18F-FMISO PET scans in 20 locoregionally advanced HNC patients treated with concomitant chemotherapy and IMRT. Each patient underwent four PET scans: one pretreatment FDG PET-CT scan, two pretreatment 18F-FMISO PET-CT scans, and a third 18F-FMISO PET (mid-treatment) scan performed 4 weeks after the start of CRT. A heterogeneous distribution of 18F-FMISO was noted in the primary and/or nodal disease in 90 % of the patients. Two patients had persistent detectable hypoxia on their mid-treatment 18F-FMISO PET scan. The positive 18F-FMISO findings of the mid-treatment PET scan were not correlated with patient outcome [119]. Another study has evaluated the influence of changes in tumor hypoxia on the efficacy of IMRT dose painting, according to serial 18F-FMISO PET imaging [120]. Seven patients with HNC were imaged twice with FMISO PET (3-day interval) before RT. IMRT plans were designed, on the basis of the first FMISO scan, to deliver a total dose of 84 Gy to the hypoxic volume. The changes in spatial distribution of tumor hypoxia, as detected in serial FMISO PET imaging, added some complexity to define an adequate coverage of hypoxic tumor volumes achievable by dose-painting IMRT, and dose painting potentially increased the equivalent uniform dose of the hypoxic volumes.

12.5.9 Other Methods

Hyperfractionation radiotherapy (HFRT) was designed to improve radiotherapy effectiveness by delivering two to three fractions daily with a reduced dose per fraction [121], which may reduce late toxicity despite an increased total dose. In addition, hyperfractionation could induce reoxygenation, and its use was associated with an 8 % improvement in survival at 5 years [122]. Other radiotherapy techniques can be of interest to overcome tumor hypoxia, such as *high linear-energy transfer* (*LET*) radiation which is less or even not oxygen dependent. For example, carbon 12 ions [123] could be a promising tool to decrease the radiation resistance induced by hypoxia and are currently under investigation.

In conclusions, tumor hypoxia continues to be a therapeutic challenge in HNC. Nonetheless, the prospect of reducing its impact is looking brighter with improved ability of detecting hypoxia and better understanding of its molecular targets for therapeutic exploitation. Testing new therapies from the laboratory will require clinical trials with innovative designs that incorporate serial novel noninvasive surrogate end points for hypoxia such as molecular makers or imaging methods.

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Imaging of Head and Neck Cancers

13

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Abstract

Head and neck cancers (HNC) include a variety of neoplasms that are traditionally associated with high morbidity and mortality. Patients with these malignancies, of which squamous cell cancer is the most common, require a multidisciplinary approach to determine optimal treatment and follow-up. Treatment depends on TNM staging, which is determined using a combination of objective findings including physical examination, endoscopies, and importantly cross-sectional imaging. CT and MR imaging are the mainstays of cross-sectional imaging and are used extensively to stage and characterize these tumors. The goals of appropriate imaging is to establish the extent and size of tumor, assess nodal disease in the neck, look for perineural spread, distinguish tumor recurrence from postoperative- or postradiation-related changes, and monitor response to treatment. Cross-sectional imaging supplements and complements anatomic and pathologic changes of the neck.

CT and MRI are both used to image HNC. They both have their own strengths and weaknesses, and these should be carefully considered before choosing the respective study. Other techniques such as MR perfusion, MR spectroscopy, and MR magnetization transfer have the ability to measure functional parameters such as tissue perfusion that can be integrated with other clinical and radiological information to assess disease progression. Imaging with ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has been found to be superior to CT and MR alone. New applications including combined PET/CT and PET/MR provide additional anatomical localization detail to assess for tumor response to treatment, tumor progression, and distant metastasis as well as spot unknown primary carcinomas or synchronous second tumor. With the rise in HPV-related tumors, imaging techniques can be used to identify these patients. From methodological development, these morphologic investigations are making the critical transition to preclinical and clinical validating methods and eventually to widespread clinical tools.

Keywords

Head and neck cancer • Computed tomography • Perfusion CT • Perfusion-weighted MRI • Diffusion-weighted imaging • Apparent diffusion coefficient • Fluorine-18 fluorodeoxy-

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glucose (FDG) • Positron emission tomography (PET) • Squamous cell carcinoma • Head and neck neoplasms • MR • Staging • Magnetic resonance imaging • PET/CT • Unknown primary • PET/MR • Synchronous second tumor

13.1 Head and Neck Cancer

Cancers of the head and neck (HNC) are common neoplasms that account for about 5 % of malignancies worldwide. They are the fifth most common cancer condition [1]. HNC include squamous cell carcinoma (HNSCC), basal cell carcinoma, many sarcomas, melanoma, and other tumors arising from a variety of sites. The primary risk factors for HNSCC in American men and women include tobacco use, alcohol use, and more recently HPV infection.

In 2015, approximately 59,340 new diagnoses and 11,260 deaths are expected in the United States due to head and neck cancer [2]. Patients with HNSCC require a careful evaluation and a multidisciplinary team approach to determine optimal management. Treatment planning depends to a large extent on TNM staging, which is evaluated with physical examination, endoscopies, and cross-sectional imaging [3].

Radiologic imaging with CT and MR imaging is extensively utilized to evaluate soft-tissue masses of the head and neck. These masses are diagnosed and staged primarily on the basis of physical examination and CT and MRI findings [4–6]. Imaging has become a vital and integral tool in characterizing and staging of malignant tumors involving the head and neck. CT and MRI provide essential information about the deep extension of clinically detected masses and also delineate additional clinically unsuspected masses [7, 8]. Accurate staging at the time of diagnosis is critical for selection of appropriate treatment strategy. Precise prediction of the extent of primary tumors, cervical lymph node status, and distant metastatic spread is important for treatment planning and prognosis. The goals of imaging in patients with head and neck cancer are to establish tumor extent and size, to assess nodal disease, for possible perineural tumor spread, and to distinguish recurrent tumor form posttreatment changes [9]. Imaging is also essential to follow up the patients after various therapeutic options available for the treatment are exercised, including surgery with or without radical dissection, lymph node dissections of various severities, radiotherapy, chemotherapy, and various combinations of all these [10]. Accurate evaluation of all these factors prior to treatment helps guide surgical extent or radiation porta, minimizing locoregional treatment failure.

CT and MRI are the most commonly utilized imaging modalities for assessment of primary malignant tumor, local extension, and lymph nodal involvement. They are also the first imaging modalities for monitoring the result and response of surgical intervention, radiation or chemotherapy, or combinations thereof. In this goal cross-sectional imaging supplements and compliments the physical examination by delineating the anatomy and pathological changes of the neck. Complex anatomic structures and regions, such as the orbit, skull base, paranasal sinuses, deep spaces of the suprahyoid and infrahyoid neck, larynx, and lymph nodes, require that the radiologist be familiar with the imaging modalities available and their appropriate applications.

CT and MRI complement each other; certain conditions are better studied with one than the other. Various strengths and weaknesses of each modality should be carefully considered when selecting them for tumor assessment and follow-up [11]. The interpretation of CT and MRI should be based on the patient's history, physical findings, comorbidities, and previous procedures that may influence the structures visualized. Comparison with previous imaging is also essential to reliably understand the present condition.

13.2 Anatomic CT

Computerized tomography (CT) was introduced about 40 years ago and has greatly enhanced clinical care. Its advantages include its speed, lower cost, and wide distribution in most medical centers. CT is excellent at delineating tumor extent and nodal disease. In head and neck tumors such as HNSCC, CT has helped in tumor staging, which dictated patient management and related to prognosis [8]. Helical multi-detector computerized tomography (MDCT) with 16 and now 64 detector rings has rapidly now become the new industry standard in CT imaging. This along with dynamic acquisition typically has resulted in reduced scan time, thinner sections, increased anatomic coverage, and better resolution of reformatted images and three-dimensional reconstruction. Section thickness as low as half an mm can be achieved along with acquisition of up to eight images per second [12, 13]. This has greatly enhanced the sensitivity and specificity of CT scan in head and neck cancer for primary staging as well as post-therapeutic follow-up (Fig. 13.1).

The anatomic coverage of a neck CT should include the base of the skull and should extend up to the medial end of the clavicles with 4 mm thick slices. Additionally, 2 mm slices and higher zoom factor may be employed at the region of interest using reconstructed spiral data. In patients with significant dental hardware, additional angulated images may also be obtained for better anatomic coverage avoiding streak artifacts.

CT has proved to be a modality of choice for initial work-up of a patient suspected of head and neck cancer and proved excellent for initial locoregional and lymph nodal staging and for post-therapeutic follow-up.

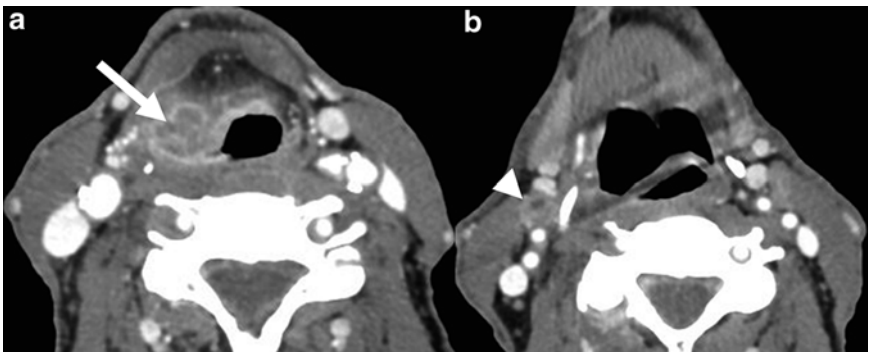

Fig. 13.1 Axial postcontrast CT scan showing T3 stage right aryepiglottic fold carcinoma (**a**) with transglottic extension (*arrow*) and metastatic right level 2 lymphadenopathy (**b**) consistent with N1 disease (*arrowhead*)

13.3 CT Perfusion

Computerized tomography perfusion (CTP) can be used to facilitate the evaluation of functional parameters such as tissue perfusion in many cancers. This can be integrated with morphologic information derived from conventional CT techniques. It is a dynamic contrast-enhanced technique which is used for quantitative assessment of tissue microcirculation [14], and it has recently been rediscovered as a promising noninvasive tool for evaluation of the microcirculatory changes associated with several neoplasms, including cancers of the head and neck [15–18]. CTP technique is based on the central volume principle, which relates blood flow, blood volume, and MTT as: blood flow (BF) = blood volume (BV)/MTT. Faggioni et al. have shown that BV, BF, and permeability-surface area product are significantly higher, whereas MTT is significantly reduced in head and neck tumor (both primary neoplasm and lymph node metastases, whenever present) compared with normal tissue and with muscle taken as a reference ($p < 0.01$); moreover, the alteration of CT perfusion parameters correlates with histopathologic diagnosis of adenocarcinoma in all cases [15]. Ash et al. have shown that CT perfusion parameters of the neck (BF and BV) correlate positively with microvessel density (MVD) of endoscopic biopsy specimens obtained from primary tumor sites of head and neck squamous cell carcinoma (HNSCC) [19]. Although, it seems unlikely that CT perfusion will replace biopsy for pretreatment assessment of MVD, CT perfusion has the potential to monitor treatment response by enabling noninvasive assessment of alterations in MVD and acting as a surrogate marker for tumor oxygenation (Fig. 13.2).

13.4 Anatomic Magnetic Resonance Imaging

Following the introduction of magnetic resonance imaging (MRI) 30 years ago, its use has enabled a quantum jump in diagnostic imaging of head and neck neoplasms. Early investigations highlighted the ability of MRI to differentiate neoplastic from inflammatory lesions. MRI provides essential information about the deep extension of clinically detected masses and also delineates additional clinically unsuspected lesions [7]. It has added value for detection of soft-tissue extent, marrow involvement, and perineural spread [20]. The excellent tissue characterization and noninvasive multiplanar imaging capability of MR imaging result in more accurate diagnosis of neoplastic and benign tumors of the head and neck [21–25]. MRI is reported to be superior to CT in detecting tumor extensions, in separation of edema from the tumor, and in evaluation of possible bone marrow invasion. Dynamic MRI is also utilized to plan and evaluate radiotherapy of head and neck cancer [26].

MRI of the neck should be tailored for the anatomic region and processed under evaluation. A standard head coil usually suffices for relatively localized examinations of the suprahyoid region and base of the skull, whereas, the infrahyoid neck requires a neck coil. Axial, coronal, and sagittal sequences are essential. Unenhanced axial T1-weighted images display anatomic relationships and can detect lesions (e.g., lymph node lesions) embedded within fat. T1-weighted coronal images can define the false vocal cords, true vocal cords, laryngeal ventricle, and floor of the mouth [27, 28].

T1-weighted sagittal images provide helpful information about the preepiglottic space and nasopharynx. T2-weighted transaxial images characterize tissue, detect tumor within the muscle, demonstrate cysts, and assist differentiation of post-therapy fibrosis from recurrent tumor [29].

Gradient moment nulling, flow compensation, cardiac gating, and presaturation pulses are some techniques used to minimize motion artifacts [27]. Gadolinium (Gd)-enhanced images improve delineation of margins in many lesions. Fat-suppression techniques, such as short tau inversion recovery (STIR) and frequency-selected fat suppression, may improve the conspicuity of soft-tissue lesions embedded in fatty tissue by selectively diminishing the hyperintensity of fat on T1-weighted images [30] (Fig. 13.3). Postcontrast T1-weighted images usually best delineate the tumor margins [31], and this may be further improved with fat saturation (fat-sat), which, however, frequently results in artifacts and image degradation [32]. However, the normal enhancement of the aerodigestive mucosa may conceal small mucosal tumors.

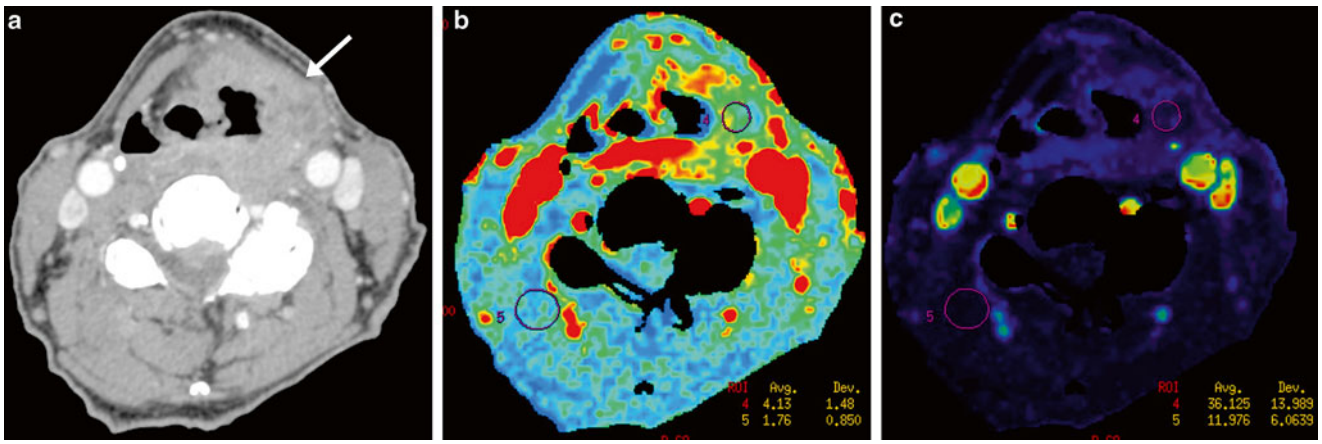

Fig. 13.2 (**a**) Contrast-enhanced neck CT image in a 69-year-old woman with history of previous surgery and chemoradiation for supraglottic and hypopharyngeal carcinoma. A patchily enhancing soft tissue is seen at the right-left anterior neck, involving the strap muscle (*arrow*), involving the lateral wall of left pyriform sinus and left aryepiglottic fold, and extending on to prevertebral spaces. (**b**, **c**) CT perfusion map shows increased blood volume and blood flow, suggestive of hyperperfusing malignant mass

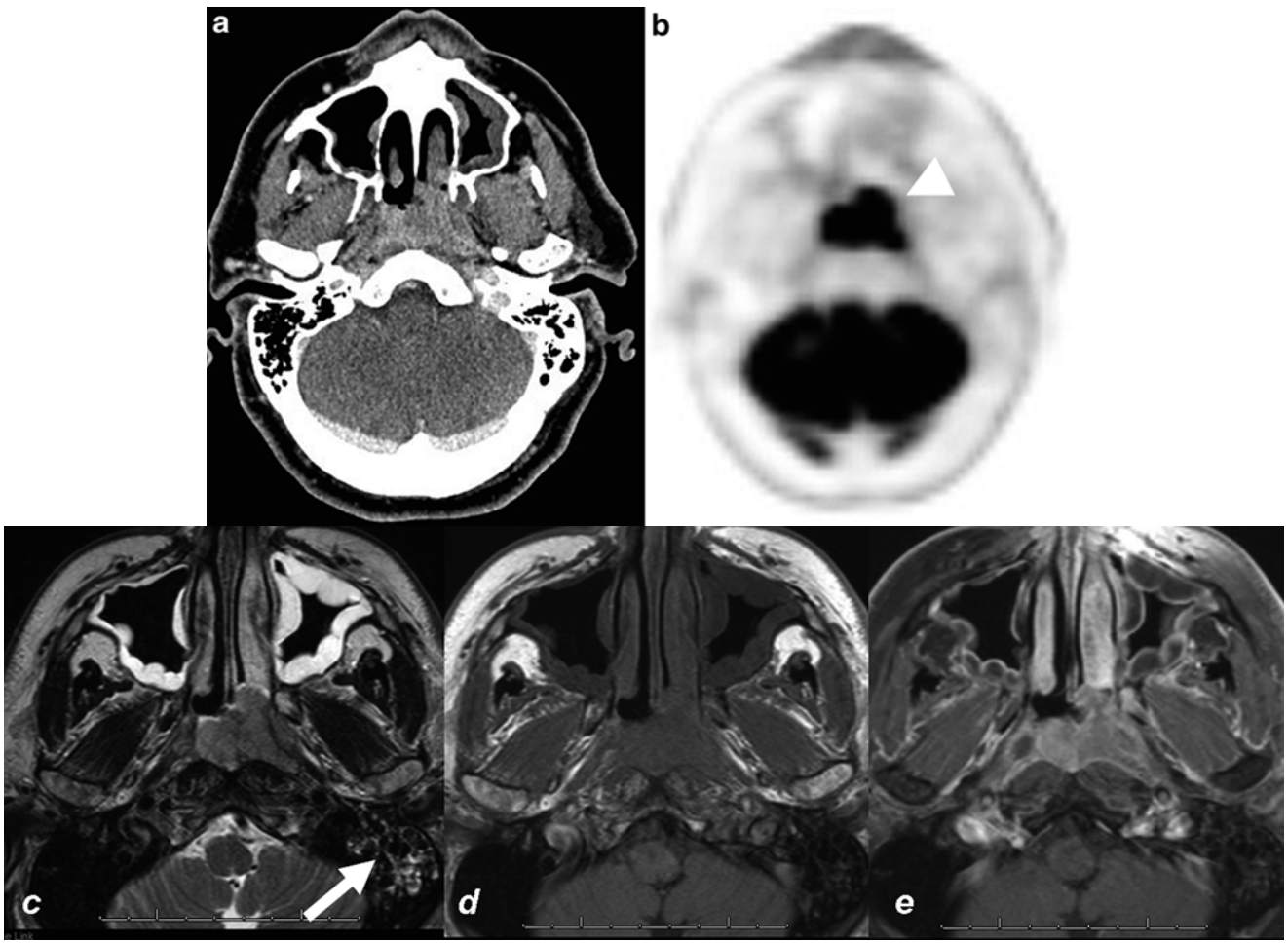

Fig. 13.3 PET/CT (**a** and **b**) images showing FDG-avid nasopharyngeal mass (*arrow head*). Axial T2W (**c**) and pre- and postcontrast fat-suppressed T1W images (**d** and **e**) showing enhancing mass within the left posterior nasopharynx crossing to the right side. Fluid in the right mastoid air cells (*arrow*) secondary to Eustachian tube dysfunction

Early investigators credited MR imaging with greater precision in head and neck imaging than was warranted [33]. Conventional MR imaging did not have the last word in histological specificity, early detection of primary malignancy, and differentiating neoplastic from inflammatory lymph nodes. In spite of early enthusiasm, MR imaging did not eliminate the need for biopsies or aspirations of lesions. Spin echo imaging is still the mainstay of MR imaging, but now various new techniques hold promise for the future of head and neck imaging [34].

13.5 MR Diffusion

MR diffusion-weighted imaging (DWI) has been traditionally used to evaluate ischemia of the brain parenchyma. Its utility in evaluating pathologies outside the calvarium has recently been recognized, specifically, extracranial neoplastic disease. Hypercellular tissue within malignant tumors will show low ADC values [35, 36], while tissue changes such as edema, inflammation, fibrosis, and necrosis show low cellularity and hence higher ADC values [34] (Fig. 13.4). Diffusion-weighted imaging of oropharynx can easily be performed at the time of MR conventional imaging and adds approximately only 1–2 min of additional time to the examination. Localization and extent of primary squamous cell cancer, one of the commonest malignant neoplasms of head and neck, is usually well defined by CT or conventional MRI. High sensitivities and specificities, better than CT or conventional MRI, are also reported in staging of neck lymph nodes in squamous cell carcinoma [37, 38]. Whole-body DWI at high b-values with ADC mapping is technically feasible and improves assessment of metastatic spread in routine MR examinations. The characterization of neck lymph nodes remains a difficult issue with anatomy-based imaging methods, and DWI may be useful in this regard [39, 40]. DW imaging performed with ADC (b0–1000) values had higher accuracy than turbo spin-echo MR imaging in nodal staging, providing added value in the detection of subcentimeter nodal metastases [40].

13.6 MR Perfusion

MR perfusion is used to evaluate dynamic microscopic blood flow changes through a region of interest. The change in tissue signal intensity on MRI can be measured during a dynamic contrast infusion. This is used to generate blood flow, blood volume, and transit time parameters within areas of interest. Perfusion characteristics of tissue demonstrate changes in blood flow or volume of the head and neck lesions depending on underlying pathologic processes [34]. This technique has been previously studied in characterizing brain ischemia, particularly in identifying infarcted tissue versus tissue at risk [41]. Changes in perfusion characteristics are also demonstrated in neoplastic tissue (Fig. 13.5). Generally, these findings may not add substantial additional information regarding tumor extent at the diagnosis. However, such imaging may be of benefit in qualitative analysis of tumor tissue. Specifically, additional recent studies have demonstrated that squamous cell carcinomas of the upper aerodigestive tract with increased blood volume/flow are more chemosensitive than other lesions with relative decreased perfusion parameters. This is likely due to relative increased oxygenation and metabolism of such lesions [17]. Such perfusion techniques could be particularly useful in determining which patients would benefit from such medical treatment, as opposed to surgical therapies which may not always preserve organ function.

An additional area of interest is in regard to tumor recurrence or regression. Conventional MRI or CT may simply demonstrate increased contrast enhancement within the treated neck. However, morphologic changes in tissue appearance (such as increase in size or nodularity) may not be well demonstrated on early posttreatment conventional imaging. Recent studies have concluded that for recurrent oral cavity and oropharyngeal carcinomas, perfusion parameters are altered. Specifically, BV and BF within recurrent tumor tissue are elevated in comparison to therapy-altered tissue, with corresponding decreases in transit time [42]. Perfusion imaging, like diffusion imaging, adds little time to either conventional MRI or CT examinations and can also be obtained noninvasively [43].

13.7 MR Magnetization Transfer

MR Magnetization transfer (MT) technique is based on the principle that the selective magnetization of protons associated with macromolecules may be transferred to the water protons that constitutes the MT image. A strong MT effect is observed where an efficient transfer mechanism exists between the two proton populations. It may be a useful technique for differentiating enhancing lesions from background tissue and defining poorly enhancing lesions. This is exploited to improve contrast between mass lesions that demonstrate an MT effect and background tissue like fat that does not [44]. Use of MT can improve contrast between head and neck lesions and background tissues. MT is shown to improve depiction of enhancing lesions adjacent to tissues with a strong MT effect [45]. MT can also aid unenhanced MR imaging in the delineation of tumors or lymph nodes in the parotid gland. MT is not indicated for cystic lesions, because they are generally well shown on a T2-weighted image or for cervical lymphadenopathy within

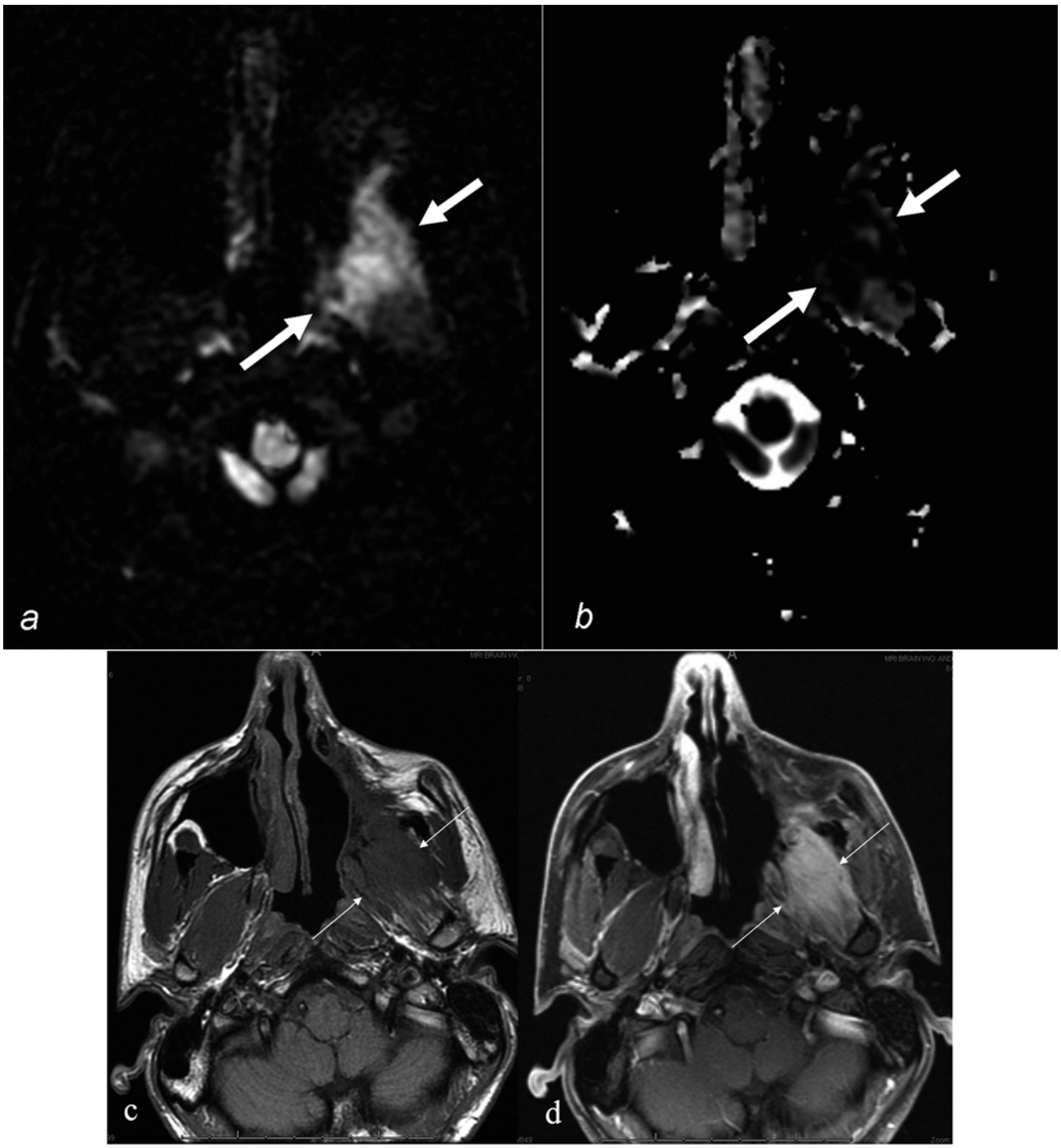

Fig. 13.4 Axial DWI (**a**) showing restricted diffusion in a left masticator space adenoid cystic cancer (*arrows*) with low ADC values (**b**) as seen on corresponding ADC maps (**c** and **d**, *arrows*)

lipoid tissue, because that has natural tissue contrast on conventional MRI [45].

However, MT has not enjoyed widespread application in head and neck imaging, partly because conventional imaging usually provides sufficient delineation of most primary lesions and lymphadenopathy.

13.8 MR Spectroscopy

Magnetic resonance spectroscopy (MRS) provides a noninvasive method for evaluation of various diseases of head and neck independent of the anatomic information provided by magnetic resonance imaging (MRI) [46]. 1H-MR

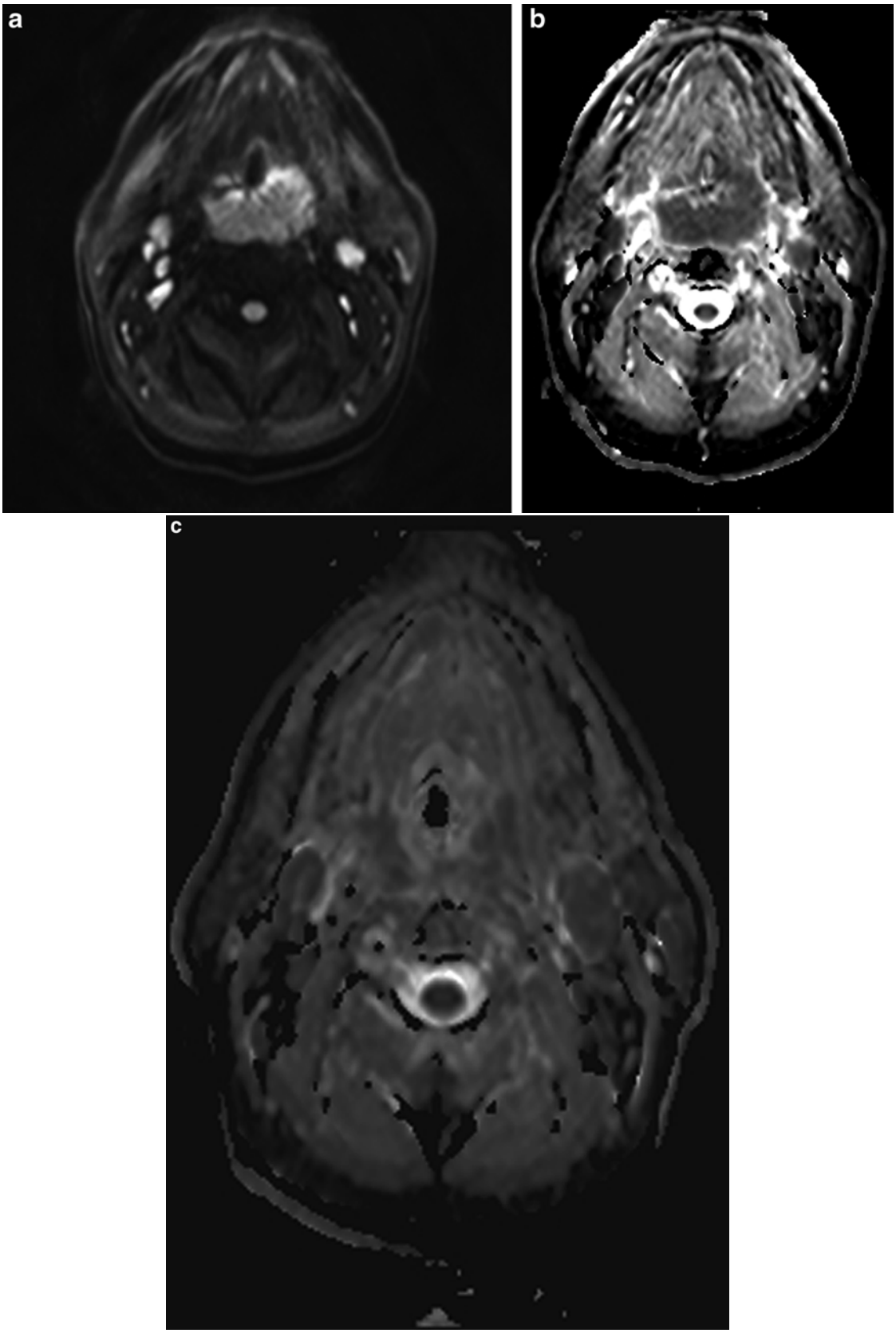

Fig. 13.5 (**a**, **b**, **c**) Large posterior oropharyngeal wall squamous cell carcinoma demonstrates increased DWI (**a**) and decreased ADC (**b**) signal intensity at presentation. Post-therapy, the lesion has decreased greatly in size (**c**). (**d**) Blood volume map of the same patient as in images (**a**–**c**) demonstrates increased perfusion values of the lesion (*circled*) in comparison to the adjacent tissues at presentation (Reprinted from Shah GV, Wesolowski JR, Ansari SA, Mukherji SK. New directions in head and neck imaging. *J Surg Oncol.* Jun 15 2008;97(8):644–648. With permission from John Wiley & Sons)

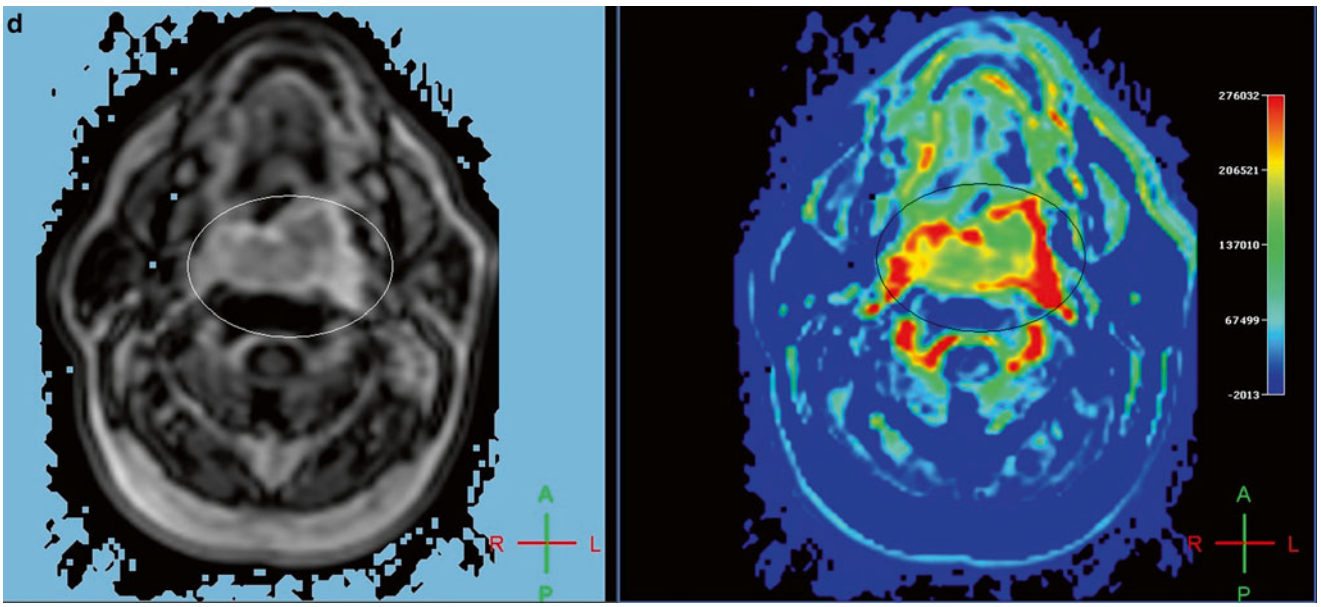

Fig. 13.5 (continued)

spectroscopy has the potential to assess biochemical composition and hence identify characteristics that could indicate malignant progression. It is widely accepted that cancer progression is accompanied by intracellular biochemical changes. It has the unique ability to analyze the tissue at the molecular level by evaluating the presence of specific metabolites. This is especially helpful to characterize lesions that have equivocal features on standard anatomic imaging. Early metastatic infiltration of nonenlarged lymph nodes or residual malignant disease in patients undergoing treatment for malignant process may also have normal or ambiguous appearance on routine anatomic CT or MR imaging [47].

In the case of HNSCC, it has been shown that 1H-MR spectroscopy has the potential to differentiate between normal and malignant tissue with a high degree of sensitivity and specificity [46, 48–51] (Fig. 13.6). MR spectroscopy of head and neck cancer and lymph nodes helps to differentiate nonmalignant from malignant tumors and lymph nodes and also helps to differentiate between residual malignancies from postradiation changes. Elevation of the Cho/Cr ratio appears to be a consistent finding for HNSCCA and has also been identified in analysis of various SCCA cell cultures and SCCA containing cervical metastatic lymph nodes [48]. Higher levels of choline metabolites in tumors are believed to be due to increased cell proliferation and biosynthesis, while reduced creatine resonance likely reflects increased energy metabolism within tumors [52].

For prognostication, MR spectroscopy has the potential to contribute to an accurate and early prediction of tumor behavior and response to treatment in squamous cell carcinoma of the head and neck region. Using the choline-to-creatine (3.2/3.0 ppm) and the 1.3/0.9 ppm spectral intensity ratios (signal due to lipid or lactic acid), a sensitivity of 83 % and a specificity of 82 % were obtained in predicting which head and neck cancer patients would fail treatment [53].

Tumor hypoxia is a common phenomenon in solid tumors and has been shown to adversely affect the treatment outcomes in patients with head and neck (HN) squamous cell carcinoma treated with conventional therapy [54–56]. Resonance from lactate (Lac, 1.3 ppm) may be a marker for tumor oxygenation and may help staging and was thought to have potential for staging and monitoring the treatment [57]. However, in a recent work, the lactate SI did not correlate with tumor pO_2, treatment response, or locoregional control in a series of 62 patients with resectable stage IV HN squamous cell carcinoma undergoing induction chemotherapy [58]. Additional research is needed to refine this technique.

13.9 Positron Emission Tomography

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is a technique that has been found to be superior to conventional imaging work-ups such as CT and MRI, which were previously the mainstay work-up for diagnosis, staging, and post-therapeutic follow-up in patients with head and neck cancer [59–61]. ^{18}FDG-PET has higher sensitivity and specificity for detecting lymph node metastases than CT or MRI. It improves detection of occult cervical lymphatic disease and distant metastasis and assists in localization of unknown primary carcinoma of the head and neck region [62–66]. ^{18}FDG-PET is considered superior to CT and MRI for local staging and detection of malignant characteristics in cervical lymph nodal enlargements [59, 60, 67–70]. It has a

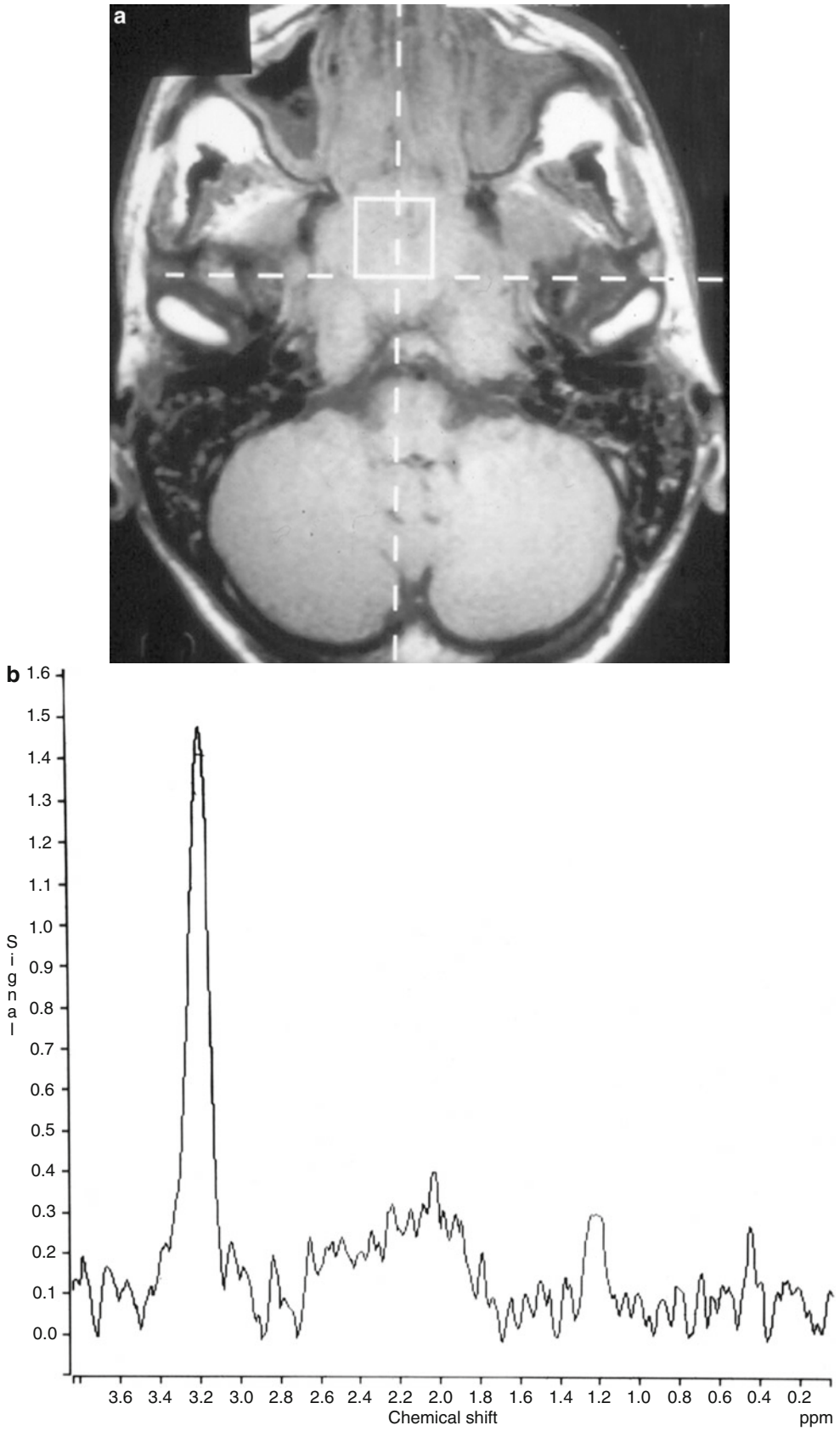

Fig. 13.6 Patient with throat pain and dry cough exhibits a nasopharyngeal mass on MR imaging. (**a**) T1 axial images show a large nasopharyngeal midline soft-tissue mass with nonspecific features and without frank aggression. (**b**) 1H-MRS reveals attenuation of *N*-acetyl aspartate peak, elevation of choline peak, and increased choline-to-creatine ratio compatible with malignant mass. This lesion was proved on biopsy to be a squamous cell carcinoma (Reprinted from Shah GV, Fischbein NJ, Patel R, Mukherji SK. Newer MR imaging techniques for head and neck. *Magn Reson Imaging Clin N Am.* Aug 2003;11(3):449–469. With permission from Elsevier)

high negative predictive value (NPV) of approximately 90 %, which is more than any other imaging modality. There is growing evidence that ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging is increasingly accepted as a valuable imaging tool in evaluation of patients with head and neck carcinomas [62–65, 71–74]. The potential clinical applications include pretreatment staging, treatment monitoring, and evaluation of the previously treated patients [75] (Fig. 13.7).

13.10 PET/CT

The use of PEt alone provides poor quality of anatomical localization of the primary tumor, and metastases on ^{18}FDG-PET can have negative impact on staging and management [76]. The poor spatial resolution of ^{18}FDG-PET is a limiting factor, especially within the intricate anatomy of the head and neck [69]. Combined PET/CT scanners overcome these limitations by fusing the anatomic data of CT with functional data of ^{18}FDG-PET [77–79]. In PET/CT, the most relevant additional effect is that the CT data adds specificity to ^{18}FDG-PET data [80, 81]. The utility of PET/CT has been evaluated extensively in head and neck neoplasms. Several of these studies showed that the integrated combination of CT and ^{18}FDG-PET is more accurate than either of the modalities alone for detection and anatomic localization of head and neck cancer, thus enhancing the patient care [82–87]. PET/CT has been shown to have high NPV but poor PPV following treatment [88, 89]. Recently, the Hopkins Interpretation system was introduced as a five-point qualitative scale for evaluation of PET/CT and was found to predict overall survival [90]. The accuracy of integrated PET/CT is also more than ^{18}FDG-PET and CT images viewed side by side [83, 91–94]. In one study, CT data improved the specificity of the images in approximately two-thirds of patients with lesions seen on ^{18}FDG-PET images [95]. In some situations, such as very small disseminated pulmonary metastases, addition of CT is able to increase the specificity and also the sensitivity of PET/CT examination [81].

PET/CT can detect unknown primary tumors of the upper aerodigestive tract [96, 97]. PET/CT can detect primary squamous cell carcinoma in 30–50 % of patients presenting with an unknown primary tumor. PET/CT is generally performed after confirming the presence of metastatic squamous cell carcinoma. It is usually performed before endoscopic biopsies to improve the tissue yield. This diagnostic yield can increase with PET/CT as it improves the anatomic localization of areas of abnormal FDG uptake [98, 99]. PET/CT is also utilized for determining response to chemotherapy and/or radiation. Comparison of pretreatment standard uptake values (SUVs) to SUVs 2 weeks into treatment can allow measurement of the speed of response and also the sensitivity of the tumor to the treatment technique [100]. Poorly responsive tumors can then be treated to higher effective tumor doses of radiation, or surgery can be performed. Initial results suggest that PET/CT can be used to assist in defining primary site and nodal tumor targets for radiation therapy approaches. PET/CT is useful adjuvant to clinical staging of squamous cell carcinoma, and its utilization will increase with advancement of technology.

13.11 PET/MR

PET/MR is a new modality that has started to become more widely distributed and allows for increased anatomical localization of lesions like PET/CT. It may provide a number of advantages over PET/CT including simultaneous imaging, decreased radiation, and better soft-tissue resolution including perineural spread and infiltration of fascia and vessels [101, 102]. These characteristics have been demonstrated when imaging the head and neck region [103]. The disadvantages of PET/MR are few but include difficulty with attenuation correction. In addition, disadvantages that broadly apply to MRI such as missing small lung metastasis are also applicable to PET/MR [104].

Several centers are beginning to develop protocols and are exploring application for PET/MR in head and neck cancers. One study retrospectively compared PET/MRI fusion with PET and MRI alone and found increased sensitivity and specificity for tumor staging [105]. However, others have found no advantages in TNM staging as compared to PET/CT or MR alone [106–109]. It remains to be seen if PET/MR will become standard of care for diagnosing and tracking neoplasms in the head and neck.

13.12 Local Tumor Detection and Staging

The most important information required before surgery for proper therapeutic planning is the accurate knowledge of location, size, extent, the depth of invasion of the primary tumor, and its relation to the surrounding structures [69, 110]. Large primary tumors of the oral cavity or the oropharynx can be detected easily by clinical examination. The sensitivity of FDG-PET was considered even higher than CT or MRI for detection of primary tumors [111]. The sensitivity of FDG-PET for detection of primary carcinoma ranged from 88 to 100 % [61, 63, 112, 113]. Both MRI and CT can provide additional information about tumor extension into the deep spaces, the relationship to adjacent structures, and bone infiltration needed for treatment planning. Sensitivity of MRI earlier was thought to be less than that of CT [62, 112]. However, with increased

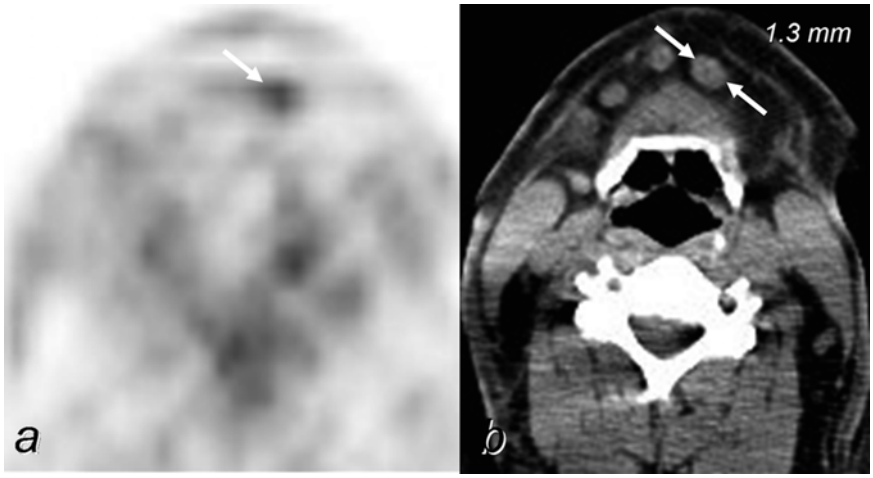

Fig. 13.7 Mantle cell lymphoma showing FDG avidity (**a**) in a nonenlarged left level 1 lymph node (*arrows*) in the neck (**b**)

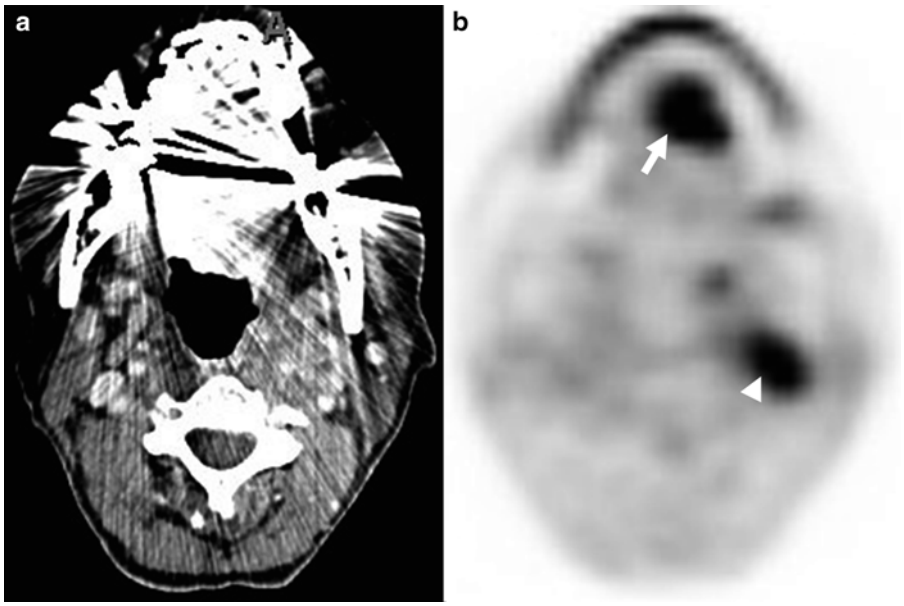

Fig. 13.8 Axial postcontrast CT scan (**a**) showing dense streak artifacts from unmovable dental hardware obscuring FDG-avid squamous cell cancer in the oral tongue (*arrow*) with metastatic left level 2 lymph node (*arrow head*) as seen on PET scan (**b**)

technical improvements, it is thought to be comparable to CT [114]. Scattering of focal uptake in primary oropharyngeal tumors can lead to overestimation of the extent of primary disease, and physiologic uptake in oropharynx may obscure small primary tumors in oropharynx [115]. Thus FDG-PEt alone cannot provide the detailed information needed for planning of tumor resection, but fusion of FDG-PET data with CT data in PET/CT can overcome this limitation.

Sensitivity of CT, especially in oropharynx, can be compromised by streak artifacts from dental hardware, especially if the size of the tumor is small [114]. However, high metabolism on FDG-PET would indicate the possibility of an underlying mass (Figs. 13.8, 13.9, and 13.10). Earlier, the sensitivity of MRI was thought to be less than that of CT [62, 112], but with increased technical improvements, it is thought to be comparable to CT [114]. Some of the earlier reports showed that FDG-PET was more accurate than CT or MRI for local detection of smaller tumors [62, 112, 113]. But some more recent studies have shown that CT and FDG-PET are equivalent in local staging [61, 116].

CT detects lytic foci of cortical mandibular invasion, which are best accomplished with a dedicated dental protocol. The reported sensitivity and specificity for standard neck CT in detection of mandibular involvement are 96 % and 87 %, respectively [117] (Fig. 13.11). However, a later study demonstrated a 93 % accuracy of MRI in detecting mandibular involvement in patients with oral and oropharyngeal cancer [118], indicating that CT may not be necessary to evaluate for cortical invasion. MRI with contrast-enhanced T1-weighted fat-sat images provides satisfactory accuracy of tumor thickness. The presence of malignant neoplasm adjacent to the neurovascular bundle is highly concerning for invasion. Tumors larger than 2 cm with aggressive margins and deep sublingual extension probably involve the neurovascular bundle [31]. Oral malignancies, especially of buccal

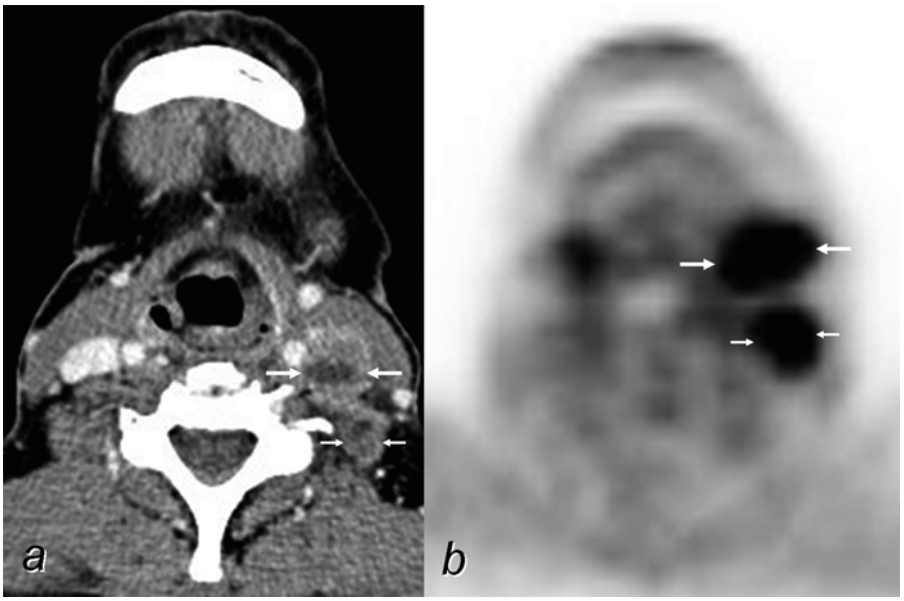

Fig. 13.9 Axial postcontrast CT scan (**a**) showing large necrotic left level 2 lymph node (*large arrow*) and necrotic left level 5 lymph node (*small arrow*), with FDG avidity on the corresponding PET scan (**b**)

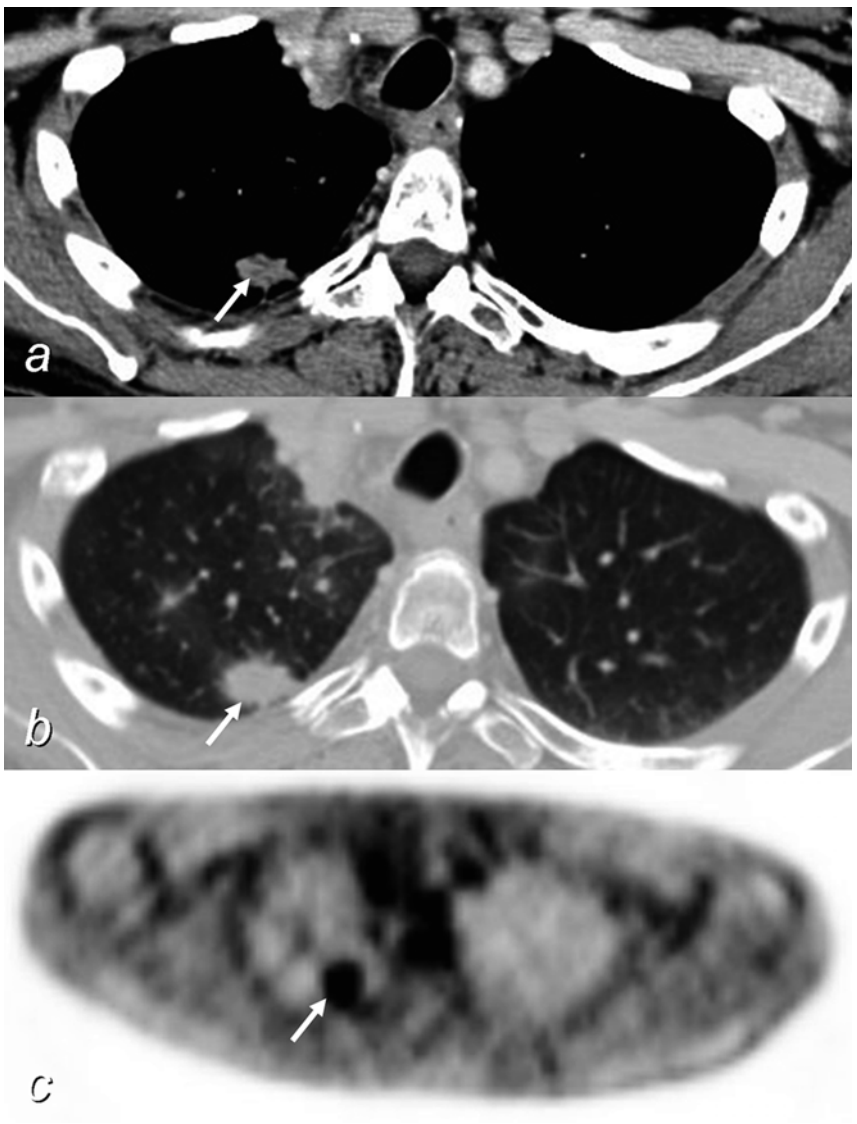

Fig. 13.10 CT thorax in mediastinal windows (**a**) and lung windows (**b**) showing a metachronous lung cancer (*arrow*) with increased FDG uptake on PET scan (**c**)

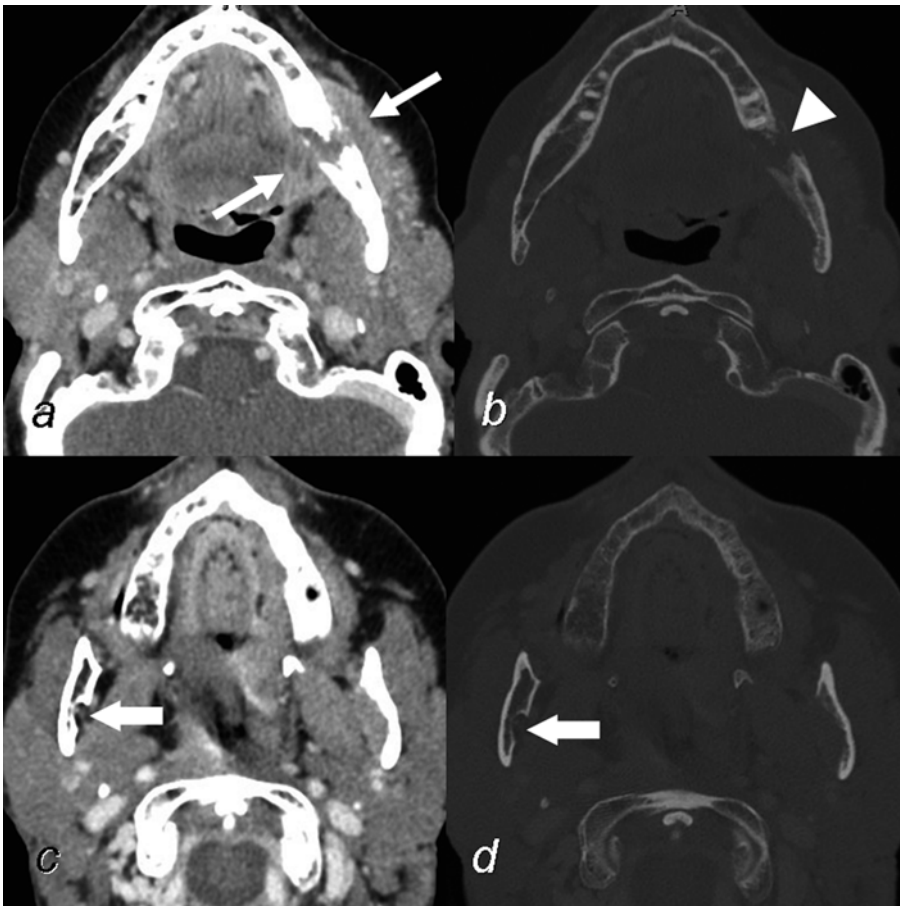

Fig. 13.11 Axial postcontrast CT scan (**a**) showing stage T4 left retromolar trigone cancer (*arrow*) with destruction of left mandibular ramus (*arrow head*) on bone windows (**b**). Perineural spread along left inferior alveolar nerve with loss of normal fat in the alveolar foramen on the *left* (**d**), compare with normal *right side* (**c**) (*arrowhead*)

spaces and retromolar trigone, are better visualized using the "puffed-cheek" CT technique, in which the patients perform a modified Valsalva maneuver during the scan distending the oral cavity by air [119].

Deep extension of nasopharyngeal cancer including the presence of skull base invasion, and intracranial spread is better evaluated with MRI than CT [120, 121]. Skull base invasion may occur through the neural foramina by perineural tumor spread, which primarily occurs after invasion of the pterygopalatine fossa, foramen ovale, and hypoglossal canal [122] (Fig. 13.12). Nonenhanced T1-weighted images are very well suited to evaluate perineural extension, revealing homogeneous gray mass of tumor against natural tissue contrast of T1 bright fat planes and bone marrow. Pre- and postcontrast T1-weighted MRI is very accurate in detection of subtle perineural tumor extension. Evaluation of possible perineural spread should be performed in all patients with facial paralysis and facial pain or numbness, because these symptoms may be the initial presentation of a head and neck malignancy [123, 124] (Fig. 13.13). Complementary direct coronal CT images with bone algorithm are recommended to evaluate subtle bone erosion which may escape detection by MRI.

Cartilage invasion by laryngeal and hypopharyngeal tumors is an important imaging finding because it automatically leads to a T4 stage [9]. The overall sensitivity is 82 %, overall specificity is 79 %, and overall negative predictive value of cartilage erosion on CT overall is 91 % [125]. Cartilage invasion on MRI shows high T2 signal intensity, a low-to-intermediate T1 signal, and postcontrast enhancement. However, due to frequent reactive inflammation, edema, and fibrosis, the MRI findings of cartilage invasion may frequently be false positive, resulting in a positive predictive value of only 68–71 % [126]. However, the advantages of MRI over CT for soft-tissue differentiation may be outweighed by motion artifacts. CT remains a valuable and frequently used screening modality for the larynx as it is fast and readily available.

Imaging studies cannot reliably distinguish benign from malignant salivary gland masses. MRI is the modality of choice for evaluation of parotid masses [21]. The real advantage of cross-sectional imaging is the ability to accurately reveal the location and extension of a tumor and to assess for perineural tumor spread. Magnetization transfer, dynamic imaging, and especially, diffusion imaging have shown promising results in detection of parotid malignancies [127].

The relationship of a tumor to the facial nerve is difficult to determine on MRI. However, the lateral margin of the retromandibular vein on cross-sectional imaging as a marker

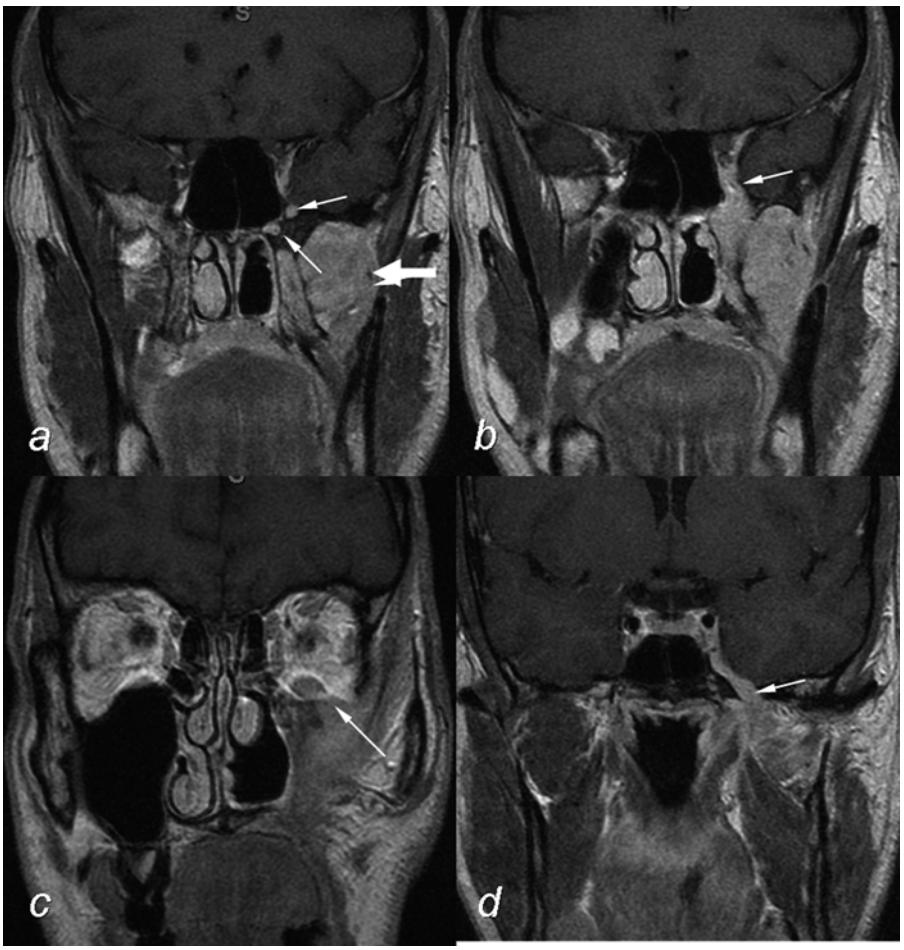

Fig. 13.12 Coronal fat-suppressed postcontrast T1W images showing large infiltrating soft-tissue attenuation mass in the left masticator space (*bold arrow*) extending into the pterygopalatine fossa (**a**). There is associated abnormal enhancement along the second and third divisions of the left trigeminal nerves and left Vidian canal (*small arrows*) (**a**, **b**, **d**). There is infiltration of the left orbital floor with enhancing soft tissue and thickening of the left inferior rectus muscle (*small arrow*) (**c**)

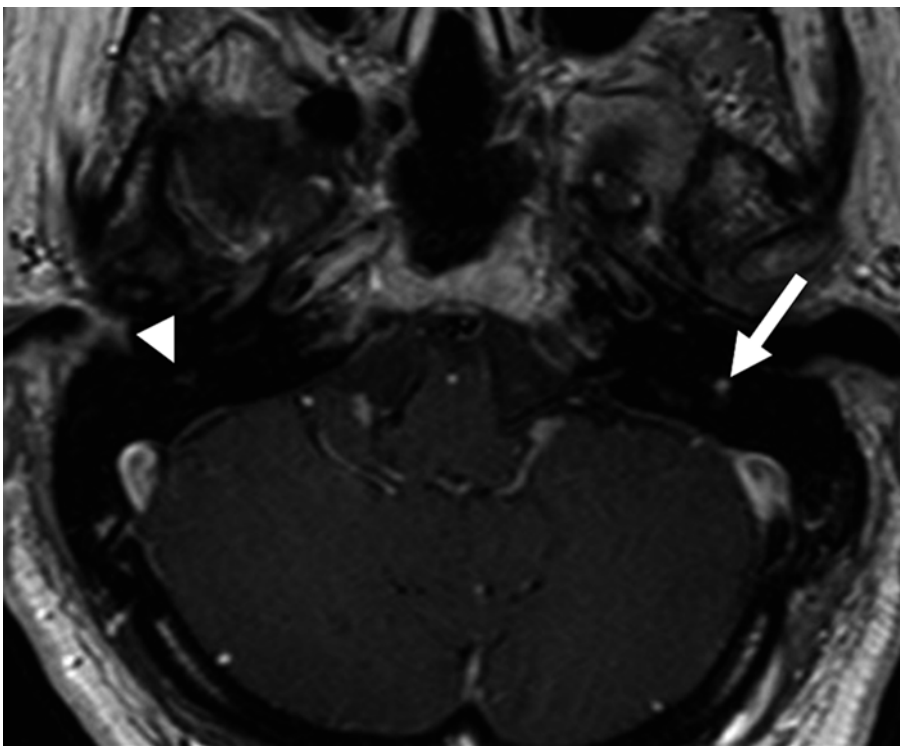

Fig. 13.13 Postradiotherapy "facial neuritis." Axial (3 mm section) postcontrast, fat-suppressed T1W image showing increased enhancement of the tympanic segment of the left facial nerve (*arrow*), compared to normal right-sided facial nerve (*arrow head*)

for the facial nerve has an accuracy of approximately 90 % [128]. A careful search for perineural tumor spread along the facial, auriculotemporal, and mandibular (V3) nerves should be undertaken on MRI scans in all patients with parotid masses [129].

Multiple series have been reported evaluating FDG-PET or PET/CT for patient with newly diagnosed HNSCC in the preoperative setting [60, 63, 130]. Sensitivity of FDG-PET was reported to be 98 % and of PET/CT 97 % for detection of primary tumors in patients with newly diagnosed HNSCC in a large series with 167 patients [69], higher than sensitivity of CT (86 %) and MRI (88 %) in the same patient set. Similar results were reported in numerous previous studies [59, 60, 63, 82, 85, 86, 130]. Even as sensitivity of PET/CT is considered higher than any morphological imaging for primary detection of HNSCC, the detailed anatomic information like depth of invasion and relationship of tumor to surrounding structures could not be provided only by the CT data of PET/CT. This may be due to inherent technical limitations of CT data set. With availability of multi-slice and multi-detector scanner capability in future with PET/CT, this situation may improve.

13.13 Lymph Node Staging

As most primary head and neck malignant neoplasm have a relatively high incidence of nodal metastasis, the staging of the neck is most important before a therapeutic plan is evolved. Staging can be done by a combination of clinical palpation and anatomic imaging. Nearly 40 % of all lymph nodes in the body are located above the clavicles. Lymph nodes are usually embedded within the fat planes that surround the vessels and separate major cervical muscles. Therefore, the fat of the neck provides an excellent natural contrast with the nodes on T1-weighted MR images [11]. Lymph nodes are divided into ten major groups [131] named for the structures in proximity to nodal location.

Patients with limited nodal spread of head and neck cancer are often treated surgically with radical neck dissection, while more extensive disease may additionally require adjuvant radiation therapy. Complete removal of all metastasis lymph nodes is essential for curative treatment. Lymph node metastases are common in patients with head and neck cancers. In up to 20–30 % of patients, lymph nodal spread of the disease is found, even though it may not be apparent on physical exam [132, 133]. The prognosis for these patients is strongly influenced by the presence of lymph node metastases [112]. Metastatic lymph node disease was found in approximately 50 % of the patients at the time of diagnosis [71, 114].

The imaging recommendations are mixed regarding an appropriate modality for evaluating lymphadenopathy [5, 134, 135]. CT is preferred because of its availability, speed, and excellent spatial resolution. Lymph nodes are usually embedded within fat, and fat is well portrayed by CT (Fig. 13.7). MRI has superior soft-tissue contrast and multiplanar capabilities. CT and MRI have a high rate of false-negative diagnoses, which can be explained by micrometastases within otherwise normal lymph nodes [32, 136]. The reported sensitivity for CT in detection of metastatic lymph nodes is from 67 to 90 % [32, 71, 136–138] and for MRI is from 71 to 91 % [32, 65, 71, 112, 114, 136]. The reported sensitivities of PET for nodal disease range from 67 to 91 % [62, 65, 71, 72, 113, 114, 116, 137, 138]. Both FDG-PET and PET/CT have technical resolution limitations of 4–5 mm and were unable to detect lymph metastases smaller than 4–5 mm, contributing to false-negative results [139–141]. The reported specificity of FDG-PET ranges from 88 to 100 % [65, 71, 72, 84, 113, 137]. The specificity value for CT is 38–97 % and for MRI is 48–94 % [32, 71, 137, 142]. False-positive FDG-PET findings may be primarily due to its inability to discriminate between inflammatory process and tumor infiltration [111]. This is because FDG is not a tumor-specific tracer but a metabolic marker, and hence various inflammatory processes can lead to increased FDG uptake, potentially returning false-positive results [143]. However, a practical benefit of employing PET/CT in presurgical evaluation for lymph node staging in patient with HNSCC is improved imaging staging for the expert and also a nonexpert interpreter [84]. PET/CT imaging is also reported to reduce equivocal head and neck image interpretations and increase evaluator confidence [144]. Combining structural information with morphological imaging like CT and metabolic information with functional imaging like FDG-PET with coregistered PET/CT is a method of choice for lymph node imaging in the future.

13.14 Distant Metastases

Distant metastasis to other organs and distant lymph nodes from HNSCC is generally a late event and usually represents an incurable disease [145]. The lung is the most common site of distant spread; however, distant bone metastasis can also occur in case of other widespread metastatic disease [146, 147] and can cause severe local morbidity at the metastatic site [148]. The reported incidence for distant bone metastases in HNSCC ranges from 17 to 31 % [149–151]. Apart from the lungs, screening for distant metastases is routinely not performed in initial staging of patients with HNSCC [146, 152]. However, some studies have shown FD-PET to be valuable in detecting distant metastasis in advanced HNSCC, suggesting a role for whole-body FDG-PET scanning, including lungs and bones for initial staging [153–155].

PET/CT may be performed in squamous cell carcinoma to evaluate for possible occult distant metastases to the lungs or bones [137] (Figs. 13.8, 13.9, and 13.10). The presence of pulmonary metastases upstages a patient from M0 to M1 and alters treatment regimen. Routine imaging work-up for patient with squamous cell carcinoma pulmonary includes conventional radiography of the chest at most institutions. Chest CT is performed in patients with advanced stage disease. A solitary nodule on CT scan may represent a metastasis or a granuloma. PET would be helpful in this evaluation as a FDG-positive nodule would likely be metastatic and may require biopsy. An FDG-negative nodule may likely indicate a granuloma.

13.15 Unknown Primary Tumor

The incidence of unknown primary tumors in the head and neck region ranges overall from 3 to 7 % of all head and neck cancers including HNSCC [64, 67, 142, 156–162]. Apart from the routine physical examination, the evaluation includes fiber-optic laryngoscopy/nasopharyngoscopy, panendoscopy, and morphological imaging including CT and MRI and directed biopsy [156, 160, 161]. More recently, transcervical and intra-oral ultrasound has shown promise in detecting the primary lesion [163, 164]. The areas most likely to harbor an occult primary, such as the tonsil, tongue, base, piriform fossa, and postnasal space, should be thoroughly evaluated with physical examination and office-based endoscopies [161]. Focused morphological imaging with CT and MRI looking for evidence of primary as well as additional areas of lymphadenopathy is also performed. Further management is often a combination of surgery and radiotherapy; however, this depends on the primary site of the disease as well as the treating center [165, 166]. In spite of thorough clinical, endoscopic, and morphological imaging, 1–2 % of head and neck cancer patients will not have a primary site detected [167, 168].

An important application of PET imaging may be in patients with nodal disease and unknown primary tumor—the primary site has been found in 10–60 % of cases when conventional imaging and clinical investigations have failed [9]. FDG-PET is generally more sensitive than morphological imaging in patients with unknown sites of the primary carcinoma [169, 170]. However, it is also associated with false-positive findings in up to 11 % of these cases [169, 171]. Tumors of oral cavity account for a majority of cases with unknown primary and can generally be detected by clinical examination. However, in the head and neck regions with lower sensitively for clinical examinations and morphological imaging, the role of FDG-PET and PET/CT becomes more evident [114].

Tumor detection rate of about 31 % of primary tumors is reported in patients presenting with unknown primary [162]. A few retrospective studies suggest FDG-PET detection rates of 24–27 % for an occult head and neck primary carcinoma [64, 172]. Another study reported a low rate of true-positive scan (33 %) but a high rate of true-negative scans (88 %) [173], suggesting that negative FDG-PET or PET/CT helps to rule out a primary site (Fig. 13.14). This is complicated by the fact that false-positive reports are reported in large lymph nodes up to 20 mm in size [136, 137] or in necrotic lymph nodes. PET/CT serves as a valuable clinical tool for occult metastatic disease of the head and neck, most commonly HNSCC and synchronous primary tumors.

13.16 Synchronous Second Tumor

Patients with head and neck tumors also have a high incidence of secondary tumors of the aerodigestive tract (estimated at approximately 8 %), and PET identifies synchronous primary neoplasms that are missed on conventional imaging. The incidence for metastatic spread to lungs in patients with HNSCC is low, but there is also a high incidence of second primary tumor in patients with head and neck cancer, with detectable lung lesion [174]. A few previous studies have shown a high sensitivity of 100 % and positive predictive value of 85 % for FDG-PET to differentiate a malignant from a benign pulmonary lesion [153, 175]. Due to its ability to conduct whole-body imaging, PET/CT can be useful for detection of distant metastases and second primary cancer (Figs. 13.8, 13.9, and 13.10) [176, 177]. PET/CT can serve as an excellent screening tool for distant metastatic disease or a synchronous primary tumor in the lungs [162].

13.17 HPV

The recent rise of head and neck cancers related to the HPV has resulted in investigations to identify these patients. They are more likely to be younger, male, nonsmokers, and nondrinkers [178]. HPV-associated cancers also carry a better prognosis. Imaging findings have been studied in this population to better identify this subset of patients. HPV+ tumors have more likely to have lower tumor volumes and glycolytic indices on PET/CT [13, 179–181]. These have been found to be predictive of tumor recurrence and overall survival [182–186]. HPV status in combination with posttreatment PET/CT further increases the negative predictive value for recurrence and may allow for less frequent surveillance [187–190].

In conclusion, morphological imaging techniques are crucial for therapy planning in head and neck neoplasms. The highest sensitivity and optimal anatomic information of the

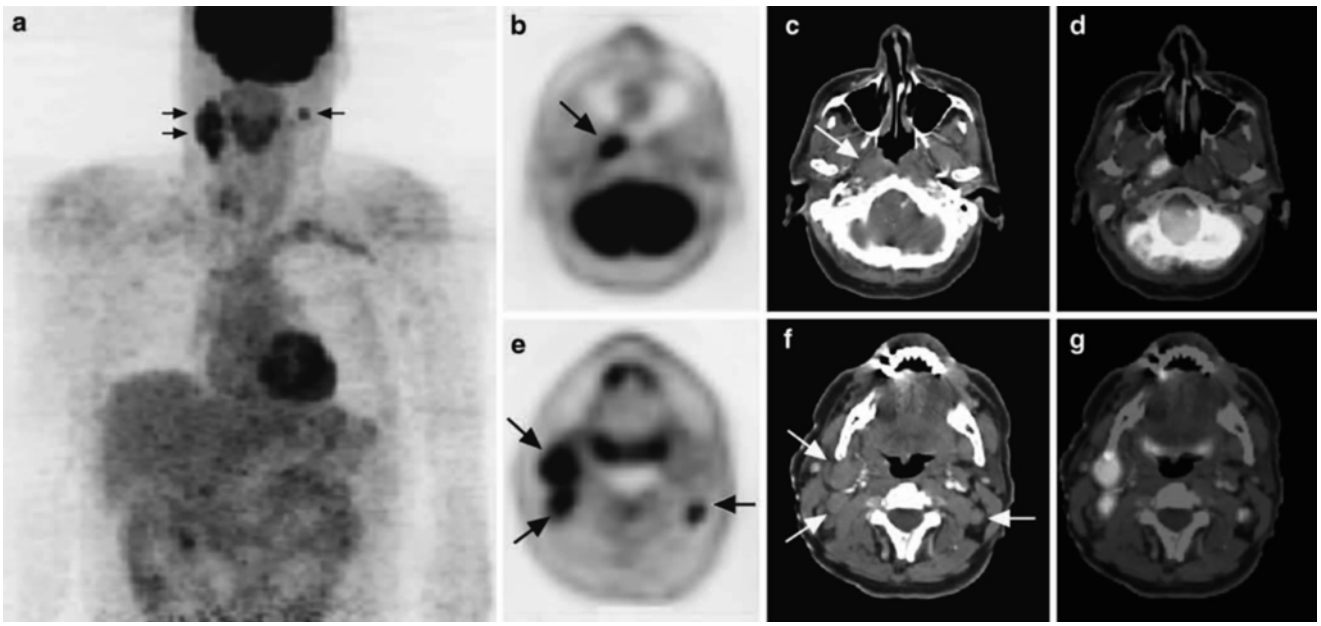

Fig. 13.14 Patient presented with bilateral lymph nodal neck masses. PET/CT reveals unknown primary neoplasm of nasopharyngeal squamous cell carcinoma. (**a**) MIP PET image demonstrates bilateral increased abnormal FDG uptake in the neck (*black arrows*). (**b**) Axial PET in the region of nasopharynx shows focal abnormal FDG uptake in the region of the right torus tubarius (*black arrow*). (**c**) Axial CT of nasopharynx shows mild soft-tissue fullness in the same region (*white arrow*). (**d**) Axial PET/CT demonstrates increased abnormal FDG uptake in the region of mild soft-tissue fullness representing primary unsuspected squamous cell carcinoma of nasopharynx. (**e**) Axial PET of the neck at the level of mandibular angle demonstrates FDG uptake in bilateral level 2 cervical lymph nodes (*black arrows*). (**f**) Axial CT shows enlarged bilateral level 2 lymph nodes (*white arrows*). (**g**) Axial PET/CT demonstrates fusion imaging signifying malignant nature of enlarged lymph nodes (Reprinted from Shah GV, Wong KK, Gandhi D, Parmar H, Mukherji SK. Squamous Cell carcinoma: Initial Diagnosis and Staging with PET/CT. PET Clinics 2007;2(4):469–480. With permission from Elsevier)

local tumor site for local staging are provided by MRI. MRI, CT, and PET are similar for detection of abnormal and pathologic lymph nodes. However, in case of equivocal findings by MRI or CT, PET provides relevant information for determining the extent of surgical neck dissection. FDG-PET and CT complement each of the strengths, providing additional accuracy for staging head and neck cancer and make a notable impact on clinical decision-making. The application of ultrasonography and PET/MR may further assist clinicians in staging of tumors as these technologies are further developed and studied.

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Ultrasound Investigations in Head and Neck Cancer Patients

14

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Abstract

The wide availability, inexpensiveness and its nonionizing nature make ultrasound an ideal initial imaging investigation in patients with head and neck cancer. Its high sensitivity and specificity (when combined with a guided FNAC) makes it a useful tool for cervical lymph node staging and investigating thyroid and salivary gland tumours. Grey-scale ultrasound evaluates the internal architecture and local extent of superficially located head and neck cancers, and colour Doppler examines the tumour vascularity. Advances in elastography and contrast ultrasound further enhance the diagnostic capability of ultrasound. In addition, following treatment of head and neck cancer, ultrasound is a useful and safe tool for disease surveillance and assessment of treatment response.

Keywords

Ultrasound • Doppler • Elastography • Thyroid • Salivary gland • Lymph node • FNAC • Biopsy

14.1 Introduction

Ultrasound (US) has a well-recognized role in imaging of patients with head and neck cancer. Its nonionizing nature, high sensitivity and specificity (when combined with a guided FNAC) make it a useful tool for cervical lymph node staging and investigating thyroid and salivary gland tumours. In addition, US is superior to CT or MR in the resolution of superficial structures and provides detailed information of the internal architecture, vascular pattern and local extent of superficially located tumours (thyroid, superficial salivary glands and lymph nodes). Therefore, the major applications for ultrasound in the head and neck cancer include characterization of neck masses, guide FNAC/biopsy, evaluate nodal status to accurately stage cancer and follow-up patients post-operatively to exclude local or regional tumour recurrence [1].

Detailed sonographic appearance of all thyroid, salivary gland cancers, malignant lymph nodes and their benign mimics in the head and neck is beyond the scope of this chapter. The following paragraphs discuss the principles and practical application of US (+FNAC) in evaluating these sites in the head and neck.

14.2 Role of Ultrasound in Thyroid Cancer

Thyroid nodules pose a treatment dilemma as the prevalence of palpable nodules is 1–5 % in iodine-sufficient parts of the world [2, 3]. The increasing use of US in the head and neck compounds this as high-resolution US detects thyroid nodules in 19–67 % of randomly selected individuals [4]. The spectrum of these thyroid nodules ranges from the common multinodular change to malignant thyroid tumours that occur in 5–10 % depending on age, gender, previous radiation his-

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tory and other factors [5, 6]. It is therefore necessary to identify the small group of patients with malignant thyroid disease so that prompt and appropriate treatment can be instituted while avoiding unnecessary imaging and treatment in the vast majority with benign nodules.

The management guidelines for patients with thyroid nodules and differentiated thyroid cancer are well established [7]. The mainstay of initial investigations include US (grey scale (GS) and power Doppler sonography (PDS)), FNAC and radionuclide thyroid scan. In patients with thyroid nodule >1–1.5 cm, an initial TSH level is obtained. If the TSH is subnormal a radionuclide scan is indicated to document whether the nodule is functioning. However, if the TSH is not suppressed, a thyroid ultrasound is indicated. This is often combined with a FNAC and nodules FNAed based on their sonographic appearance rather than their size, as the US characteristics such as echogenicity, microcalcifications and vascularity are better than nodule size in predicting malignancy [8, 9].

Sonographic features that help to *differentiate malignant from benign* tumours:

- *Echogenicity* (Figs. 14.1, 14.2 and 14.3): Hypoechoic thyroid nodules have an increased risk of malignancy. It represents microfollicular structure on histology, compared to macrofollicular lesions which tend to be isoechoic/hyperechoic [10]. The risk of malignancy is 4 % when the nodule is hyperechoic and this increases to 26 % with hypoechoic nodules. However, echogenicity alone is a poor predicator of malignancy, specificity 49 % and positive predictive value 40 % [11].
- *Margins* (Fig. 14.4): Malignant nodules, are invasive by nature and tend to have irregular margins.
- *Halo* (Fig. 14.3): Benign hyperplastic nodules are slow growing, lack a true capsule and displace adjacent vascularity. Therefore they demonstrate a "vascular halo" on colour Doppler. Thyroid cancer may demonstrate an "avascular halo" on Doppler which represents the fibrous capsule around the tumour [12]. The absence of a halo has a specificity of 77 % and sensitivity of 67 % in predicting malignancy [13].
- *Multinodularity*: high-resolution US is far more sensitive than palpation in picking up small thyroid nodules. However, multinodularity does not bestow benignity on a thyroid nodule as patients with multiple thyroid nodules have the same risk of malignancy as those with solitary thyroid nodules [8, 14].
- *Cystic change* (Figs. 14.5 and 14.6): true cysts of the thyroid gland are rare, and most "cystic" nodules seen on US are complex thyroid nodules with haemorrhage and necrosis. These complex nodules are predominantly cystic with internal septa and a "solid" component/debris which is often avascular and possibly represents blood clots. Pure cystic nodules have no risk of malignancy, and complex, non-calcified nodules harbour a 3 % risk of malignancy [15]. The presence of a comet tail artefact is

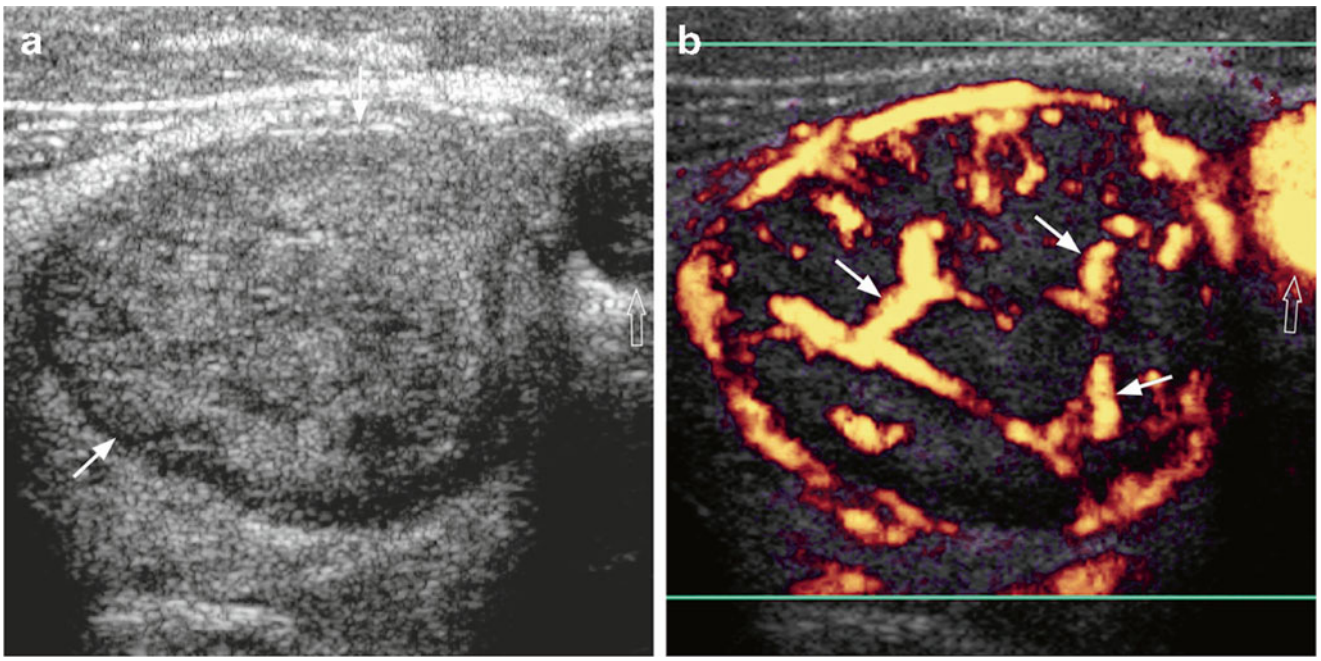

Fig. 14.1 Transverse GS US (**a**) shows a solid, ill-defined, hypoechoic thyroid nodule (*arrow*). The corresponding PDS (**b**) shows marked intranodular vascularity (*arrows*). The overall appearances are suspicious of malignancy. Histology confirmed a follicular carcinoma. *Open arrow*: CCA

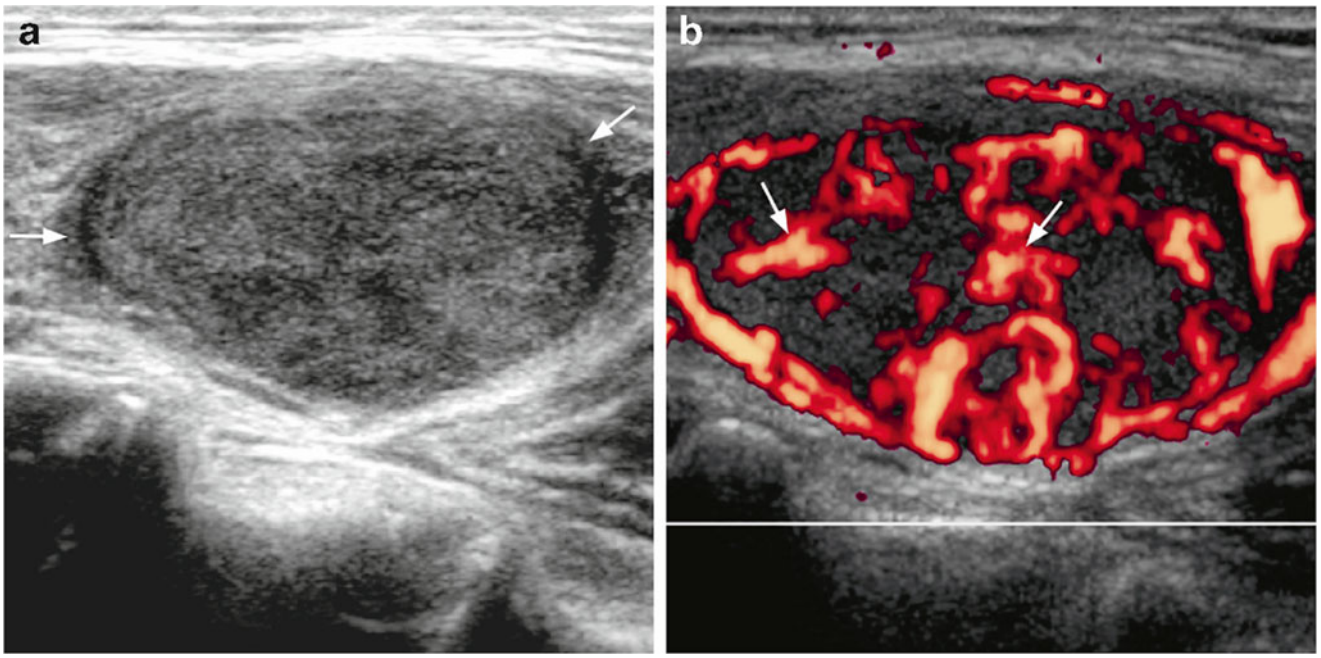

Fig. 14.2 Longitudinal GS US (**a**) shows a solid, fairly well-defined, hypoechoic, non-calcified thyroid nodule (*arrows*). Corresponding PDS (**b**) shows marked intra-tumoural vascularity (*arrows*). The combination of GS US and PDS suggest a malignant lesion which was confirmed at surgery

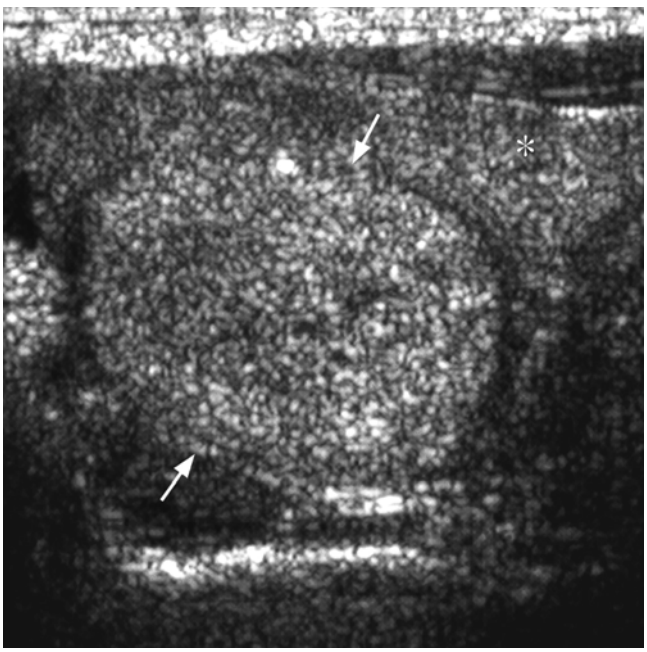

Fig. 14.3 Transverse GS US shows a well-defined, partially haloed, solid, homogeneous, non-calcified thyroid nodule (*arrows*). Note its echogenicity is similar to the adjacent thyroid (*asterisk*). Hypoechoic solid nodules are suspicious for malignancy. The incidence of malignancy (*downward arrow*) as the echogenicity (*upward arrow*)

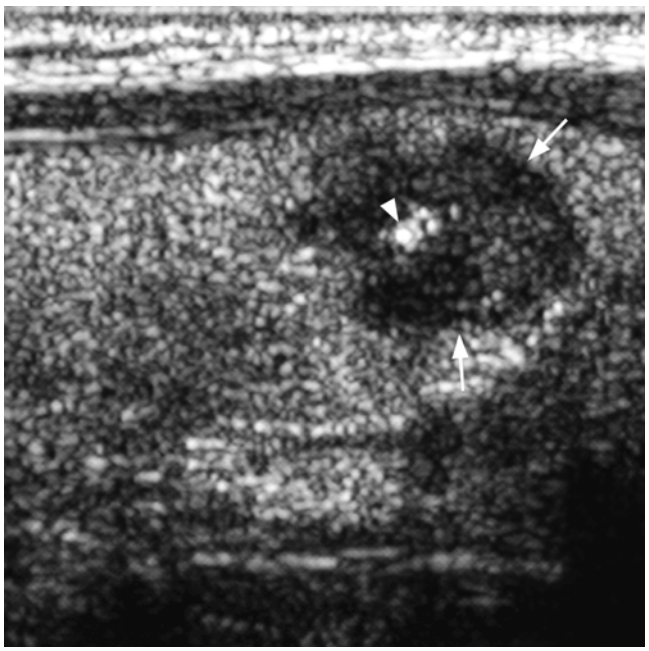

Fig. 14.4 Longitudinal GS US shows a solid, ill-defined, hypoechoic thyroid nodule (*arrows*) with focal intranodular punctate calcification/microcalcification (*arrowhead*). Typical appearances of a papillary carcinoma

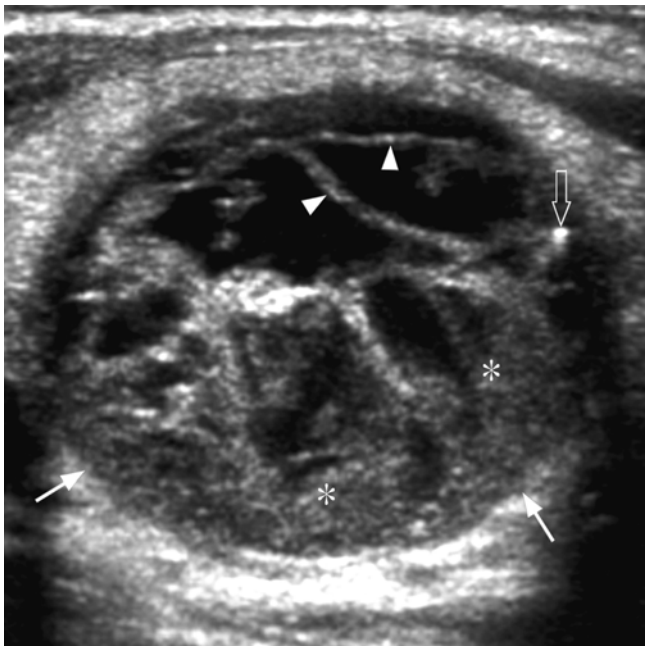

Fig. 14.5 Transverse GS US shows a heterogeneous cystic nodule (*arrows*) with intranodular septa (*arrowheads*), debris (*asterisk*) and comet tail artefact (*open arrow*) suggestive of colloid nodule. The debris is usually avascular on Doppler and is suggestive of intranodular haemorrhage

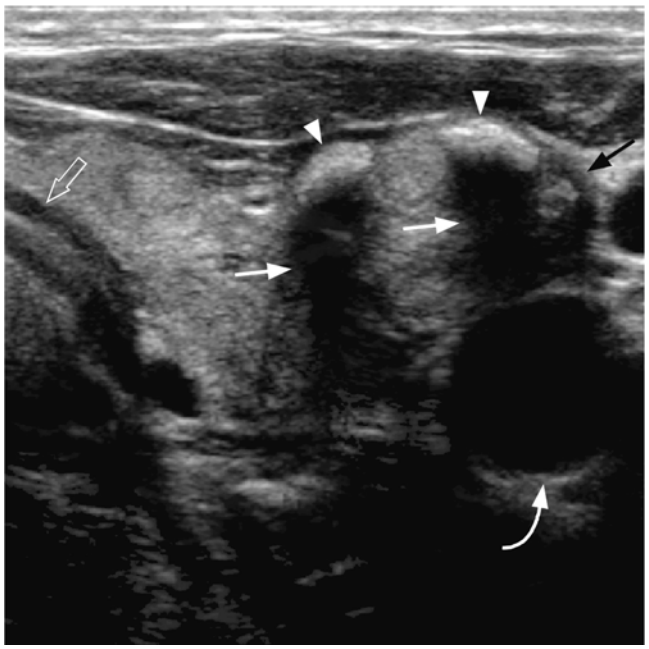

Fig. 14.7 Transverse GS US shows a thyroid nodule (*black arrow*) with focal areas of dense calcifications (*arrowheads*) with posterior shadowing (*white arrows*) suggesting benignity. *Curved arrow*: CCA, *open arrow*: Trachea

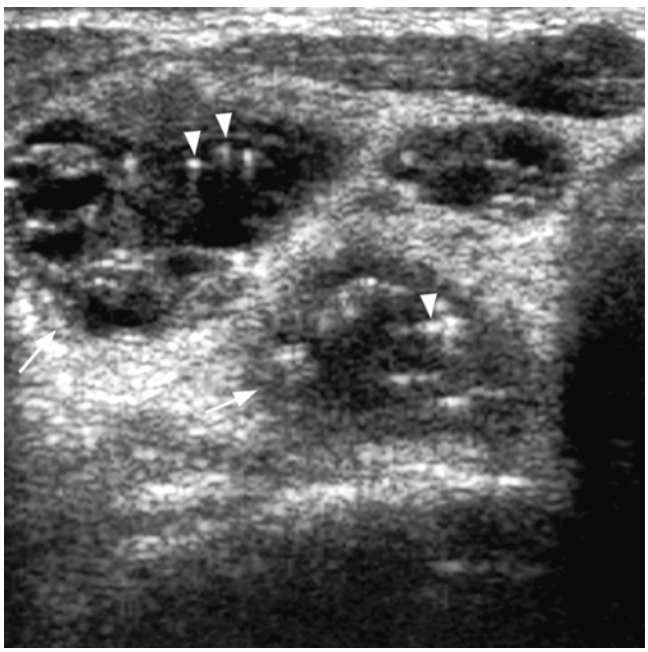

Fig. 14.6 Transverse GS US shows multiple, septated, heterogeneous nodules (*arrows*) with cystic change and comet tail artefacts (*arrowheads*) suggestive of colloid nodules in multinodular thyroid

a good indicator of benignity and reflects condensed colloid within the nodule [16].

– *Calcification* (Figs. 14.4 and 14.7): *fine punctate calcification* (microcalcification, <1 mm) which represents aggregates of psammoma bodies is seen in 25–40 % of patients with papillary carcinoma [17]. As a sole predictor of malignancy it has an accuracy of 76 %, specificity of 93 %, positive predictive value of 70 % [11] and also has good interobserver variability [18]. *Coarse, dense shadowing calcifications* are a reflection of fibrosis, necrosis and tissue degeneration. Although often seen with benign nodules their presence with/without microcalcifications, in the centre of a hypoechoic nodule are worrisome for malignancy [15, 19]. *Curvilinear or "egg-shell" calcification* was once considered as benign calcifications. However, interrupted rim calcification raises the possibility of malignancy [20].
– *Vascularity* (Figs. 14.1b and 14.2b): Most benign nodules have absent intranodular vascularity and most malignancies have intranodular flow [8, 21]. However, as the negative predictive value is 88 %, a negative study does not eliminate the need for a biopsy [21, 22]. It has been reported that follicular nodules with no intranodular flow have a 3 % probability of being malignant, compared to 15–20 % likelihood in unselected follicular nodules. Vascular follicular nodules have a 50 % probability of being malignant [23].
– *Shape*: It has been reported that anterior-posterior to transverse diameter (A/T ratio) ≥1 (taller than wide nodule) has a sensitivity of 84 % and specificity of 82 % in the detection of a malignant nodule.
– *Elastography*: is a technique that is beginning to be routinely used in the evaluation of thyroid nodules. It estimates the

tissue stiffness on application of external force. Malignant nodules tend to be stiffer than benign nodules with increased tissue stiffness seen in malignant nodules compared to benign nodules [22, 24, 25]. Previous reports have indicated that high elasticity scores were highly predictive of malignancy with a sensitivity of 97 %, specificity 100 %, positive predictive value of 100 % and negative predictive value of 98 % [24]. Despite generally promising results, considerably worse accuracy has also been reported in a small but significant number of reports [26].

– *Associated lymphadenopathy*: US examination for thyroid nodules must include a detailed examination of the neck for lymph nodes as they are frequently seen in thyroid cancers and may alter management. Although most patients with thyroid cancer present with a thyroid nodule, 15–30 % present clinically with an enlarged palpable node [27]. Thirty to forty percent of patients with papillary carcinoma have nodal metastases at presentation [28–30]. Follicular carcinomas show a lower incidence of cervical nodal metastases in the range of 10–15 % [31]. Patients with medullary carcinoma, anaplastic carcinoma, lymphoma and thyroid metastases also have a high incidence of adjacent nodal involvement [17, 32]. Nodes from thyroid cancers commonly involve the pretracheal, paratracheal, nodes and those along the internal jugular vein. Metastatic nodes from papillary carcinoma have characteristic US appearances [33]: hyperechoic to adjacent muscle (80 %), intranodal cystic necrosis (25 %), and 50 % show punctate calcification (reflecting psammoma bodies). The metastatic nodes often resemble the primary thyroid tumour. Metastatic nodes from medullary cancer may also show intranodal calcification, but the nodes are usually hypoechoic and the calcification dense shadowing in type (reflecting amyloid deposition).
– *Extrathyroid invasion*: Although US is able to evaluate extrathyroid invasion, CT and MR better evaluate the spread of thyroid cancer to the larynx, trachea and involvement of adjacent vessels [34]. Shadowing from the trachea makes US suboptimal in evaluation pretracheal, paratracheal, laryngeal and tracheal involvement. The above limitation also applies to sonographic evaluation of malignant nodes at these sites.

In evaluating the above sonographic features of thyroid nodules, one must note that none of them alone are accurate in predicting malignancy. It is well accepted that US is a reliable predictor when multiple signs are present in the same nodule [13]. However, as the predictive value increases, its sensitivity decreases [13]. The useful combinations to predict malignancy include:

– Microcalcification and solid nature of the nodule [11] showed the highest accuracy (77 %), specificity (96 %), positive predictive value (75 %) but a low sensitivity (30 %).
– Absent halo combined with microcalcification had a specificity of 93 % but a sensitivity of 27 % [13].
– Combination of absent halo, intranodular flow and microcalcification had a specificity of 97 % and a sensitivity of 16 % [13].

14.3 Role of Ultrasound in Recurrent Thyroid Disease

The evaluation of a patient for recurrent tumour includes clinical examination, biochemical parameters and imaging findings. The imaging modalities include US, CT, MR and PET/CT. The post-operative distortion of anatomy makes US difficult but the superficial location of the recurrent tumours makes US (+FNAC) a useful examination as it clearly evaluates the thyroid bed and the neck for lymphadenopathy. Post-operative suture granulomas must not be mistaken for recurrent tumours in the thyroid bed. The granulomas are usually solid, hypoechoic, avascular/hypovascular and may show dense shadowing foci within (sutures). A guided FNAC quickly establishes the nature of the lesion.

CT and MR are easier to perform and have the added advantage that it is able to evaluate regional recurrence and any disease in the chest/mediastinum.

14.4 Role of Ultrasound in Salivary Gland Cancer

Imaging plays an important role in the evaluation of these tumours and the various modalities have complementary roles. In many cases, US may suffice, in others it may be necessary to follow it with a CT/MR, and in some the role of US may be restricted to guiding a biopsy. Irrespective of the modality used, imaging appearances are not a substitute for tissue diagnosis.

The following *limitations of US* must be borne in mind when evaluating salivary gland cancers [35]:

– US does not adequately visualize the deep lobe of the parotid gland and the minor salivary glands. It is therefore unable to evaluate tumours in the deep lobe of the parotid gland and minor salivary gland tumours in the oral cavity, pharynx and tracheo-bronchial tree.
– US does not evaluate deep tissue involvement, perineural spread, bone invasion and presence of nodes in the oropharyngeal/retropharyngeal regions.
– US cannot identify the course of the intraparotid portion of the facial nerve. However, its location can be inferred by identifying the intraparotid portion of the external

carotid artery and the retromandibular vein which run alongside the facial nerve.

Despite the above limitations, in our experience:
US is the ideal *initial* investigation for:

- Salivary gland mass with no obvious signs and symptoms suggestive of malignancy.
- Masses in the superficial lobe of the parotid gland (where most parotid tumours are located and are benign) and submandibular and sublingual tumours.

In this group of patients, the high resolution of US helps to characterize tumours, evaluate associated lymphadenopathy and establish the diagnosis by a guided FNAC (sensitivity 88–93 %, specificity 75–99 %) [36–38]. If the tissue diagnosis suggests a malignancy, an MR helps to evaluate deep extension of the tumour, perineural spread, bone infiltration and the presence of deep-seated nodes.

MR is the *initial* investigation of choice for:

- Salivary gland mass with signs and symptoms suggestive of a malignant salivary gland tumour (short duration history, rapid enlargement of tumour, progressive facial paralysis, pain, trismus or cranial nerve palsies associated with a salivary mass)
- Tumours arising from the deep lobe of the parotid gland or large tumours bulging into the oral cavity

In this group of patients, the use of US is restricted to its assistance in image-guided biopsy. Compared to CT, MRI better delineates perineural spread, skull base involvement, parapharyngeal involvement and minor salivary gland cancers [39]. However, in centres with no access to MR, CT may be used as it appears to have the same diagnostic value for salivary gland tumours [40].

Sonographic features that help to *differentiate malignant from benign* tumours:

- *Edge* (Figs. 14.8 and 14.9): Malignant tumours have ill-defined edges and are irregular in outline compared to benign salivary gland tumours.
- *Internal architecture*: Malignant tumours have a heterogeneous internal architecture with focal areas of haemorrhage and necrosis (Fig. 14.10). Benign tumours such as pleomorphic adenomas (Fig. 14.11) tend to be more homogeneous and show posterior enhancement, whereas Warthin's tumour (Fig. 14.12) may be heterogeneous with areas of septation and cystic change. Large (>3 cm) pleomorphic adenomas may also demonstrate haemorrhage and cystic change. The presence of calcification (Fig. 14.13) within benign mixed tumours indicates chronicity of the lesion. 9.5 % of malignant transformations are seen in patients where the tumour has been present over 15 years [41].
- *Tumour extent*: Malignant tumours may be associated with extraglandular spread and invasion of the overlying muscle, subcutaneous tissues and skin.
- *Tumour vascularity* (Fig. 14.9b): Malignant tumours are more vascular with a resistive index (RI) >0.8 and pulsatility index (PI) >1.8 [42] and may demonstrate a hilar vascular pattern compared to pleomorphic adenoma which has peripheral vascularity [43].
- *Lymphadenopathy*: the presence of associated malignant looking nodes in the known draining sites of salivary gland cancer is another clue towards the malignant nature of a salivary mass.
- *Elastography*: preliminary data from a few small scale pilot studies suggests that ultrasound elastography is suboptimal for detection of malignancy in the salivary gland [26].

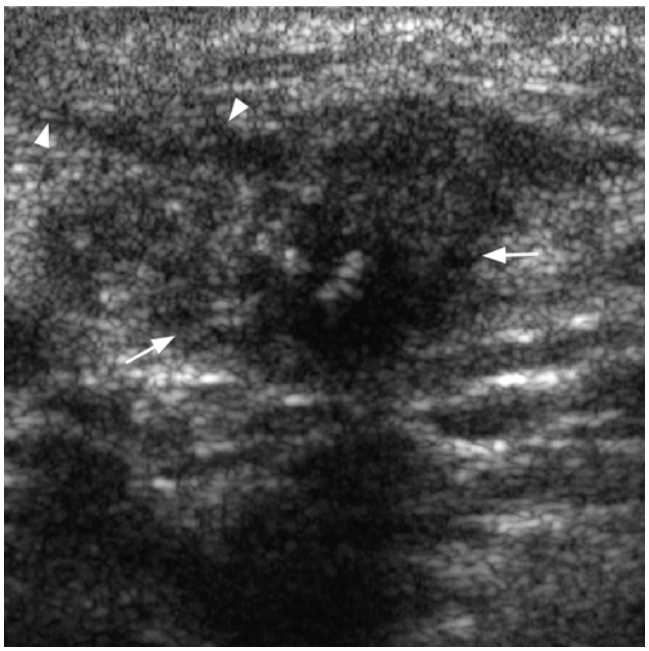

Fig. 14.8 Transverse GS US shows a solid, hypoechoic, ill-defined malignant submandibular tumour (*arrows*). Note the extracapsular extension into subcutaneous soft tissues (*arrowheads*)

However one must note that:

- Although US may help to differentiate benign from malignant lesions it is unable to distinguish between the various types of malignant tumours.
- Sonographic appearances of low-grade malignant tumours simulate benign salivary gland lesions, and guided FNAC may be indicated for some benign-looking salivary tumours to rule out a low-grade carcinoma.

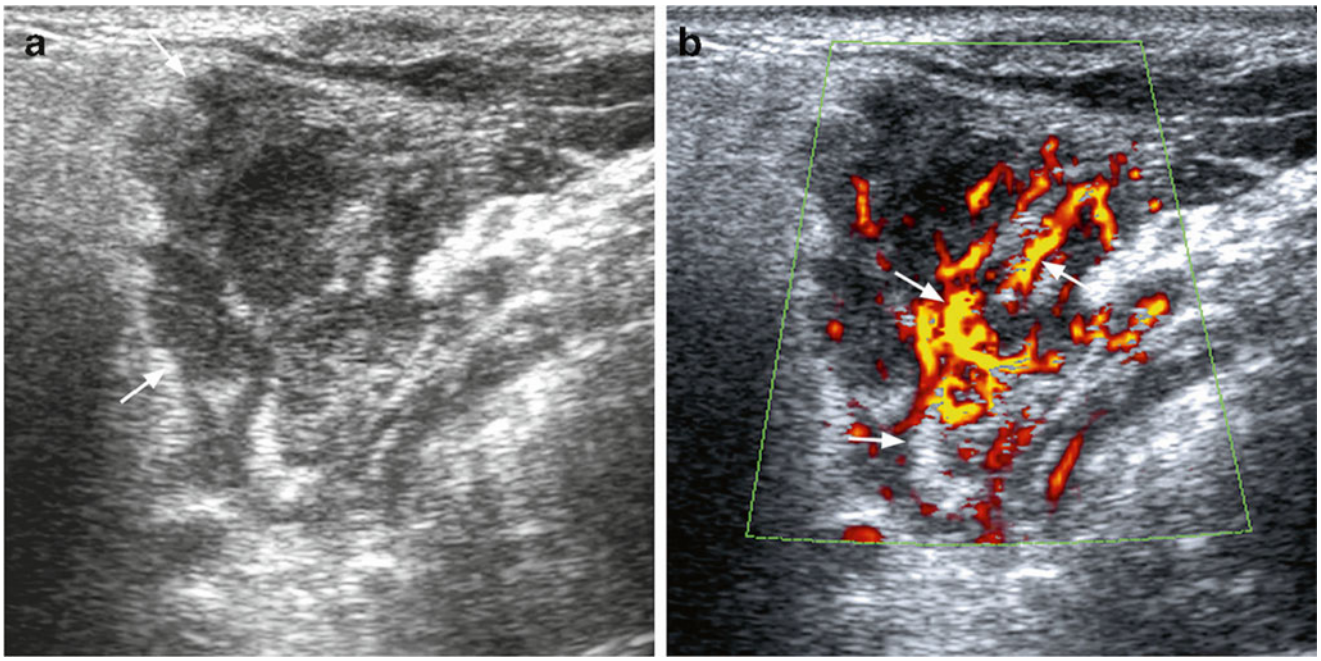

Fig. 14.9 Transverse GS US (**a**) shows typical features of a malignant tumour (*arrows*). Note its ill-defined edges and heterogeneous internal architecture. Corresponding PDS (**b**) shows marked intra-tumoural vascularity (*arrows*)

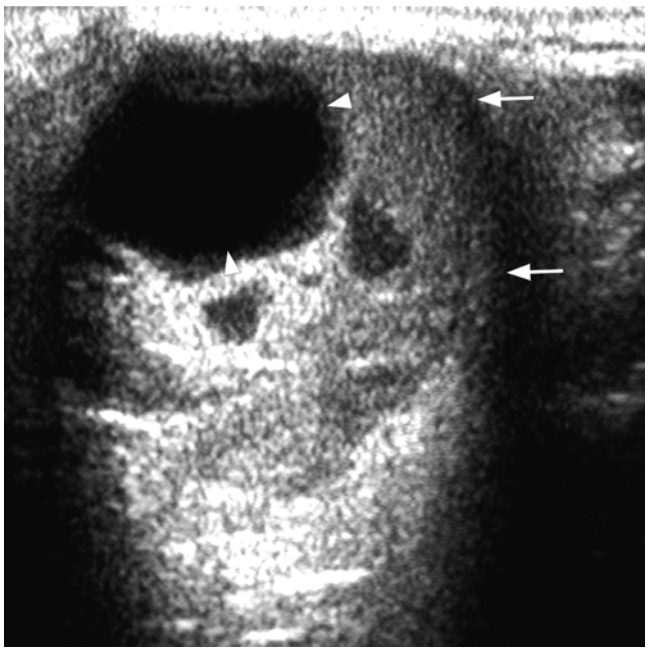

Fig. 14.10 Transverse GS US shows an ill-defined, heterogeneous parotid mass (*arrows*) with intra-tumoural necrosis (*arrowheads*). The US appearances are suspicious of a malignant tumour, mucoepidermoid carcinoma confirmed at surgery

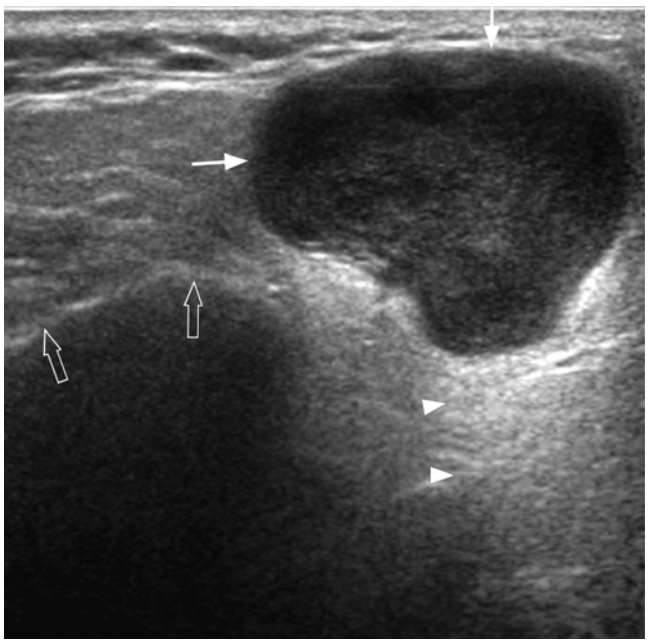

Fig. 14.11 Transverse GS US shows a well-defined, solid, lobulated, hypoechoic nodule (*arrows*) with posterior enhancement (*arrowheads*). The US appearances are typical of a pleomorphic adenoma. *Open arrows*: mandible

14.5 Role of Ultrasound in Recurrent Salivary Gland Tumours

Distortion of anatomy and scarring often makes ultrasound difficult in the post-operative state. However, due to the superficial location of these recurrent lesions, US again is an ideal investigation, and when combined with FNAC, it provides the information necessary for treatment planning.

Benign tumours: pleomorphic adenomas may recur following surgery with a recurrence rate of 1–50 % [44].

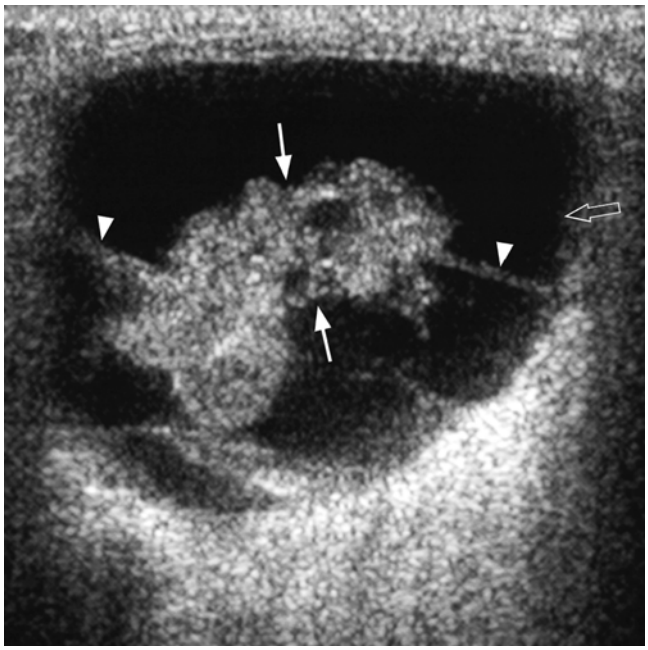

Fig. 14.12 Transverse GS US shows a predominantly cystic tumour (*open arrow*) with internal septa (*arrowheads*) and a "solid" component (*arrows*) in the superficial parotid. A similar smaller tumour was seen in the contralateral parotid. FNAC confirmed Warthin's tumour

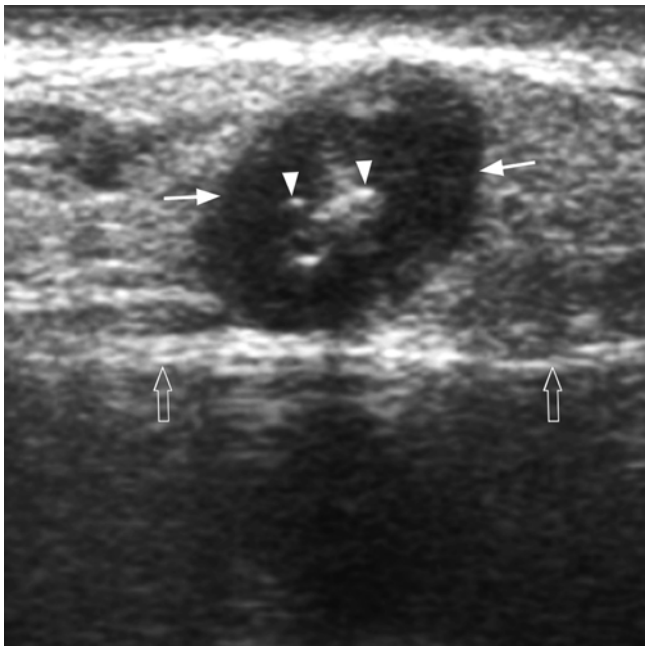

Fig. 14.13 Longitudinal GS US shows a well-defined, solid, hypoechoic, parotid pleomorphic adenoma (*arrows*). Note intratumoural calcification (*arrowheads*), suggesting a long-standing lesion. *Open arrows*: mandible

The recurrences are frequently localized to the site of surgery and may be multiple. US readily evaluates these tumours, and the recurrent "nodules" are well defined and homogeneous with posterior enhancement and peripheral vascularity.

Malignant tumours: MR is the investigation of choice for evaluating recurrent disease as in such cases the previous surgery may have been extensive with significant distortion of anatomy. MR clearly evaluates the operative site and extent of invasion of any recurrent tumour. The role of ultrasound is often restricted to guiding a confirmatory biopsy.

14.6 Role of Ultrasound in Neck Node Evaluation

The presence of metastatic nodes in the neck in a patient with HN cancer affects prognosis and treatment options [45, 46]. High-resolution ultrasound, with its excellent spatial resolution, ease of dynamic multiplanar imaging, wide availability and lack of ionizing radiation, is a recognized modality for assessment of cervical lymph node metastasis [47–49]. It is superior to CT and MR in its resolution, ability to show vascular characteristics and the ease to combine with FNAC. The use of Doppler has clearly improved the specificity of ultrasound [50–52] and US + FNAC has a sensitivity of 97 % and specificity 93 % [53].

In routine clinical ultrasound of neck nodes, the sonographic features assessed are divided into grey-scale features and Doppler parameters. The grey-scale features include nodal size, shape, border, internal architecture (echogenicity, nodal hilum, calcification, intranodal necrosis, intranodal reticulation), nodal matting and associated soft tissue oedema. The Doppler parameters include the presence and distribution of intranodal vessels and intranodal vascular resistance.

Sonographic features (grey scale and Doppler) that help to differentiate *malignant from benign* nodes:

- *Size*: Nodal size alone cannot differentiate malignant from benign nodes. Nodal size is relevant in (a) increase in nodal size on serial examination in a patient with known HN carcinoma is suspicious for metastasis and (b) serial reduction in size is useful in evaluating patients response to treatment [54].
- *Shape* (Figs. 14.14 and 14.15): Normal/benign nodes are elliptical whereas metastatic nodes tend to be round [46, 47, 55]. Similarly, eccentric cortical hypertrophy (due to focal tumour infiltration) is another useful sign to identify nodal metastasis [47].
- *Nodal border* (Figs. 14.14, 14.15 and 14.16): malignant nodes are associated with sharp borders whereas benign nodes have unsharp borders [56]. However, ill-defined border in a metastatic node indicates extracapsular spread [55]. Nodes that have previously received radiotherapy may also have ill-defined borders (Fig. 14.17).

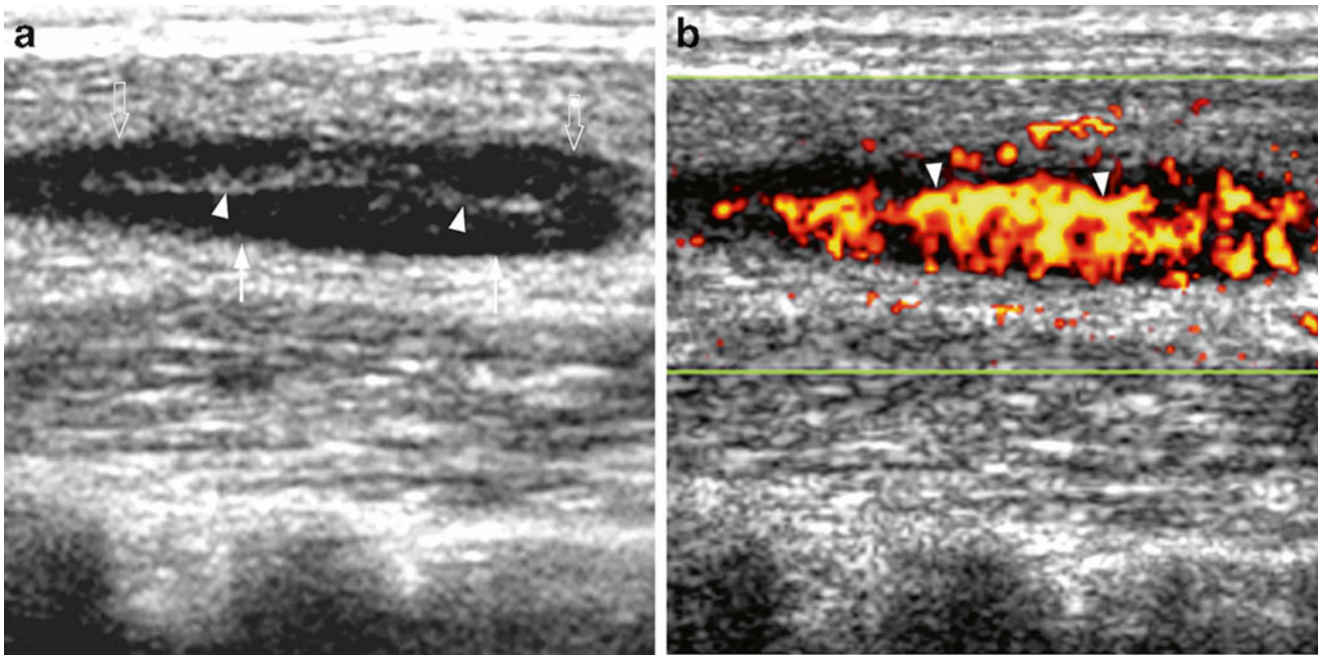

Fig. 14.14 Longitudinal GS US (**a**) shows an elliptical hypoechoic reactive lymph node (*arrows*). Note the ill-defined border (*open arrows*) and the linear echogenic hilum (*arrowheads*). Corresponding PDS (**b**) shows prominent hilar vascularity (*arrowheads*)

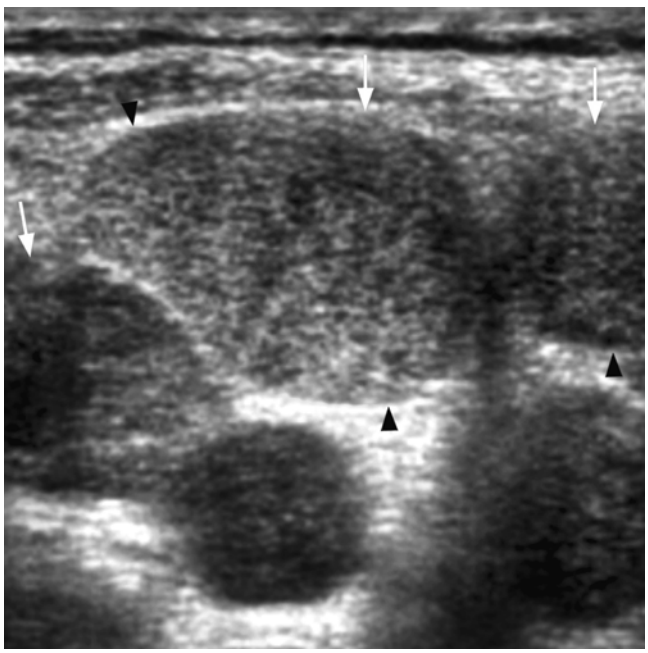

Fig. 14.15 Transverse GS US shows multiple, solid, hypoechoic metastatic nodes (*arrows*). Note their sharp borders (*arrowheads*) and the absence of the echogenic hilum

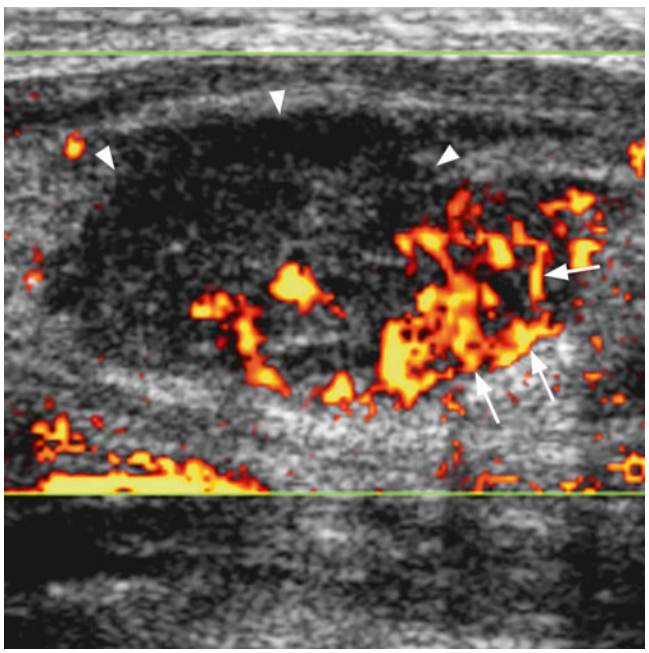

Fig. 14.16 PDS of a metastatic node shows abnormal peripheral vascularity (*arrows*). Note the ill-defined edges anteriorly (*arrowheads*) suggesting extracapsular spread

– *Echogenicity*: Metastatic nodes are usually hypoechoic in relation to adjacent muscle [50, 55] except metastatic nodes from papillary thyroid carcinoma which are often hyperechoic relative to muscle [33].

– *Nodal Hilum*: In a normal neck, most nodes >5 mm will demonstrate the presence of an echogenic hilum [57]. The presence of such an echogenic hilum (Fig. 14.14a) was thought to indicate benignity [46]. However, other studies

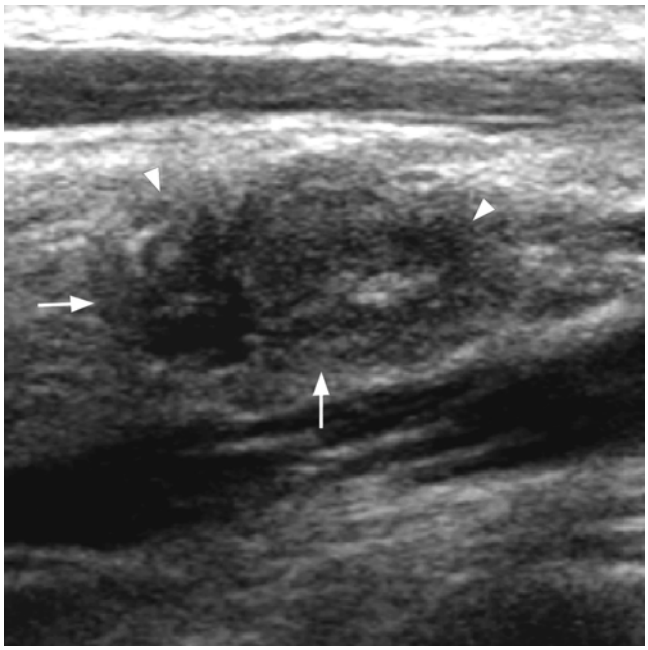

Fig. 14.17 Longitudinal GS US of a metastatic node (*arrows*) previously treated with radiotherapy. Note the diffuse, ill-defined borders (*arrowheads*) of the lymph node. The presence of such ill-defined borders in a metastatic node with no previous history of radiotherapy would indicate extracapsular spread

have shown that the echogenic hilum may also be seen in metastatic nodes [58].

- *Calcification* (Fig. 14.18): Metastatic nodes from papillary carcinoma tend to show punctate calcification, with faint shadowing on high-resolution ultrasound [33]. Calcification is also seen in a small proportion of metastatic nodes from medullary carcinoma and nodes treated with chemotherapy or radiotherapy [33, 59].
- *Intranodal necrosis* (Fig. 14.19): irrespective of nodal size the presence of intranodal necrosis indicates abnormality [59]. It is seen in metastatic and tuberculous nodes in the neck [55, 59].
- *Intranodal reticulation* (Fig. 14.20): It was previously reported that lymphomatous nodes have a pseudocystic appearance, i.e. solid, hypoechoic with posterior enhancement, especially in non-Hodgkins lymphoma [60, 61]. However, with the advent of newer high-resolution ultrasound, this pseudocystic appearance in non-Hodgkins lymphoma is not often seen, and an intranodal micronodular reticulated pattern is commonly found in lymphomatous nodes [62].
- *Nodal matting and soft tissue oedema*: are commonly seen in tuberculous neck nodes [55]. However, these features may also be seen in metastatic nodes with adjacent soft tissue infiltration and in patients who have received radiation therapy of the neck [63, 64].

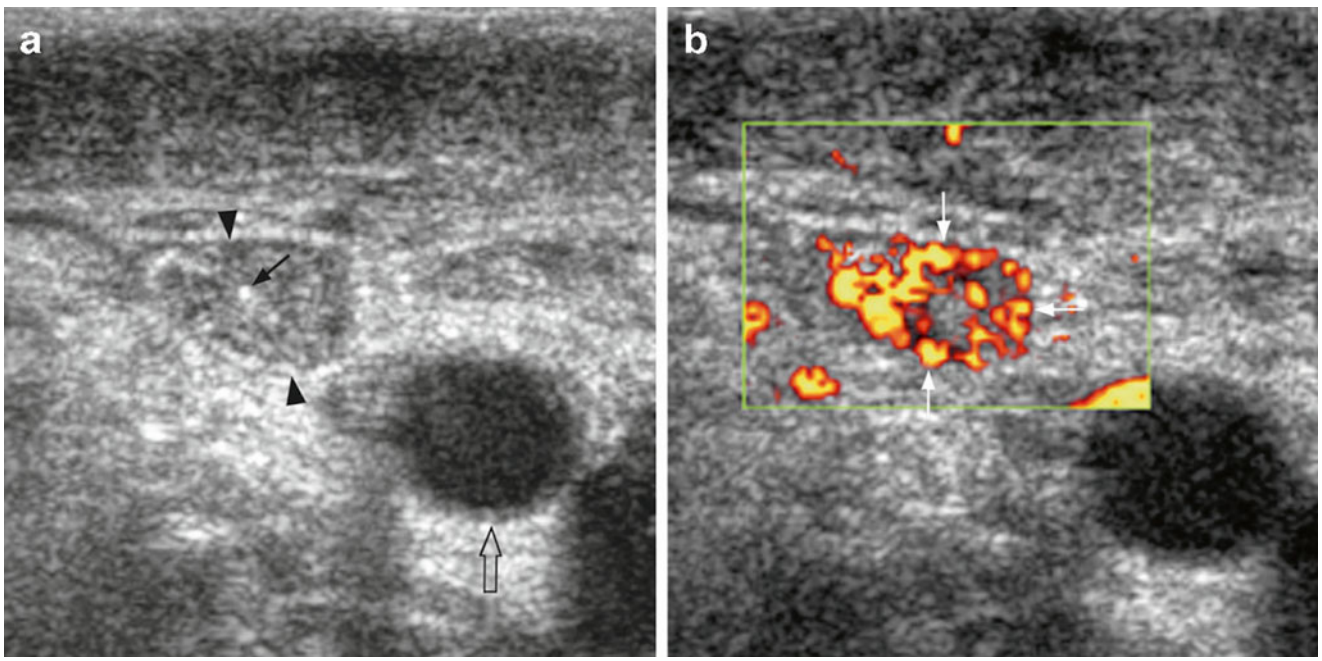

Fig. 14.18 Transverse GS US (**a**) shows a small, hyperechoic, solid node (*arrowheads*) with focal punctate calcification (*arrow*), adjacent to the common carotid artery (*open arrow*). The sonographic appearances are typical for metastatic lymph node from papillary carcinoma. Corresponding PDS (**b**) shows profuse, abnormal peripheral vascularity (*arrows*), typical of a metastatic node

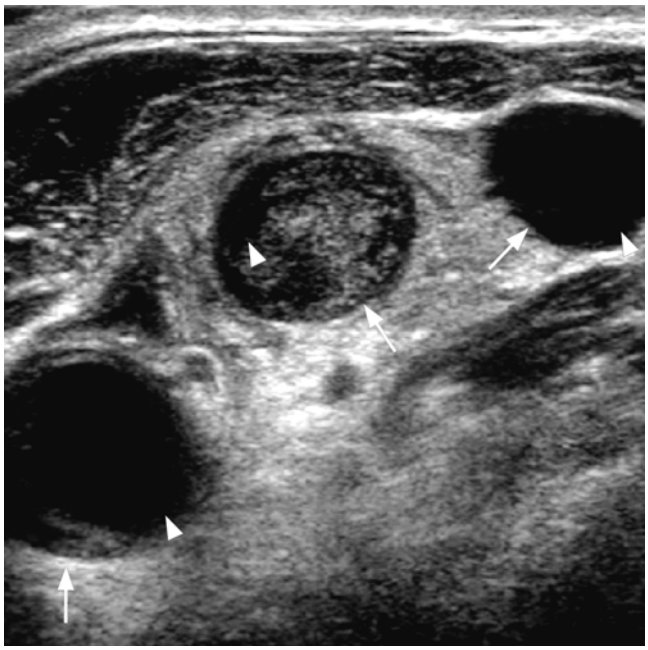

Fig. 14.19 Transverse GS US shows multiple, round metastatic nodes (*arrows*) from HN SCCa. Note the cystic change (*arrowheads*) within the nodes. Cystic change within a node, irrespective of nodal size indicates abnormality

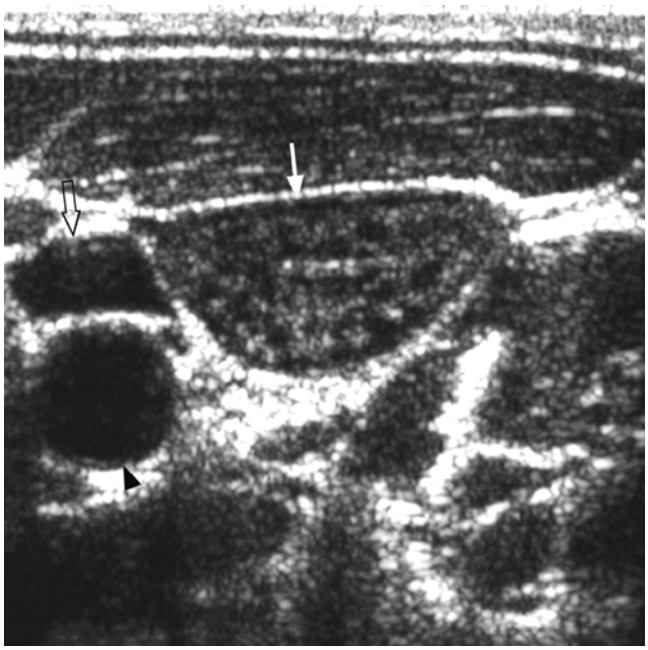

Fig. 14.20 Transverse GS US shows a lymphomatous (*arrow*) node with a typical reticulated/micronodular echopattern. *Arrowhead* identifies CCA and *open arrow* the IJV

– *Intranodal vascular distribution*: evaluation of the vascular pattern within nodes is a reliable predictor of abnormality [65]. On Doppler, most normal nodes >5 mm will demonstrate the presence of hilar vascularity [57]. Normal or reactive nodes may be apparently avascular or demonstrate hilar vessels (Fig. 14.14b) [50, 66, 67]. However, metastatic nodes demonstrate peripheral or hilar and peripheral (mixed) vascularity (Figs. 14.16, 14.18b and 14.21) [68, 69].
– Therefore the presence of peripheral intranodal vessels should strongly raise the possibility of metastasis in a patient with known HN carcinoma. This abnormal vascularity is related to angiogenesis within metastatic nodes [66].
– *Intranodal vascular resistance*: Using spectral Doppler one can estimate intravascular resistance within small vessels in the node. This is measured as resistive index (RI) and pulsatility index (PI). However, in routine clinical practice such measurements take a lot of time (guided FNAC is much quicker) and their overall values in differentiating benign from malignant nodes is unclear. In our experience, the optimum cut-off values for RI and PI are 0.7 and 1.4 with a sensitivity of 86 % and 80 % and specificity of 70 % and 86 %, respectively [69].

In addition to the above criteria, the *number of nodes* in the known draining site of the tumour may also help in predicting their nature. It has been suggested that one should have a high degree of suspicion if there are >3 equivocal/suspicious nodes in the draining site of the tumour, with specific measurements for minimal axial diameter of the nodes at these sites [70, 71].

One must note that for sonographic evaluation of neck nodes the operator must be familiar with anatomy and pay

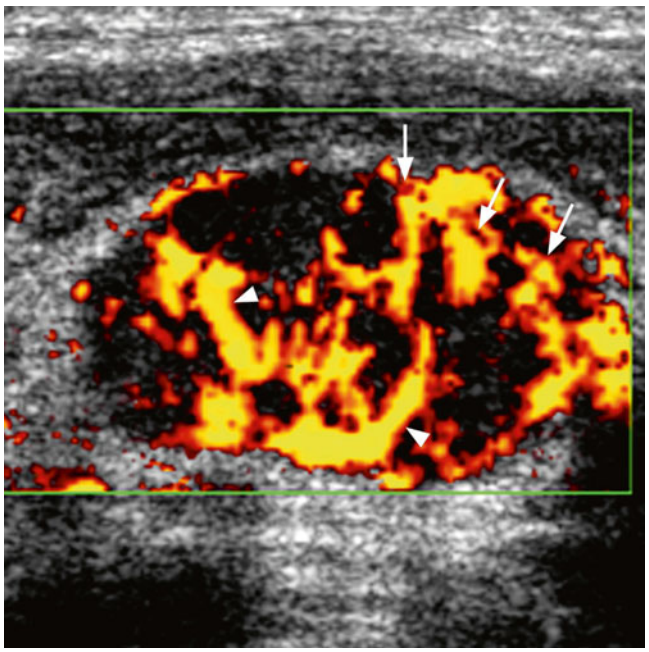

Fig. 14.21 PDS of a metastatic node shows abnormal mixed intranodal vascularity, hilar (*arrowhead*) and peripheral (*arrows*)

meticulous attention to detail as many of the nodes and vessels are small. None of the criterion used alone may accurately reflect the nature of the node, and it is a combination of sonographic features that helps in predicting the pathology. In clinical practice, the easiest criteria to evaluate are nodal shape, intranodal necrosis, presence/absence of echogenic hilum, punctate calcification and abnormal vascularity. These signs in summation are fairly accurate in predicting the nature of the node and at the same time repeatable and not time consuming.

To date, a small number of pilot studies evaluated elastography for detection of malignancy in the cervical node. The overall preliminary evidence suggests that elastography may be useful to differentiate between benign and malignant lymph node although further research is required [26].

14.7 Contrast Enhanced Ultrasound of Lymph Nodes

Contrast enhanced ultrasound demonstrates more intranodal vessels allowing for better visualization and characterization of these vessels [72, 73]. In addition, it provides objective time-dependent enhancement curves which help to identify the nature of the nodes and better evaluate nodal parenchymal perfusion [73]. We have used contrast to evaluate treatment response to patients with lymphoma and showed a delay to peak enhancement following treatment [74, 75]. However, the change in the magnitude of peak enhancement was variable after treatment with some post-treatment nodes enhancing more than the others. Its use in routine clinical practice is still under consideration.

14.8 Role of Ultrasound in Evaluating Post-treatment Nodes

Following chemotherapy or radiation therapy, it may not always be possible to predict the nature of residual nodes using US. However, in our experience, some features that predict good response to treatment are:

- Serial reduction in size of node on treatment
- Serial change in shape of node from round to elliptical
- Reappearance of the echogenic hilum in nodes with absent hilum prior to treatment
- Prompt reduction in intranodal vascularity [76]

14.9 Conclusion

Despite its limitation in assessing deep-seated lesions, ultrasound, combined with FNAC, plays an important role in imaging patients with thyroid and salivary gland cancer and metastatic neck nodes. It is quick, non-invasive, office-based procedure (with a short learning curve) and provides the clinician with key information (diagnosis, extent of local and distant disease [77]) necessary to comprehensively manage a patient with head and neck cancer.

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Sentinel Node Biopsy

15

Oliver J. Smith, Lee W.T. Alkureishi, and Gary L. Ross

Abstract

The presence of cervical lymph node metastases remains one of the most important prognostic factors for various solid tumours of the head and neck, including melanoma, squamous cell carcinoma and Merkel cell carcinoma. In patients with clinically evident neck involvement, the regional lymphatics clearly require directed treatment, and this may involve therapeutic neck dissection or radiotherapy. However, the decision whether or not to electively treat patients with clinically uninvolved cervical lymphatics is usually less clear-cut. On the one hand, elective neck dissection simultaneously allows for accurate pathologic neck staging and definitive surgical management of patients found to harbour occult metastatic disease. On the other hand, the majority of patients with clinically negative necks do not harbour occult disease and would therefore be overtreated by an elective neck dissection. The significant morbidity associated with neck dissection means that this is a real concern, and efforts to minimise the extent of surgical intervention while maintaining oncologic safety are ongoing.

The radical en bloc cervical lymph node dissections introduced at the start of the twentieth century have largely been surpassed by more focused surgical procedures, including the modified radical neck dissection (MRND) and, more recently, selective neck dissection (SND). The operative morbidity of MRND and SND procedures compares favourably with more extensive dissections, though it remains significant. Sentinel lymph node biopsy (SLNB) represents an extension of this principle; by super-selecting the small subset of lymph nodes most likely to harbour disease, the extent of surgical intervention can be further minimised without adversely affecting diagnostic accuracy. The sentinel node concept states that tumour spread occurs in a stepwise progression from the primary tumour to the first-echelon lymph nodes, before progression to the remainder of the lymphatic basin.

These first-echelon lymph nodes, known as the sentinel nodes, can be harvested, examined for the presence of tumour and used to predict the disease status of the entire basin. In the head and neck region, considerable variability exists in the patterns of lymphatic drainage

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from each primary tumour site, and the exact location of the sentinel nodes therefore varies between patients. In order to accurately locate the SLNs, a number of techniques may be employed. Preoperatively, radiolabelled tracer is injected in a peritumoral fashion, travelling via the lymphatics to the first-echelon nodes where it may be detected by gamma camera during lymphoscintigraphy (LSG). A handheld gamma probe is utilised intraoperatively to afford more precise radiolocalisation, and some surgeons choose also to inject peritumoral blue dye, easing visual identification of the lymphatics. These comprise the sentinel lymph node biopsy technique, which has been applied to a variety of solid tumours including breast cancer, malignant melanoma and penile cancer.

This chapter describes SLNB as it relates to the management of solid tumours in the head and neck region, particularly malignant melanoma, squamous cell carcinoma and Merkel cell carcinoma. A brief history of the development of the technique and its reported accuracy are presented, and the advantages and disadvantages of this relatively new application are discussed. Finally, this chapter will explore the possible roles that SLNB may play in the future management of head and neck cancer.

Keywords

Sentinel node biopsy • Head and neck cancer • Neck dissection • Melanoma • Squamous cell carcinoma • Merkel cell carcinoma

15.1 Introduction

Head and neck cancers comprise a diverse group of tumours arising from the epidermis, with significant differences in tumour biology, disease characteristics and prognosis. The three most common types of head and neck cancer are malignant melanoma (MM), arising from melanocytes; squamous cell carcinoma (SCC), arising from keratinocytes; and Merkel cell carcinoma (MCC), a rare aggressive skin tumour arising from neuroendocrine cells.

Despite their differences in many regards, these cancer types share one important characteristic: their prognosis is heavily dependent on the presence or absence of lymph node metastases. Patients with malignant melanoma and nodal involvement demonstrate less than 50 % 5-year survival [1], and similar figures have been reported for patients with SCC [2]. In Merkel cell carcinoma, the presence of nodal disease has been shown to be the most important prognostic indicator by multivariate analysis [3], with a further study demonstrating a drop from 40 months to 13 months median survival with nodal involvement [4].

Virchow [5] was the first to postulate that lymph nodes act as a barrier to particulate matter, and in particular cancer cells. The contention that cancer progression followed a sequential route from the primary site to the regional lymphatics before distant metastasis laid the way for development of regional surgical treatments for a variety of cancers: first, Halsted's radical mastectomy for breast cancer [6] and, in the case of the head and neck, the radical neck dissection as described by Crile [7].

15.2 Anatomy of the Cervical Lymph Node Basin

The lymphatic anatomy of the head and neck is complex, comprising approximately 250–350 lymph nodes and demonstrating great variability in the patterns of lymph flow observed [8]. The cervical lymph nodes may be divided into superficial and deep chains. The superficial chain lies between the skin and the superficial fascia of the face and scalp, following the anatomy of the major veins, and eventually drains into the deep chain. The deep chain lies along the course of the internal jugular vein under the sternocleidomastoid muscle, draining inferiorly from the base of the skull to the brachiocephalic junction, where the lymph is returned to the venous system. The most popular system of classification for cervical lymphatic anatomy was developed at the Memorial Sloan Kettering Cancer Center [9] and forms the basis for describing the various types of neck dissection in current usage [10]. In this system, the cervical lymph nodes are divided into levels I through VI. The anatomy and classification system are illustrated in Fig. 15.1.

15.3 Neck Dissection

The introduction of the radical neck dissection (RND) in 1906 [7] represented an important step for both staging and treatment of patients with head and neck cancer. However, the morbidity associated with such an extensive dissection was considerable. Complications included shoulder stiffness,

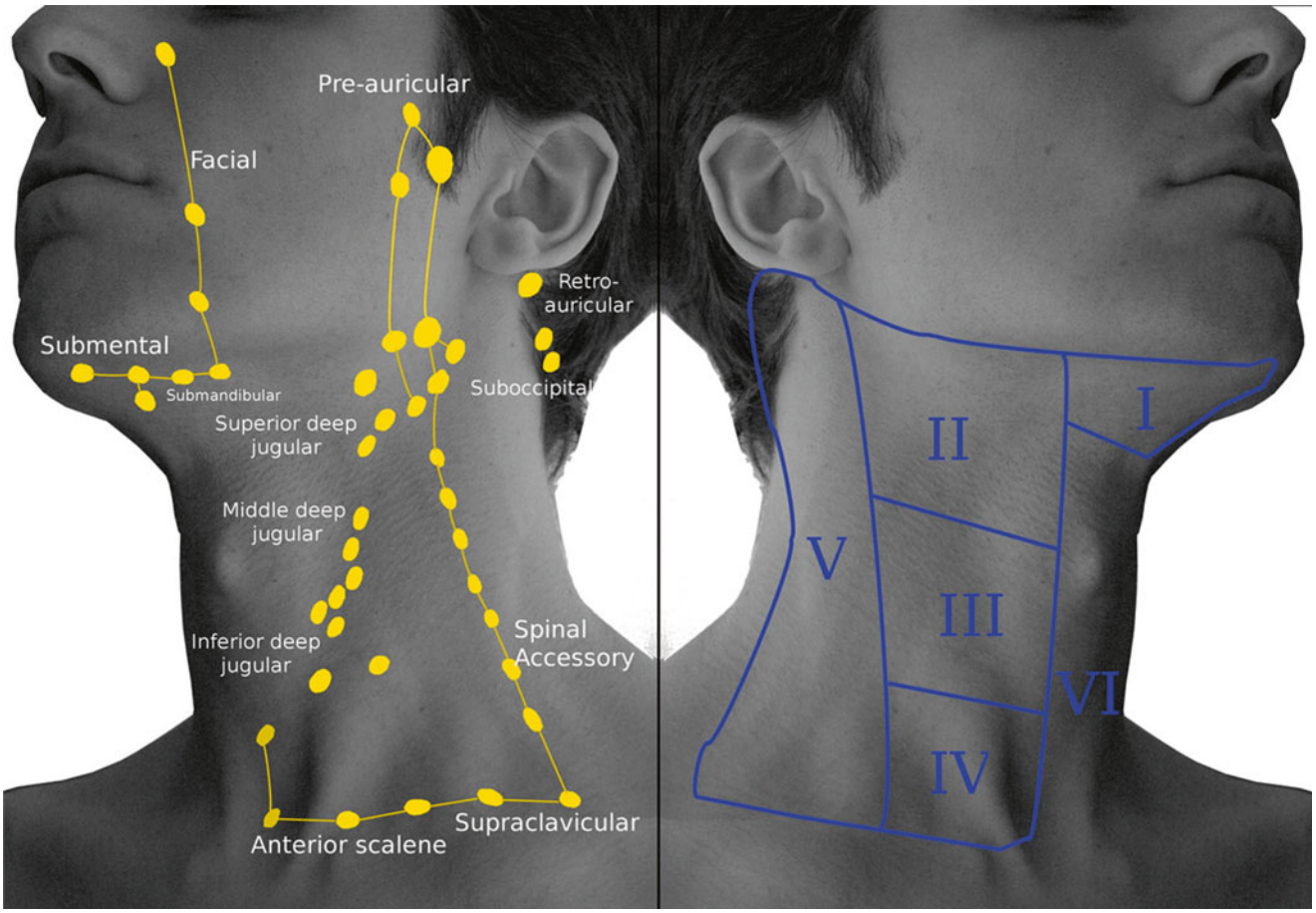

Fig. 15.1 (**a**) Individual lymph node groups in the head and neck. Superficial chain is denoted in *yellow*; Deep chain is in *orange*. (**b**) Robbins' Classification of cervical lymph node levels

pain, muscle atrophy, facial swelling and cosmetic defects, while the mortality rate following bilateral RND was reported as high as 10 % [11]. A number of "modified radical" neck dissections were developed as a means of minimising associated morbidity, being designated MRND I–III depending on the structures preserved (accessory nerve, sternocleidomastoid and/or internal jugular vein) [12]. Studies demonstrating the oncologic safety of the MRND led to its adoption as the standard of care, and the radical neck dissection fell out of favour [13].

The goal of reducing morbidity continues to push the development of more conservative surgical management techniques, however, and this is particularly true for patients with clinically uninvolved necks. Improved understanding of the lymphatic anatomy of the head and neck has facilitated the development of more selective lymphadenectomies, concentrating on the groups of lymph nodes most likely to be involved [14–16]. These selective neck dissections (SND) require less extensive dissection, leaving more of the normal lymphatic anatomy intact, and have been shown to cause less morbidity when compared with MRND [17]. The various types of neck dissection are outlined in Table 15.1.

Despite these recent advances, neck dissection remains an invasive procedure with appreciable morbidity [18], and, while its use in clinically node-positive patients is well established, elective neck dissection for patients with clinically negative (cN0) necks remains controversial. Traditionally considered the gold standard, END provides tissue for accurate pathologic staging while also treating the neck by removing lymph nodes at risk for involvement [19]. However, the majority of cN0 patients do not in fact harbour occult nodal metastases and may be unnecessarily subjected to the morbidity associated with the procedure.

As a result, selection of patients who would benefit most from neck dissection becomes increasingly important. Clinical staging of the cervical lymph nodes is unreliable, with poor reported sensitivities for both palpation and clinical imaging, and it is generally accepted that an occult nodal metastasis rate of 20–30 % persists despite meticulous clinical staging [20–22]. For SCC, elective neck dissection is currently recommended for patients with a greater than 20 % risk of occult nodal metastases based on primary tumour characteristics such as site and T-stage [23]. The role of END for cN0 head and neck melanoma patients is unclear, with no

Table 15.1 Neck dissection classification

Current neck dissection classification
Radical neck dissection
Modified radical neck dissection (MRND)
Selective neck dissection (based on anatomical locations) Supraomohyoid SND Lateral SND Posterolateral SND Anterior SND
Extended neck dissection

Based on data from Ref. [10]

consistent survival benefit demonstrated [24]. It has been suggested that END may be most beneficial for patients with primary tumours between 1.5 mm and 3.99 mm in thickness [25].

15.4 Sentinel Node Biopsy

Sentinel node biopsy represents a means of super-selecting the group of lymph nodes most at risk for disease involvement, allowing histopathologic staging of the neck while minimising the extent of surgical intervention for patients without nodal involvement. The sentinel node concept is based on the assumption that spread from the primary tumour occurs to a single node (or group of nodes) before progressing to the remaining nodal basin and systemic metastasis (Fig. 15.2). Identification of these sentinel nodes allows for selective biopsy and pathologic evaluation of the nodes most likely to represent the disease status of the remaining nodal basin [26]. The results of sentinel node biopsy (SNB) can then be used to guide further management, with SNB-positive patients going on to receive definitive (therapeutic) neck dissection and/or parotidectomy, while SNB-negative patients may be followed clinically. These SNB-negative patients may therefore avoid some of the morbidity associated with neck dissection [27].

The potential advantages of sentinel node biopsy over neck dissection are manyfold, including its minimally invasive nature, a lower per-patient cost compared with comprehensive neck dissection [28, 29] and a drastic reduction in the number of lymph nodes submitted for pathologic evaluation. In turn, this allows a more in-depth search for micrometastatic deposits utilising techniques such as step-serial sectioning and immunohistochemistry [30, 31]. However, SNB can be a technically challenging technique with a steep learning curve [26, 32], and as such, investigators wishing to begin using the technique for SCC are recommended to do so within the context of SNB-assisted END [33]. As with any biopsy technique, there exists the potential for sampling error, and the reported false-negative rate ranges from 0 to 10.5 % in most studies for both SCC and melanoma [33–39]. Finally, the usefulness of SNB is currently restricted to cN0 patients, since distortion of the normal lymphatic anatomy by extensive tumour infiltration may lead to unexpected drainage patterns and increase the likelihood of false-negative results [40].

15.5 Development of the Sentinel Node Concept

The first description of a "sentinel" lymph node dates back to 1960 with a total parotidectomy reported by Gould et al., during which frozen section examination of a single facial lymph node was used to guide the decision for neck dissection [41]. Subsequently, Cabanas et al. reported direct drainage from the penis to the lymph nodes associated with the superficial epigastric vein in a series of 46 patients with penile SCC and described 90 % survival for sentinel node-negative patients [42]. Similarly, Weissbach and Boedefeld suggested a limited retroperitoneal lymph node dissection in patients with testicular cancer, in order to detect lymphatic involvement while minimising operative intervention [43]. Holmes et al. introduced the use of colloidal gold injections to demonstrate the actual patterns of lymph drainage for ambiguous areas such as the midline [44] and followed this in 1992 with the description of intraoperative vital dye injection, providing a means of visually tracing dye-stained lymphatics to the first-echelon nodes [26]. In 1993, Alex and Krag described the intraoperative use of a handheld gamma probe, easing the detection of the sentinel nodes and improving identification rates [45]. Since these early studies, SNB has gone on to become increasingly important as a staging tool for patients with early-stage melanoma [46], and work is underway to fully elucidate its utility in SCC management [33, 47]. The role played by SNB in the management of these and other head and neck cancers will be described later in this chapter.

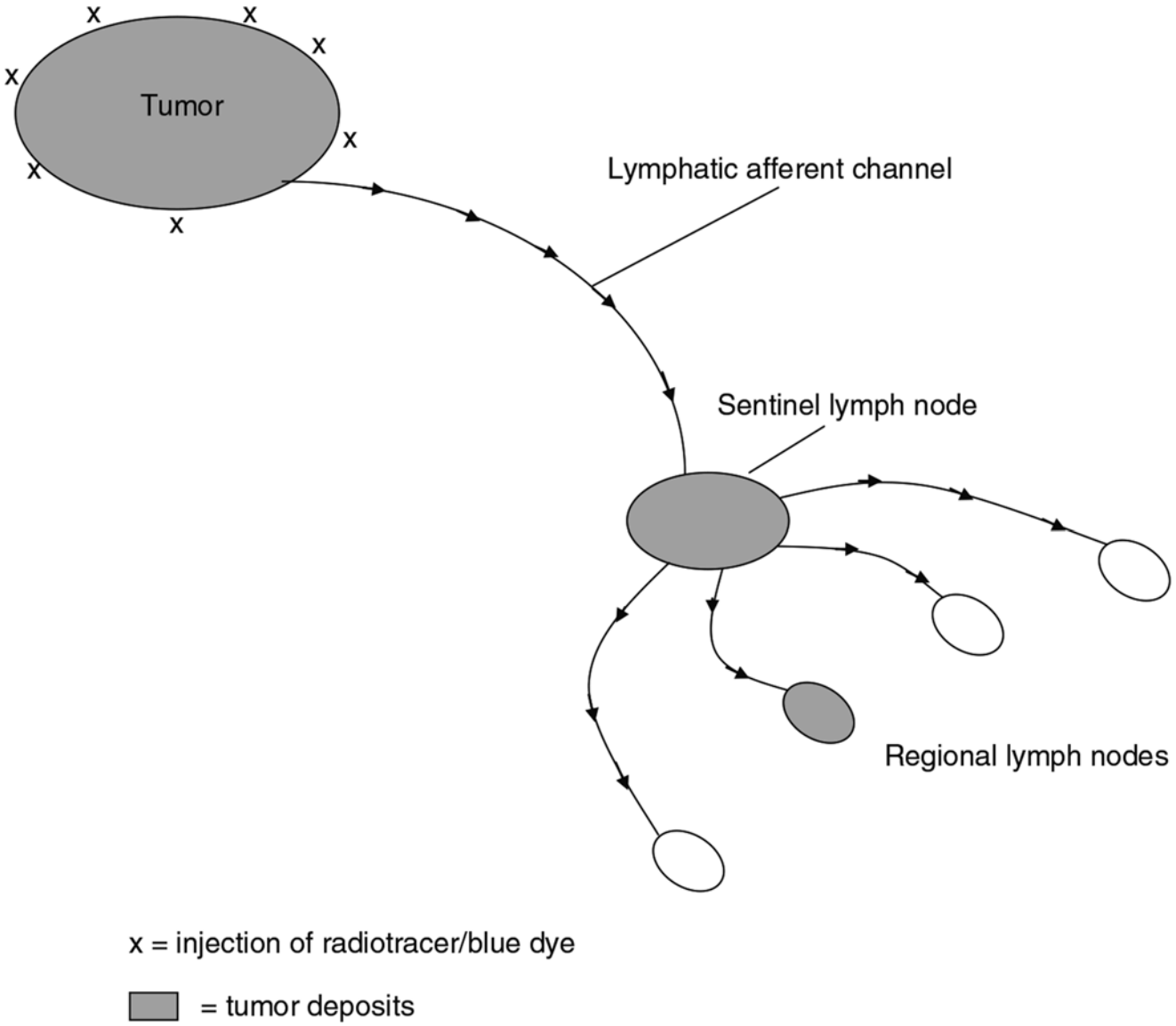

Fig. 15.2 The sentinel node concept

15.6 Technique of Sentinel Node Biopsy

In general, sentinel node biopsy is comprised of three parts: preoperative lymphoscintigraphy, intraoperative identification and harvest and pathologic evaluation of sentinel nodes. These components will be described in detail in this section, with reference to the minor differences in protocol for each of the major head and neck cancer types.

15.6.1 Preoperative Lymphoscintigraphy

The lymphatic anatomy of the head and neck is complex and variable, with discordance between predicted and actual lymphatic drainage in up to 67 % of patients [8]. Aberrant drainage patterns can lead to inaccurate placement of the initial access incision and may contribute to failure of sentinel node identification [15]. The goal of preoperative lymphoscintigraphy is to demonstrate the location of sentinel nodes prior to incision. This begins with injection of a radiolabelled colloid solution at the site of the primary tumour. The radiocolloid may then track along the same afferent lymphatics draining the tumour, accumulating in the first-echelon lymph nodes where the resultant radioactivity may be detected by gamma camera. Lymphoscintigraphy may be carried out up to 24 h before surgery, or on the day of surgery, and this should be coordinated between the nuclear medicine physician and the surgeon.

The technique of radiocolloid injection varies according to the type of cancer being studied. For melanoma and other

cutaneous tumours, multiple intradermal injections should be employed to completely encircle the tumour or site of previous excision biopsy. There has been considerable debate regarding the accuracy of lymphoscintigraphy, and SNB in general, in cases where wide local excision (WLE) has previously been carried out. While it is strongly preferred that SNB be performed prior to excision, there is some evidence to suggest that previous WLE is not an absolute contraindication [48]. For intraoral lesions, the majority of which are SCC, multiple mucosal/submucosal injections should be performed around the periphery of the tumour or scar margin, and deeper injections may be employed according to the depth of the lesion [49]. Ideally, the operating surgeon should be present for the injections to ensure consistency with injection of blue dye if used. The volume injected varies according to the location and size of the lesion and ranges from two to four aliquots. A mouthwash should be employed following intraoral injections, to prevent sumping or swallowing of radiotracer.

The ideal radiotracer should emit only gamma rays, be cleared rapidly from the injection site, have a uniform particle size and persist in the lymph nodes until imaging can be performed [50, 51]. A variety of technetium99m (99Tcm)-labelled colloids are available, including 99Tcm human serum albumin, 99Tcm colloidal albumin, 99Tcm antimony sulphur colloid and 99Tcm sulphur colloid, although regional licensing issues may restrict the available choices. In Europe and parts of the USA, Albures™ and Nanocoll™ (Nycomed Amersham, Buckinghamshire, UK) are the most commonly available colloidal albumin preparations. The larger particle size of Albures™ (500 nm) limits its use to primary tumour sites with high lymphatic density, such as the anterior tongue or floor of the mouth, while the 50 nm particle size of Nanocoll™ allows its use in other sites [33, 51]. For regions where human albumin-based colloids have not been approved, sulphur colloid preparations are available in both unfiltered (300–340 nm) and filtered (<200 nm) forms [52]. There is little consensus on the optimum activity for injection, which varies from 15 to 120 MBq between studies with higher doses or repeat injections being employed for the 2-day protocol [53–55]. However, it has been suggested that much lower doses (0.37–2.2 MBq) may be used in the setting of head and neck melanoma [56].

Planar lymphoscintigraphic imaging may be static or dynamic or a combination of the two. The addition of dynamic imaging for melanoma patients improves the detection of "in-transit" nodes, which are reported to occur in 5–8 % of the population and should also be considered sentinel nodes [57, 58]. To date, there have been no reports of in-transit nodes in patients with SCC. There is currently no evidence favouring either technique in these patients, and the exact timing of static image acquisition varies between centres. Images should be obtained in two planes: anterior and lateral or lateral oblique. A gamma camera fitted with a low-energy, high-resolution (LEHR) collimator is used to image the patient, whose silhouette can be delineated by a flood source of 57Co or 99mTc placed behind the patient or by tracing his/her outline with a 57Co-labelled marker pen. At this point, it may be helpful to mark the skin overlying visualised sentinel nodes with indelible marker pen [33, 49, 51]. However, this practice has not been universally accepted due to concerns that the change in positioning between lymphoscintigraphy and surgery may misguide the placement of initial access incision [59].

Recent studies have reported potential improvements in preoperative sentinel node identification through the use of single-photon emission computed tomography (SPECT/CT) imaging [60, 61]. This hybrid anatomical/functional imaging modality affords better topographical orientation and separation of SLNs from adjacent structures, compared with planar lymphoscintigraphy alone, allowing the surgeon to see 3-dimensional images of the nodes. It may also provide more consistency in identification of sentinel nodes, as evidenced by Uren et al. [62] who found that different nodes may be identified on lymphoscintigraphy performed on the same site a day apart. However, this problem may also be found in SPECT, and no studies have shown that ~SPECT performed on different days always identifies the same nodes. This problem may be addressed intraoperatively with freehand SPECT, but studies are required to investigate this.

In the melanoma literature, it appears that SPECT/CT can lead to more accurate incision placement and improvements in SLN detection rates [61, 63–65], *and freehand SPECT has shown encouraging results for intraoperative imaging* [66]. For SCC there have been promising reports regarding the use of SPECT/CT [67]; however, these have yet to be consistently reproduced [68].

Bluemel et al. showed that freehand SPECT can accurately predict SLN status intraoperatively in oral/oropharyngeal SCC including for floor of the mouth tumours where it may reduce the shine-through effect. One limitation of freehand SPECT is the need for repeated scans due to artefacts.

15.6.2 Surgical Technique

Within 24 h of lymphoscintigraphy, patients may undergo the operative portion of SNB. Although SNB of cervical lymph nodes under local anaesthesia has been reported [69], most surgeons prefer to employ general anaesthesia for this technique. The patient is prepared and draped as for a standard excision and neck dissection. Preoperative lymphoscintigraphy images should be available for reference in the operating suite, in electronic or hard-copy form, and these may be used to guide the placement of the initial access incision. If skin markings have been placed in the nuclear

medicine suite, underlying radioactivity levels should be verified using a handheld gamma probe prior to making the incision. The orientation of the incision should be such that it may be easily excised in the event of a future neck dissection.

If injection of vital (blue) dye is desired, this may be carried out prior to preparing and draping. Injections should be undertaken by the same operator as the radiotracer injection in order to ensure consistency, and the pattern and depth of injection should mirror that of the radiotracer. The brand of dye used varies according to geographical region, with Patent Blue V Dye (Laboratoire Guerbet, Aulnay-Sous-Bois, France) available in Europe and Lymphazurin™ (Tyco Healthcare Group LP, Norwalk, CT, USA) in the USA. The technique of blue dye injection, introduced by Morton et al., provides a means of visually identifying the small lymphatic vessels intraoperatively, allowing them to be traced to the first-echelon nodes [26]. However, the success rate for identification of SLNs by blue dye injection is less than that for radiolocalisation by gamma probe, and the technique has a steeper learning curve [70]. In a study of 55 patients with head and neck melanoma, Wells et al. reported a 67 % identification rate by blue dye mapping and 95 % utilising a combined approach [38].

While most blue dye-stained SLNs are also found to be radioactive or "hot", a small minority of SLNs are "cold", and proponents of blue dye injection report facilitation of intraoperative identification [33, 49, 71]. The major perceived disadvantages to blue dye are related to persistent cutaneous staining and masking of true surgical margins; however, rare cases of anaphylactic reactions have also been reported [72]. As a result, the use of blue dye is considered optional, though many authors employ a combined approach.

Guided by the preoperative lymphoscintigraphy images, skin markings (if present) and the handheld gamma probe, a small skin incision (2–4 cm) is made and limited skin flaps elevated. Dissection is carried through the superficial fascia and is guided by the handheld gamma probe. If blue-stained lymphatics are visualised, these may be followed to the draining lymph node(s); if no staining is present (or dye was not used), the dissection may be guided solely by the gamma probe, which is fitted with a 14 mm diameter straight collimated probe. The angle of the probe may be gradually altered while watching or listening for a change in the counts per second (cps). In cases where the primary tumour site lies in close proximity to the regional lymph nodes, a particular problem for floor of the mouth SCCs, radioactive "shine through" from the primary tumour site may mask the true position of the sentinel node. In these patients, the use of malleable lead plates between the injection site and the nodal basin may address this issue [26, 45, 49, 51]. All radioactive and/or blue-stained nodes are clipped and excised, and radioactivity is confirmed *ex vivo*. Following excision, the remaining basin is examined with the gamma probe, and no further SLNs are considered present when the residual count rate is less than 10 % that of the "hottest" excised SLN [73]. This strategy is somewhat arbitrary, as there are no specific guidelines on the optimum strategy for SLN identification. The 10 % rule has been reported to lead to unnecessary removal of non-SLNs [74], and some authors advocate for removal of the "hottest two plus blue rule" which potentially reduces operative time and number of nodes removed without increasing false-negative rates in melanoma [75]. In SCC it has been shown that removing the hottest three nodes would be sufficient to ensure accurate results [76, 77]. Patients undergoing SNB-assisted END may then proceed to completion neck dissection.

15.7 Further Developments in Lymph Node Identification

Several studies have reported initial successes with near-infrared imaging using indocyanine green dye. Benefits of this include good tissue penetration, direct real-time transcutaneous intraoperative visual feedback of draining lymph channels and excellent safety profile. It has poor results when used alone particularly as transcutaneous feedback is unreliable, but it has excellent results when combined with radioisotopes [78–80]. However, due to the small particle size and speed of travel through lymphatics, non-sentinel lymph nodes may be inappropriately identified and removed, and the technique's usefulness has yet to be clarified by large randomised studies [79]. More studies are required to further evaluate the role of indocyanine in SNB.

15.8 Pathologic Evaluation of Sentinel Nodes

Detection of metastatic disease in sentinel nodes by pathologic examination is intrinsic to the success of the procedure and offers a number of advantages over traditional elective neck dissection. Principally, the absolute number of lymph nodes examined is far fewer during SNB, allowing the pathologist to perform a more thorough search for micrometastatic deposits.

15.9 Metastases, Micrometastases and Isolated Tumour Cells

Previously, the degree of tumour burden identified in lymph nodes was classified as metastases, micrometastases or isolated tumour cells (defined as tumour size <0.2 mm, single cells or small clusters, with no stromal reaction or contact with the vessel wall). Isolated tumour cells did not previously

upstage the neck to node positive. However, according to the most recent American Joint Committee of Cancer (AJCC) guidelines, a single isolated cell detected by IHC defines positive SLN involvement [81]. The recent AJCC guidelines (shown in Table 15.2) state that nodal metastases can be confirmed using either H&E or IHC to identify at least one melanocyte-specific marker.

In order to compare results across studies, uniform reporting standards for pathologic staging are critical. For each of the head and neck cancer types, the sequence of pathologic examination is broadly similar and involves gross examination, bivalving of the lymph node, sectioning at predefined intervals and staining with a variety of histopathologic techniques. However, there are a number of minor differences in protocol according to the type of tumour being studied, and exact sectioning/staining protocols vary between centres. In some cases, additional techniques such as real-time polymerase chain reaction (RT-PCR) may also be employed; these differences are briefly outlined below [82, 83].

15.10 Melanoma

The addition of immunohistochemical techniques to standard H&E examination has been shown to increase melanoma detection rates by at least 10 % [84], and a number of sectioning/staining protocols have been described in an effort to maximise detection rates while minimising unnecessary workload. Some authors have advocated examination of only the central portion of the lymph node, based on the suggestion by Cochran et al. that the vast majority of micrometastases occur centrally [85], while other suggested protocols have included sectioning of the entire node into 1 mm slices [86], or examination of one half of the SLN using a combination of histology and immunohistochemistry, and the other half using RT-PCR with a variety of probes [87].

RT-PCR detection of occult metastatic deposits is an attractive technique, potentially reducing the cost and labour associated with SLN evaluation. However, disadvantages include its destructive nature, inability to distinguish benign and malignant cells and positivity rates of up to 70 % in some studies [88]. False positives may be due to capsular or trabecular naevus cells, nerves or macrophages. In a recent report by Cook et al., utilising an extended stepwise study of bivalved nodes with immunohistochemistry, the discrepancy between detection rates using histology/IHC and RT-PCR was found to be only 3–5 %. Several studies have since shown that RT-PCR can upstage up to 30 % of patients who were initially found to have negative SLNs on H&E or IHC staining [89, 90]. Nevertheless, the exact role of RT-PCR remains to be fully elucidated, and the authors therefore recommend the routine use of their extended histology/IHC protocol, which sections deeper into the periphery of the node, until further data become available [82].

The protocol currently recommended by the EORTC is illustrated in Fig. 15.3. Briefly, the sequence involves bivalving the formalin-fixed SLN, embedding in paraffin and sectioning at 50 μm intervals to a total depth of 250 μm. Several sections are taken at each interval and are alternately stained with H&E, S100 and/or HMB45 for IHC. Sections found positive by IHC are compared with adjacent H&E-stained sections in order to confirm the presence of viable tumour cells. The use of this extended sectioning protocol results in thorough evaluation of the central 700–800 μm of each SLN and is thought to represent the best balance between sensitivity, cost-effectiveness and pathologist workload [82]. The EORTC protocol outlined above involves more extensive processing when compared to techniques used in trials such as MSLT-1 suggesting that the false-negative rate reported in such trials could potentially be lowered by more thorough histopathologic processing.

Table 15.2 Latest American Joint Committee on Cancer staging of nodal metastases in melanoma

N classification	Number of nodes	Nodal metastatic mass
Nx	N/A	Regional nodes cannot be assessed (e.g. previously removed)
N0	0	No nodal mets
N1	1	(a) Micrometastasis[a]
		(b) Macrometastasis[b]
N2	2–3	(a) Micrometastasis
		(b) Macrometastasis
		(c) In-transit met(s)/satellite(s) *without* metastatic nodes
N3	Four or more	Four or more metastatic nodes, *or* matted nodes, *or* in-transit met(s)/satellite(s) *with* metastatic nodes

[a]Micrometastases are diagnosed after sentinel node biopsy and completion lymphadenectomy (if performed)
[b]Macrometastases are defined as clinical detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastases exhibit gross extracapsular extension
Adapted from Compton CC, Byrd DR, Garcia-Aguilar J, et al. Melanoma of the skin. In: Compton CC, Byrd DR, Garcia-Aguilar J, et al. (eds). AJCC Cancer Staging Atlas. New York, NY: Springer-Verlag; 2010: 385–416. With permission from Springer Verlag

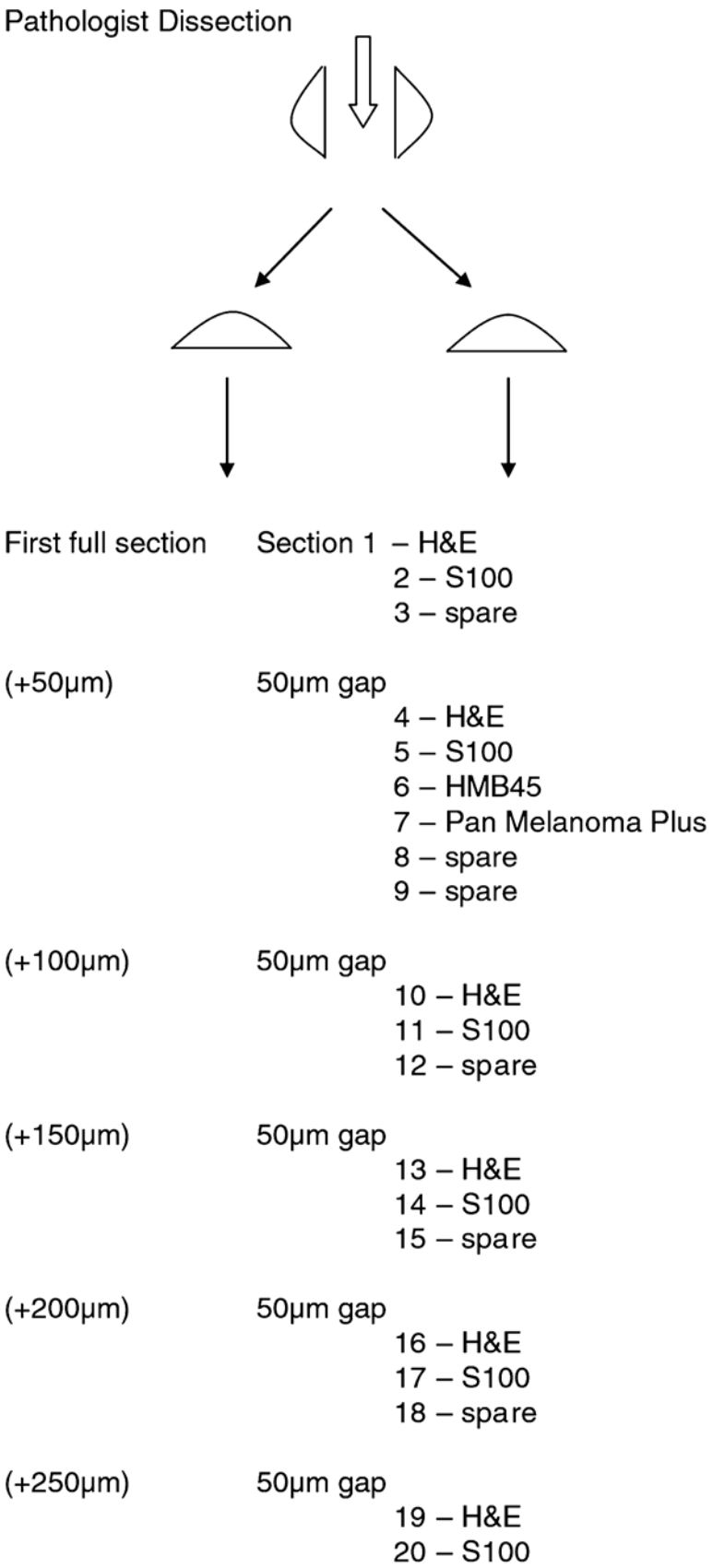

Fig. 15.3 Extended stepwise examination of bivalved SLNs with immunohistochemistry using S100 and HMB45 stains

False positive may arise as a result of the inability to distinguish between malignant melanoma cells and benign intranodal naevi cells. HMB45 is often used to distinguish but can still be present in a significant number of nodal naevi [91]. Lee et al. [92] showed that benign naevi cells retain high levels of nuclear staining for the epigenetic hallmark 5-hydroxymethylcytosine which has the potential to accurately distinguish benign and malignant cells. This was confirmed in their study with all 18 malignant cases showing complete loss of staining and all 10 benign naevus cases retaining staining. Chen et al. [93] also found the nuclear biomarker SOX2 to have potential to differentiate benign and malignant cells.

15.11 Squamous Cell Carcinoma

For SCC, there remains considerable debate regarding the optimal method for sectioning SLNs. Current recommendations were formulated during the Second International Conference on Sentinel Node Biopsy in Mucosal Head and Neck Cancer in 2003 and are included in the recent joint guideline published by the European Association of Nuclear Medicine (EANM) and European Sentinel Node Trial (SENT) committee [54, 83].

SLNs less than 2 mm in longest dimension are processed whole, while those measuring 2–5 mm should be bivalved and both halves processed en face. Nodes greater than 5 mm are cut into 2 mm slices, and each slice is processed en face. A section from each slice is stained with H&E, and positive nodes/slices result in upstaging of the patient. Step-serial sectioning (SSS) at finer intervals of 150 μm (six sections per interval) should be carried out for SLNs found negative after initial sectioning, and these are H&E stained and examined as before. Finally, SLNs that remain negative are subjected to immunohistochemical (IHC) staining with pancytokeratin antibody (AE1/AE3 or MNF116). The combination of SSS and IHC has previously been shown to detect an additional 10 % of occult/micrometastatic deposits compared with H&E alone [33]. If no disease is found following H&E and IHC staining, the lymph node is considered free of tumour. For SLNs with positive IHC staining, the positive section must be compared with the immediately adjacent serial section in order to avoid false positives due to non-viable tumour cells, artefacts and/or inclusion of other cell types [54].

The use of intraoperative frozen section analysis of SLNs offers the potential advantage of avoiding a second anaesthetic for SNB-positive patients, but has traditionally been avoided due to concerns regarding freezing artefacts and loss of tissue. However, several recent studies have shown promising results with only 10–17 % of SNB-positive patients requiring a second procedure [35, 94, 95]. The technique has not yet gained universal acceptance, and others have questioned the sensitivity of frozen section when compared with standard practices [34] for identification of micrometastases and isolated tumour cells [96, 97].

Novel techniques such as imprint cytology [98] and intraoperative real-time genetic evaluation [99] currently remain under investigation. In particular, one-step nucleic acid amplification has the potential to allow fast intraoperative detection of lymph node metastases, reducing the need for a second procedure. Ferris et al. [100] showed excellent reproducibility and 94.2 % accuracy in 103 lymph nodes with their tumour-associated calcium signal transducer 1 and pemphigus vulgaris antigen assay. Although in the early stages, this technique has exciting potential.

15.12 Merkel Cell Carcinoma

Pathologic evaluation of the sentinel nodes in MCC is similar to that for melanoma, though no standardised protocol has yet been adopted. The differences lie mainly in the type of step-serial sectioning, which varies from 2–3 mm slices [101] to 1 mm slices with multiple 200 μm sections per slice [102], and the use of anti-CK-20 staining (Dako Corp, Carpinteria, Calif.) in place of S100/HMB-45 for immunohistochemistry. CK-20 is well established as the most sensitive and specific marker currently available for the detection of MCC [103].

15.13 The Role of SNB in Current Practice

15.13.1 Melanoma

Following the initial reports of SNB for cutaneous melanoma using blue dye only, technical difficulties and the significant learning curve associated with the procedure led to variable technical success rates ranging from 60 to 80 % [46]. Subsequently, the introduction of radiolabelled tracer injection, preoperative lymphoscintigraphy and intraoperative gamma probe guidance led to significant improvements in identification rates to greater than 90 %, and the use of both blue dye and radiotracers quickly gained acceptance [36, 59, 104]. Since then, the technique of SNB has been demonstrated to accurately predict the disease status of the remaining nodal basin in a number of landmark studies of cutaneous melanoma (all sites) [48, 105, 106].

The presence of metastases within SLNs has been demonstrated to be the most accurate predictor of outcome in melanoma patients without clinical lymph node involvement [107], and its benefits as a prognostic tool are universally accepted. As a result, SNB is widely regarded as the gold standard for staging the lymphatic basins of intermediate-thickness melanoma (1–4 mm) patients without clinical

evidence of nodal involvement [46]. The recently published results of the MSLT-1 trial confirmed that SNB is the most effective staging tool for primary melanoma [108]. Current guidelines recommend sentinel lymph node staging in all primary melanomas greater than 1 mm Breslow thickness; however, there remains debate as to the benefits of SLNB in patients with thick and thin melanomas, and this will be discussed further.

The greatest area of controversy surrounding SNB in melanoma is whether there is a survival benefit for therapeutic lymphadenectomy in the clinical-negative SNB-positive patient group. A small but significant survival benefit was reported in an early report, based on subgroup analysis [109]. However, the final results after 10 years of follow-up of the landmark MSLT-1 trial published in 2014 have provided more reliable evidence as to the benefits of SNB in melanoma [108].

The MSLT-1 trial randomised patients with melanoma greater than 1.2 mm Breslow thickness to either wide local excision (WLE) of primary tumours plus SNB and lymphadenectomy if positive or WLE plus observation and lymphadenectomy if nodal disease developed. The study found no significant melanoma-specific survival advantage for patients having SNB compared to those undergoing observation and therapeutic lymphadenectomy in intermediate-thickness melanoma (1.2–3.5 mm). However, some authors have argued that the trial was underpowered and that the data showed a trend towards a likely melanoma-specific survival benefit as well as demonstrating a significantly improved 10-year disease-free survival in both intermediate and thick melanomas [110].

Furthermore, the trial did show a statistically significant improvement in melanoma-specific survival for sentinel node-positive patients with intermediate-thickness tumours who underwent immediate lymphadenectomy after SNB. The overall 10-year melanoma specific survival was 62.1 % in this group compared to 41.5 % in the observation arm. This survival benefit was also shown to remain significant even when false-negative cases were included in the analysis, confirming the accuracy of the findings. This group of SNB-positive patients constitutes approximately 20 % of the overall population, a significant proportion of patients.

However, critics argue that this benefit is only conferred upon 20 % of the population despite the morbidity of the procedure affecting the entire SNB cohort and that the overall population did not show a survival advantage even when thick tumours, which are most likely to affect survival, were excluded from the analysis [111, 112]. They argued that the trial was always unlikely to show survival advantage from SNB, given that the majority of patients will not develop nodal disease and therefore will gain no benefit from further staging after primary resection [113]. Authors also highlight the limitations of the study design with possible ascertainment bias and small population size limiting the value of the conclusions [114].

However, others have argued that the clinically and statistically significant survival benefit of early treatment to patients with positive nodes, even if they only constitute 20 % of the patient population, is a justification for SNB [115]. They argue this is particularly true as MSLT-1 also showed that morbidity from lymphadenectomy was significantly reduced when done early after positive SNB compared to when performed later after nodal recurrence, with the benefits most marked in lymphoedema [114]. Also, early intervention guided by SNB reduces the extent of nodal involvement at surgery by half [115]. Furthermore, similar melanoma-specific survival has been demonstrated in other large studies [116]. The MSLT-1 trial also showed an improvement in recurrence-free survival in both intermediate and thick tumours. However, some authors have argued that this result was inevitable given the flaw in the study design in that the observation arm had an intact nodal basin and therefore had a much higher chance of nodal recurrence than those with previously treated nodal basins [112, 117]. Thomas also argued that a proportion of SNB-positive patients were false positive and therefore influenced the final results [117]. He argued that because the cumulative incidence of nodal recurrence was not the same even after 10-year follow-up, then some cases must be false positive. However, in response Thompson and colleagues point out that the difference in nodal recurrence is beginning to converge after 10 years and that differences are not statistically different and therefore are unlikely to skew the results [115].

Given the continuing controversies surrounding the results of MSLT-1, it can only be stated that the results offer guidance rather than definitive proof of the survival benefits of SNB in melanoma.

The issue of whether SNB should be offered to patients with thick melanomas also remains controversial. Current NCCN and ASCO guidelines recommend SNB for all patients with tumours greater than 1 mm Breslow thickness due to its value as prognostic tool [118, 119]. However, MSLT-1 showed that SNB offered no benefit to melanoma-specific and distant recurrence survival compared to observation for patients with thick tumours. Moreover, the survival benefits seen in SNB-positive patients with intermediate-thickness tumours are not found in patients with thick tumours. In fact overall melanoma-specific survival was worse in thick tumours compared to the observation arm, most likely because the false-negative patients did particularly poorly. This has led some authors to argue that SNB in patients with thick tumours is unnecessary given the high risk of metastases and lack of survival benefit of early intervention given that the only benefit SNB provides is prognostic information [114]. However, MSLT-1 did find improved recurrence-free survival in thick tumours undergoing SNB

compared to observation as well as a short time to recurrence in patients under observation suggesting that offering early intervention with SNB may be justifiable [114].

The benefit of SNB in patients with thin tumours is also controversial particularly given that a large proportion of melanoma patients have tumours <1 mm thick [120]. Guidelines recommend that patients with tumours 0.76–1 mm should be considered if there are other high risk factors such as high mitotic rate, but there is little proof that the procedure provides any benefit [119]. Van der Ploeg et al. found no survival difference for patients undergoing SNB versus observation with thin tumours [121]. Bartlett et al. showed that patients with thin tumours and no other significant histopathologic features have an extremely low nodal positivity rate of 0.7 %, but this increases to 3.7 % in patients with mitoses or high Clark level [122]. The NCCN guidelines state that when offering patients SNB for tumours 0.76–1 mm, patients must be informed of the limited evidence to suggest benefit and low rate of positivity [118].

An argument for the use of SNB in melanoma is that early staging may allow early enrollment into adjuvant trials and mutation testing for targeted therapies. There have recently been developments in the drug agents available to treat patients with advanced melanoma. In particular the BRAF signalling molecule inhibitors vemurafenib and dabrafenib have shown some survival improvement in melanoma patients who have positive BRAF V600 mutations [123, 124]. Early staging with sentinel node biopsy would allow patients to be BRAF tested early and allow them to receive drug therapy or start adjuvant trials early. In addition many trials stipulate that patients must have been staged via sentinel biopsy before being considered for enrolment. Currently, the benefits of current adjuvant therapies are limited, with many patients only showing partial response or developing resistance to treatment. As these adjuvant treatment options improve, there may be stronger indications for SNB to direct early treatment, particularly in thin and thick melanomas, and in the long term, this may potentially show an improvement in survival.

There is some debate as to whether the results of MSLT-1 are applicable to head and neck tumours due to the complex anatomy and often close proximity of lesions to first-echelon nodes [125, 126]. This means that there is less consensus amongst surgeons as to the benefit of SNB in head and neck tumours, as illustrated by SEER database analysis which reports only 60 % patients of SNB-positive patients undergoing lymphadenectomy in head and neck melanoma [127].

In the head and neck, the prognostic significance of sentinel node status is less clear, with SLN-negative patients demonstrating a 5-year disease-free survival rate of only 55 % in one report. In their review of the existing head and neck melanoma literature, the authors noted false-negative rates in excess of 10 % in 12 of 21 studies and suggested that this high false-negative rate may contribute to the poor survival they observed in their series [127]. Similar results were described in the large Sunbelt Melanoma Trial, where false-negative rates were 12 % for the head and neck, compared with 2–3 % for other sites [37]. However, this view has been challenged by Civantos et al., who contended that surgeons with a subspecialty focus on the head and neck may achieve negative predictive values comparable to the 98.2 % for cutaneous malignancies and 92 % for oral cancer described in their series of 106 patients with head and neck malignancy [91]. Furthermore, a large single centre study showed that SNB status was the best prognostic indicator in HNM and that its results are comparable to those of other nodal basins for false positivity [128]. Several other studies have also illustrated that SNB in HNM is an accurate and safe staging technique [129]. Concluding their review, Tanis et al. stated that there is currently no conclusive survival advantage for either elective lymph node dissection or SNB in patients with intermediate-thickness melanoma of the head and neck; however, the benefits of SNB may potentially justify its use in this patient population. These benefits include early prognostic information for patient and physician, reduced tumour load due to earlier lymphadenectomy and the possibility of a survival advantage based on subgroup analysis [127].

A variety of micromorphometrical parameters of SN tumour deposits have been used in an attempt to determine the likelihood of further disease in the remaining nodal basin, such as tumour penetrative depth from the central plane, location within the node and size. The potential applications for these measurements would include guidance of the decision to proceed with formal lymphadenectomy and prediction of survival.

For example, the knowledge that only 10–30 % of patients with positive SLNs are found to have additional positive "non-SLN" nodes following lymphadenectomy has led some authors to suggest that formal lymphadenectomy may not be required in patients with SLN deposits <0.1 mm in size [130]. However, despite several studies suggesting that patients with low volume disease may be able to avoid lymphadenectomy in the head and neck [131–133], these results have not been universally reproduced in other studies, and as a result the prognostic significance of tumour burden in the sentinel nodes has not yet been fully elucidated. In the meantime, it is recommended that all patients with detectable disease in the sentinel nodes be treated as SN positive and offered formal lymphadenectomy [46, 87].

15.14 Future Application of SNB for Melanoma of the Head and Neck

For melanoma, SNB is well established as a staging tool for patients with intermediate-thickness primary tumours and for selected patients in other groups. The main questions now focus on the optimal management of SNB-positive patients, and these questions are still unanswered as we await the results of the MSLT-2 trial. The MSLT-2 trial is a prospective randomised controlled trial, comparing the outcomes of completion lymphadenectomy and observation alone for SNB-positive patients. The study aims to address whether completion lymph node dissection is always required or whether sentinel node-positive patients can be safely observed. MSLT-1 showed that benefits of SNB and lymphadenectomy are combined, and current guidelines recommend completion lymphadenectomy for all positive cases. A study by Kachare et al. showed that melanoma-specific survival was improved in patients undergoing immediate lymphadenectomy after positive SNB compared to delayed, although this did not reach statistical significance due to small population size [116]. Conversely, Wong et al. showed no difference in melanoma-specific survival between immediate lymphadenectomy and observation in SNB-positive patients in a study of 298 patients. Similarly Gyorki et al. found no difference in the head and neck although this was a small study [125, 134]. In addition to the main question, the differences in technical success and false-negative rates for SNB in the head and neck compared with other sites suggest that the results of large-scale prospective RCTs reporting all-sites melanoma data may not be immediately applicable to the head and neck population. Therefore, similar prospective trials tailored specifically to this patient group are required before definitive conclusions regarding optimal management can be reached.

15.15 Oral/Oropharyngeal Squamous Cell Carcinoma

In patients with oral/oropharyngeal SCC, the current gold standard staging procedure for the clinically node negative neck is elective neck dissection (END). However, this can lead to overtreatment in up to 80 % of cases with associated morbidity, as only 20 % cases have occult metastases. Therefore, SNB has been extensively investigated as a staging procedure for these patients. The vast majority of the tumours studied to date are located in the oral cavity or accessible oropharynx, and, while some reports do exist of SNB for other locations such as the hypopharynx and larynx [135–137], the status of the technique should remain "investigational" in these sites until further data becomes available. Furthermore, the use of SNB may be limited in patients with larger tumours which may be difficult to completely surround with tracer injections and which may ultimately require a neck dissection for tumour access or reconstruction purposes [51].

Early validation studies demonstrated that SNB may be safely and successfully applied to patients with T1 or T2 disease and clinically negative necks in oral/oropharyngeal tumours [33, 54]. These studies demonstrated a false-negative rate of approximately 5 %, comparable to rates with melanoma, leading some centres to adopt SNB as the sole staging tool for patients with early OSCC with only those SNB positive undergoing completion lymphadenectomy [33, 35].

The applications for SNB in early OSCC include staging of the ipsilateral cN0 neck, staging bilateral cN0 necks for tumours with ambiguous drainage (i.e. midline) and staging the contralateral cN0 neck for a midline tumour with an ipsilateral cN+ neck. Other applications, including the use of SNB for patients with recurrent primary tumours or following prior treatment to the neck, remain under investigation.

In a large prospective study, the European multicentre trial included patients from six centres and demonstrated a 93 % SN identification rate and 91 % sensitivity in cT1/T2 N0 OSCC at 5-year follow-up. The authors concluded that SNB is a safe staging tool in early OSCC but advised caution in floor-of-mouth tumours due to lower identification rates and sensitivity likely because of technically challenging access to these tumours and close proximity to the first-echelon lymph nodes [33]. Stoeckli et al. [35] reported a 98 % identification rate and 94 % negative predictive value in the largest single centre study at the time of publication.

Since these early studies, several authors have reported promising results with regard to SNB for OSCC. A meta-analysis by Thompson et al. [136] showed a sensitivity and NPV of 94 and 96 % illustrating the technique is both accurate and of value in providing prognostic information and allowing selection of patients who would benefit from further neck dissection. The authors also concluded that patients with negative SNB can avoid further neck dissection without compromising recurrence, a finding also shown in the study by Yuen et al. [138]. Another study also found that patients who were sentinel node negative had improved survival rates compared to those undergoing observation illustrating the prognostic value of SNB [139]. The accuracy and prognostic value of SNB in OSCC have also been validated by several other studies [140, 141]. The ACOSOG trial [142] also found a 96 % NPV in a study that included floor-of-mouth tumours; however, they did find a higher false-negative rate in FOM similar to Alkureishi et al., highlighting the caution required in these patients [143]. The ACOSOG trial also found that increased surgical experience significantly improved the NPV suggesting that centres and surgeons specialising in this procedure are more likely to demonstrate benefit from it. Broglie et al. found that SNB is not only accurate in assessing nodal status but also in identifying unexpected drainage patterns as 12 % of their study

population showed aberrant drainage pathways which would have led to under- or overtreatment by traditional methods [77]. SNB can be particularly useful in identifying unexpected drainage patterns and tailoring dissection in previously treated necks which are more likely to have aberrant drainage pathways [144]. In addition to the accuracy of SNB as a staging procedure, some authors have suggested that SNB is both cheaper [145] and associated with better quality of life outcomes compared to immediate END, due to reduced surgical morbidity [146, 147].

However, despite its benefits as a staging procedure and prognostic tool, several trials have failed to demonstrate any survival benefit of SNB versus END [147, 148] and early intervention versus observation [138, 149]. Therefore, the exact role of SNB in patients with head and neck SCC has yet to be fully elucidated, and END remains the gold standard in most centres.

The European Sentinel Node Trial is a large prospective multicentre study incorporating data from the previous two European trials. In a report of their preliminary results, the authors reported that 52 % of additional nodes found on completion lymphadenectomy after positive SNB were located in the same level as the original positive sentinel node and only 4 % were located outside the two adjacent neck levels. Therefore, they concluded that it may be reasonable to limit therapeutic lymphadenectomies following positive SNB to three levels—one above and one below the positive SLN—potentially further reducing the morbidity associated with treatment of the neck. Follow-up results of this trial have yet to be published, and no further studies have ratified their conclusions.

There is controversy over which neck levels require dissection in oral SCC. Some authors have argued that oral SCCs show predictable drainage patterns to ipsilateral levels I–III, and these should be targeted [148]. However, dissection of level IV nodes may also be required due to the potential of skip metastases to this level without involvement of levels I–III [143, 150–152]. Broglie et al. [77] demonstrated that the majority of OSCCs show predictable drainage to levels I–III; however, 12 % showed unexpected drainage patterns. There is no current consensus on the most appropriate level of dissection required; however, less radical dissection is desirable due to increased morbidity and reduced quality of life with more radical surgery [150, 153].

15.16 Cutaneous SCC of the Head and Neck

For patients with cutaneous SCC, the rate of nodal metastasis is much lower, ranging from 0.3 to 16 % [154, 155]. As a result, SNB has not been well studied in this patient group. As part of a larger series of multiple tumour types, Civantos et al. undertook SNB in a series of 10 patients with "high-risk" cutaneous SCC and detected occult nodal disease in only one patient [156]. Since this study, a review of the literature found that the false-negative rate is approximately 4.76 % similar to that of other regions suggesting that SNB is accurate for cutaneous SCC [157]. Furthermore, a study by Takahashi et al. showed that SNB-positive patients had a worse survival rate compared with SNB-negative patients, suggesting SNB may be used as a prognostic indicator [158]. Several small studies have suggested that tumour thickness is the most reliable predictor of nodal positivity, with tumours less than 2 mm extremely unlikely to be positive and those greater than 6 mm having approximately a 16 % positivity rate [159, 160]. However, there remains a severe lack of evidence as to the value of SNB in cutaneous SCC, and larger prospective studies are required to determine the most appropriate management.

15.17 Merkel Cell Carcinoma

Merkel cell carcinoma (MCC) is a rare, highly aggressive neuroendocrine tumour arising from the Merkel mechanoreceptor of the skin. It is associated with the Merkel cell polyomavirus [161] and has an overall 5-year survival of 30–64 %, with a high incidence of local recurrence, regional lymph node involvement and distant metastasis [162, 163].

In part due to the rarity of this tumour, there is no consensus on the current standard of care for management. Excision of the primary tumour may require wide margins for elective local control [164] or the addition of adjuvant radiotherapy if smaller margins are used [165]. In some series, radiotherapy alone has been shown to achieve similar local control rates to primary excision [166]. Elective treatment of the lymph nodes should be strongly considered due to a clinically N0 neck being a poor indicator of nodal metastases with a high occult metastatic rate [167] and reported nodal recurrence rates of up to 76 % of stage I MCC patients in some series [107]. Prophylactic lymph node dissection appears to improve regional control, but does not lead to improved survival [168]. As a result, there is some disagreement regarding the utility of prophylactic node dissection in this population [102, 169].

Similarly, the utility of SNB in patients with early-stage MCC is a topic of considerable debate. It is extremely difficult to predict metastatic risk in MCC with no accurate histopathologic risk factors identified, meaning there is no clear consensus as to who the procedure would benefit. Furthermore, even with negative risk factors and small primary tumours, the risk of metastatic disease is high [170–172]. The lack of consensus is particularly notable in head and neck MCC, as highlighted by analysis of the SEER database which found that only 8.6 % patients undergo SNB, significantly less than at other sites [173].

Advocates of the technique contend that SNB can help identify patients with occult nodal disease, demonstrate aberrant drainage patterns and may prevent unnecessary neck dissection, parotidectomy and/or irradiation [101, 102]. In a review of the literature by Mehrany et al. [174], the authors found that SNB-positive patients were 18.9 times more likely to have nodal recurrence than SNB-negative patients, although the follow-up was only 7 months. Schmalbach et al. [101] also highlighted only one case of false positivity in a study of 10 cases with 34-month follow-up. These two studies suggest that SNB is both accurate and of prognostic value in MCC.

In a meta-analysis by Sadeghi et al., the authors demonstrated that positive sentinel node status is a strong predictor of poor survival and recurrence [175]. They argued that SNB gives a survival benefit versus nodal observation due to early diagnosis of metastases, early surgical intervention and commencement of adjuvant therapies. However, all the studies analysed had low numbers, short follow-up and heterogeneous methodologies which reduces the robustness of their conclusions. A large study of 403 cases by Shibayama et al. with a positive SNB rate of 31.8 % demonstrated that positive SNB was a predictor of distant recurrence, highlighting the possible prognostic benefits of SNB [176]. However, the study had a high false-negative rate of 12.9 % illustrating the unpredictability of MCC and the caution of interpreting conclusions with regard to SNB. A large study by Paulson et al. [177] found that patients with negative SNB had improved outcomes compared to those undergoing a watch and wait policy. In the most recent large study published on the subject, Kachare et al. analysed SEER database data and found that SNB does improve survival in patients with MCC [178]. However, their conclusions have been questioned by some authors due to possible biases in their methodology. In particular, the fact that patients who underwent SLNB were more frequently given radiotherapy could be partly responsible for the improved outcomes [179]. Several other methodology biases were also highlighted including the large number of patients excluded and the fact SNB was more likely offered to younger and fitter patients. This may be of particular importance given that older age has been shown to be significantly associated with SLNB positivity [173].

Despite the positive findings in some studies, several authors have questioned the benefit of SNB in MCC. Warner et al. [180] found that SLN status is not an accurate predictor of locoregional recurrence, and the authors instead advocate the use of local and regional radiotherapy to obtain disease control. This is an argument also advocated by Shibayama et al. who suggest that the high rate of false positivity in their study (12.9 %) justifies the use of adjuvant radiotherapy in SNB-negative patients [176]. Other studies have shown false-negative rates of up to 33 % [179, 181–183] leading many authors to question the validity of SNB as a prognostic tool. In the largest single centre study conducted to date, Fields et al. [184] did not find SLN status to be a predictor of recurrence or survival in MCC. Frisch et al. [173] also concluded that SLN status did not predict survival in 173 patients studied. Given the lack of evidence for any benefit, and the high rates of metastases in high-risk MCC, some authors advocate that SNB is unlikely to be beneficial in high-risk cases, particularly as radiotherapy and chemotherapy provide relatively good outcomes [179]. Some authors also argue that alternative staging modalities such as FDG-PET may be a more accurate and less invasive method and further studies are warranted to determine their suitability [185]. However, Shnayder concluded that, in this patient population with very high rates of occult micrometastatic lymph node involvement, the true utility of SNB may be in ensuring that all at-risk nodes are adequately addressed, even in cases of "aberrant" drainage. Furthermore, SNB may allow for accurate staging in patients who are reluctant to undergo formal lymphadenectomy [102].

As with melanoma and SCC, the true prognostic significance of submicroscopic lymph node metastases, which are reported to occur in up to 100 % of MCC patients, remains unclear [186]. Further study will be required to clarify the exact role of SNB in this population.

In the USA, the National Comprehensive Cancer Network (NCCN) currently recommends SNB for all patients presenting with previously untreated, localised stage I disease [118].

15.18 Complications of Sentinel Node Biopsy

The steep learning curve, technical difficulty and minimally invasive approach of SNB may potentially lead to a higher risk of complications compared with formal lymphadenectomy, principally damage to the facial or spinal accessory nerve. In addition, the requirement for a completion lymphadenectomy in SLN-positive patients represents a second procedure in an inflamed, recently operated surgical field, theoretically contributing to the risk of iatrogenic injury [91]. However, in experienced hands the incidence of complications following SNB is reported to be as low as 1 % [37, 187], and several large studies have shown that the effect on morbidity and quality of life is significantly higher in those undergoing lymphadenectomy versus SNB.

For nodes located in the parotid gland, high rates of facial nerve paresis in selected studies have led some authors to recommend superficial parotidectomy over biopsy alone. However, others have shown that SNB can be safely and accurately performed in the parotid gland with continuous nerve monitoring and careful dissection [188–190].

15.19 Summary

Sentinel node biopsy represents a useful tool for staging the clinically negative lymphatic basins in patients with selected head and neck malignancies. For patients with melanoma, SNB is widely accepted as the gold standard staging tool for patients with intermediate-thickness tumours. It has also been shown to give a survival benefit to patients with sentinel node-positive disease who then undergo immediate lymphadenectomy. However, questions remain with regard to the overall survival benefit of SNB, the optimal management of SNB-positive patients, its usefulness in thin and thick tumours and the prognostic significance of very small tumour deposits. For the management of patients with early OSCC, SNB has not yet gained universal acceptance as a sole staging tool despite encouraging results, and further studies are required to clarify its role. Finally, the prognostic value of SNB for Merkel cell carcinoma has been questioned, and its utility may ultimately be limited to improvements in staging.

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Intensity-Modulated Radiation Therapy for Head and Neck Cancer

16

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Abstract

Intensity-modulated radiation therapy (IMRT) has revolutionized the treatment of head and neck cancer. A general overview of IMRT in the treatment of head and neck cancer is provided, focusing on guidelines for target determination and delineation for the different subsites within the head and neck. General facts, general management, target delineation, and IMRT results of specific anatomic subsites are outlined, including the nasopharynx, the oropharynx, the hypopharynx, the larynx, the oral cavity, and the thyroid which are discussed along with cancer of unknown primary.

Keywords

Intensity-modulated radiation therapy • Head and neck cancer • Target determination • Target delineation • Subsites

16.1 Introduction

Intensity-modulated radiation therapy (IMRT) has revolutionized the treatment of head and neck cancer. Compared with conventional opposed lateral fields that were used to treat these tumors, IMRT has provided comparable, if not better, local control with significantly improved long-term toxicities associated with high doses of radiation therapy. The ability to tightly conform to irregularly shaped tumors while limiting the dose delivered to the surrounding critical structures is the hallmark of IMRT. This advantage is especially seen when tumors are located near critical structures, i.e., the brain stem and optic structures, where there are great limitations in delivering effective therapeutic doses of radiation using conventional radiotherapy techniques. In addition, because there is minimal organ motion in the head and neck, with the use of proper immobilization, the planned dose distribution can be delivered with great assurance. The theoretical dosimetric advantage of IMRT has translated clinically into improvement in patient's quality of life. Several phase III trials have now demonstrated the beneficial effects of IMRT when compared with conventional radiotherapy in terms of minimizing late toxicities and in particular xerostomia. The purpose of this chapter is to provide a general overview of IMRT in the treatment of head and neck cancer, focusing on guidelines for target determination and delineation for the different subsites within the head and neck. Clinical updates will also be presented.

16.2 Target Determination and Delineation for Head and Neck Cancer

The complexity of the head and neck anatomy requires the treating radiation oncologist to carefully and accurately delineate the target volume prior to initiating IMRT. One must have an understanding of the relationship of the various structures to one another and the patterns of spread from the primary tumor site as well as the nodal drainage. Contouring guidelines have been evolved as more experience with IMRT was gained. Initial expert consensus recommendations for

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N0 nonsurgically violated neck [1] and proposed guidelines for node-positive or postoperative cases [2] have recently been updated in Table 16.1 [3]. Please note that although the updated lymph node level definitions are listed in Table 16.1 for your information, the target delineation suggestions in the remainder of the chapter utilize the old system shown on the left of the table for ease of use and comparison with other sources. It is important not to use the N0 guideline in which the nodal planes are not as well defined either due to the presence of nodes or surgical violation of tissue planes. The probability of nodal drainage to a specific ipsilateral lymph node level is directly related to the location and stage of the primary tumor. Table 16.2 specifies the likelihood of pathologic lymph node involvement in both the clinically positive and negative neck, by anatomic subsites.

16.2.1 General Delineation Guidelines

- An excellent reference in the delineation of nodal levels as visualized on computed tomography (CT) slices has been published by the Radiation Therapy Oncology Group (RTOG) (http://www.rtog.org/atlases/hnatlas/main.html) and the European Organization for Research and Treatment of Cancer (http://groups.eortc.be/radio/ATLAS.html).

Table 16.1 Lymph node levels

Commonly used classification level	Terminology	Definition	Updated terminology	Updated definition
Ia	Submental	Contains submental triangle		
Ib	Submandibular	Bounded by the posterior belly of digastric muscle, hyoid bone, and the body of mandible		
II	Upper jugular	Contains upper internal jugular lymph nodes. Extends from level of hyoid bone to skull base		Contains upper internal jugular lymph nodes. Extends from level of hyoid bone to the lateral process of 1st vertebra
III	Middle jugular	Contains middle internal jugular lymph nodes from hyoid bone to cricohyoid membrane		
IV	Lower jugular	Contains lower internal jugular lymph nodes from cricohyoid membrane to clavicle	IVa lower jugular	Contains lower internal jugular lymph nodes from cricohyoid membrane to 2 cm cranial to sternal manubrium
			IVb medial supraclavicular	Continuation of IVa to the sternal manubrium
V	Spinal accessory	Posterior triangle lymph nodes bounded by trapezius, sternocleidomastoid, clavicle	Va and Vb spinal accessory	Va and Vb posterior triangle lymph nodes bounded by trapezius, sternocleidomastoid and extending to the plane below transverse cervical vessels
			Vc lateral supraclavicular	Continuation of the posterior triangle nodes from the transverse cervical vessels to 2 cm cranial to the sternal manubrium
VI	Anterior compartment	From hyoid bone to suprasternal notch bounded laterally by the carotid sheath	VIa anterior jugular	From hyoid bone to suprasternal notch bounded laterally by anterior edges of the sternocleidomastoid
			VIb prelaryngeal, pretracheal, paratracheal	Contains anterior compartment nodes in the deep previsceral space between the common carotid arteries
VII	Upper mediastinal	Lymph nodes inferior to suprasternal notch in the upper mediastinum	VIIa retropharyngeal	From first cervical vertebra to the hyoid
			VIIb retrostyloid	Continuation of level II up to the base of skull

Table 16.2 Incidence and distribution of lymph nodes in N0 and N+ neck[a]

	Radiologically enlarged retropharyngeal nodes (%)			Pathologic nodal metastasis (%)									
				Level I		Level II[b]		Level III		Level IV		Level V	
Clinical presentation	N–	N+		N–	N+	N–	N+	N–	N+	N–	N+	N–	N+
Nasopharynx	40		86	–	–	–	–	–	–	–	–	–	–
Oral cavity													
Oral tongue	–	–		14	39	19	73	16	27	3	11	0	0
Floor of mouth	–	–		16	72	12	51	7	29	2	11	0	5
Alveolar ridge and RMT	–	–		25	38	19	84	6	25	5	10	1	4
Oropharynx													
Base of tongue	0		6	4	19	30	89	22	22	7	10	0	18
Tonsil	4		12	0	8	19	74	14	31	9	14	5	12
Hypopharynx													
Pharyngeal wall	16		21	0	11	9	84	18	72	0	40	0	20
Pyriform sinus	0		9	0	2	15	77	8	57	0	23	0	22
Larynx													
Supraglottic larynx	0		4	6	2	18	70	18	48	9	17	2	16
Glottic larynx	–	–		0	9	21	42	29	71	7	24	7	2

[a]Using prior definitions of lymph node levels as in (Refs. [1] and [2])
[b]Contains current level II and level VIIb
Reprinted from Chao KSC, Wippold FJ, Ozyigit G, Tran BN, Dempsey JF. Determination and delineation of nodal target volumes for head and neck cancer based on patterns of failure in patients receiving definitive and postoperative IMRT. Int J Radiat Oncol Biol Phys 2002;53(5):1174–1184. With permission from Elsevier

- Gregoire et al. [2] have published recommendations for the treatment of the node-positive or postoperative neck. Selected recommendations are as follows:
  - Target delineation should include the retrostyloid space up to the skull base when level II is involved.
  - Supraclavicular fossa would be included when level IV or Vb is involved.
  - The entire muscle should be included in the target when there is clear extracapsular extension.
  - The entire surgical field ("surgical bed") should be included in the target in postoperative cases.
- Extracapsular extension is a significant independent risk factor for local recurrence and distant metastasis. The clinical target volume (CTV) should be extended to the skin to account for microscopic spread.
- An "all-in-one" IMRT technique where all treated regions are being included in the IMRT fields is preferred over "split-field" IMRT when the low neck contains involved lymph nodes or if the primary tumor is located in the larynx, hypopharynx, and thyroid. A "split-field" technique is preferred in all other scenarios in an attempt to minimize the dose delivered to the normal larynx. A low anterior neck field is then matched to the IMRT fields. The common match point is just above the arytenoid cartilages, which will ensure adequate dosimetric coverage to the level II lymph nodal regions.
- A "cheater" spinal cord block is placed at the match point, approximately 2×2 cm, to add an extra layer of protection over the spinal cord in the region of the match line.
- The size of the lymph node denotes whether it should be included in the gross target volume (GTV). Lymph nodes with a minimal axial diameter of more than 1.1 cm in the subdigastric region and more than 1.0 cm in other nodal regions are considered suspicious for metastasis. Lymph nodes with a necrotic center should also be considered within the GTV.
- Communication between the operating surgeon and the radiation oncologist is crucial to ensure adequate delineation of the postoperative case.
- Imaging studies that are helpful to accurately define the gross extent of disease include CT with contrast, magnetic imaging resonance (MRI) with gadolinium, and positron emission tomography (PET) scans. Nodes that are smaller than 1 cm but are PET avid should be included in the target volume as GTV.
- PET and MRI fusion treatment planning is being used at an increasing number of institutions. While the treating physician should exercise caution in strictly defining the GTV and CTV in correlation with areas of increased fluorodeoxyglucose (FDG) uptake, these more sensitive imaging studies can provide useful information in target delineation.
- Different CTVs are established for all targets within one plan along with suggested dosing as listed below. Please note that several other fractionation schemes using either the cone-down or integrated boost techniques have been described and successfully used, and these represent a guideline only.

16.3 Treatment of Specific Anatomic Subsites

16.3.1 Nasopharynx

16.3.1.1 General Facts

- Anterior border: posterior choanae
- Posterior border: at the level of the first two cervical vertebrae and clivus
- Superior border: basisphenoid and basiocciput
- Inferior border: soft palate
- Lateral border: pharyngeal fascia including the eustachian tube
- Approximately 85–90 % of patients with nasopharyngeal cancer have lymph node involvement and 50 % have bilateral lymph node involvement. Nodal drainage can be direct to level V, through the lateral pharyngeal walls to the retropharyngeal and subdigastric nodes. Therefore, levels II–V are all at risk for involvement. Level Ia is rarely involved.
- Anatomic knowledge of the skull base is important as nasopharyngeal tumors can involve multiple cranial nerves including II–VI and IX–XII.
- The World Health Organization divides nasopharyngeal carcinoma (NPC) into the following: keratinizing squamous cell carcinoma; nonkeratinizing carcinoma, which subdivides into differentiated and undifferentiated; and basaloid squamous cell carcinoma. Lymphoepithelial carcinoma is a further subtype that represents nonkeratinizing and undifferentiated carcinomas with an abundance of lymphocytes.

16.3.1.2 General Management

- Treatment consists of definitive radiation therapy ± cisplatin followed by adjuvant chemotherapy, though there are debates regarding the added benefit of adjuvant chemotherapy.
- The 5-year overall survival rates range from 35 to 60 %.
- In the phase III trial (Al-Sarraf et al. [4]), patients with stage III–IV NPC were randomized to radiotherapy alone (70 Gy) or radiotherapy with concurrent cisplatin (100 mg/m^2) every 3 weeks during treatment, followed by cisplatin (80 mg/m^2) and fluorouracil (1000 mg/m^2/day), 4 days every 4 weeks after the completion of radiation therapy. At 5 years, overall survival was 37 % versus 67 % in the radiotherapy alone versus chemoradiation arms, respectively, and progression-free survival was 29 % versus 58 % in the radiotherapy alone versus chemotherapy arms, respectively.
- A more recent phase III study from Singapore [5] randomized 221 patients to radiation alone (70 Gy in 7 weeks) or concurrent cisplatin (weeks 1, 4, and 7 of radiation, 25 mg/m^2), followed by adjuvant cisplatin (20 mg/m^2) and fluorouracil (1000 mg/m^2) every 4 weeks for three cycles after the completion of radiation therapy. This trial has a design nearly identical to the US Intergroup Trial. The 3-year overall survival rate was 80 % versus 65 % for the chemoradiation versus the radiation-alone arm, respectively, with a hazard ratio for overall survival of 0.51 ($p=0.0061$). This trial confirmed the findings of the Intergroup Trial.
- Several meta-analyses demonstrated that the addition of chemotherapy to radiation therapy increased both progression-free and overall survival.

16.3.1.3 Target Delineation for IMRT

- Table 16.3 contains the suggested guidelines for target delineation in NPC. The GTV includes the primary tumor and involved lymph nodes. Please refer to the current NRG protocol (NRG-HN001) for more detailed target delineation guidelines.
- Due to the high probability of lymph node metastases, levels IB–V and the retropharyngeal lymph nodes should be included in the CTV bilaterally. Level I can be omitted in N0 cases or in node-positive cases with low risk of level IB involvement such as isolated retropharyngeal nodes or isolated level IV nodes. CTV also includes areas where NPC is likely to spread: the entire nasopharynx, posterior 1/3 of the nasal cavity and maxillary sinuses, parapharyngeal fat, clivus, and skull base.
- Figure 16.1 depicts a sample target volume for a patient with locally advanced NPC. The planning target volume (PTV) represents the final treatment volume and is the CTV with an "adequate" margin at the physician's discretion, to account for patient's day-to-day setup errors as well as organ motion.

Table 16.3 Suggested target delineation guidelines for nasopharyngeal cancer

Stage	CTV1	CTV2
T1–T4N0	GTV + 5–10 mm	Entire nasopharynx, posterior 1/3 of the clivus (entire clivus, if involved), skull base including foramen ovale (V3) and foramen rotundum, pterygoid fossae, parapharyngeal space, inferior sphenoid sinus (entire sphenoid sinus in T3–T4 disease), posterior 1/4 of maxillary sinuses and nasal cavity, bilateral retropharyngeal regions, bilateral levels II–V, cavernous sinus for advanced T3–T4 lesions
T1–T4N1–3	GTV + 5–10 mm	As above and include bilateral level IB (level IB may be omitted in low-risk node-positive patients, e.g., isolated retropharyngeal nodes or isolated level IV nodes)

At the discretion of the treating physician, the CTV margin can be as small as 1 mm in regions near critical normal tissues, i.e., the brain stem

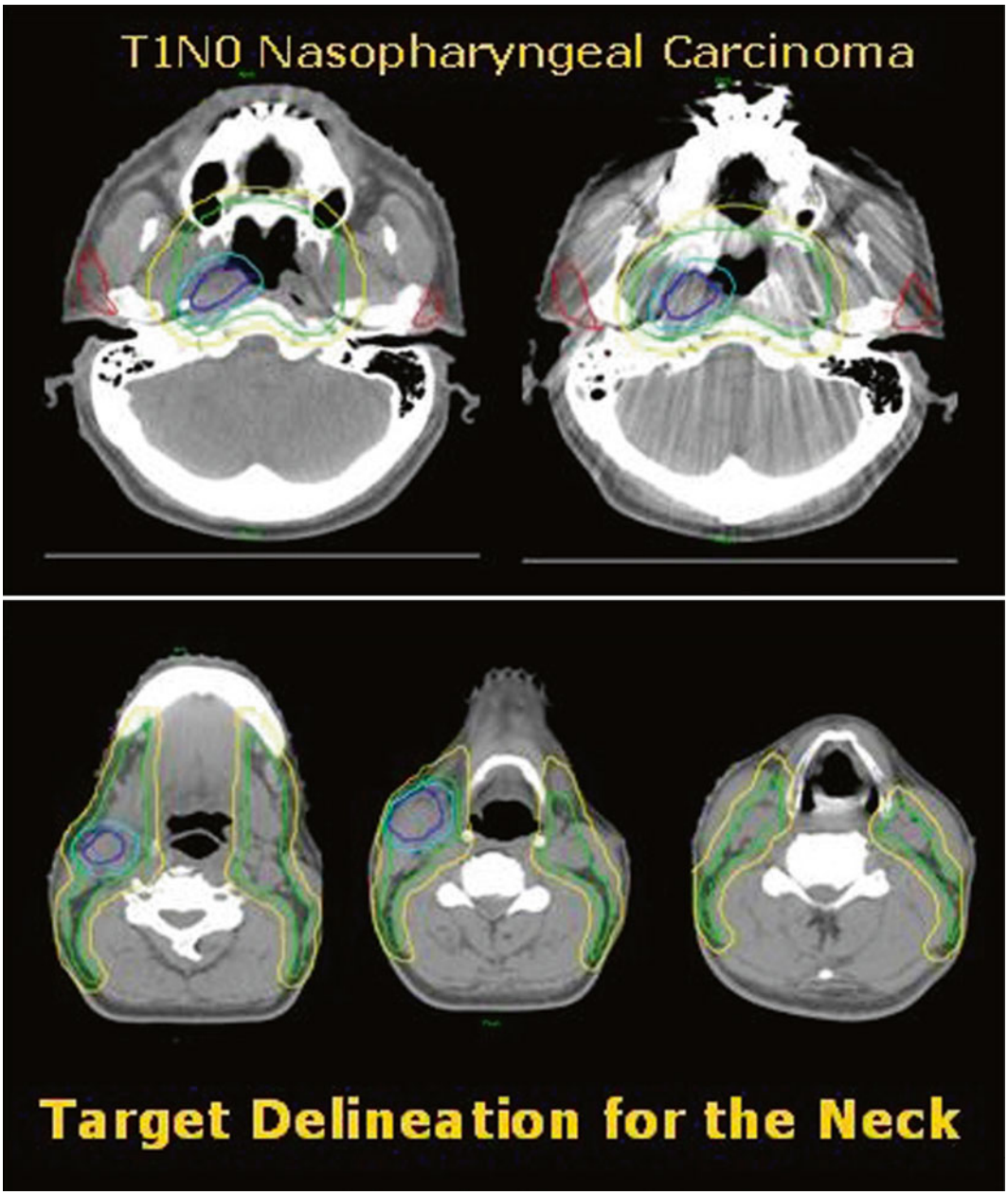

Fig. 16.1 Axial slices of representative slices of a nasopharyngeal carcinoma patient undergoing IMRT

16.3.1.4 IMRT Results

- Two randomized studies on early-stage NPC have demonstrated an advantage of IMRT over conventional techniques in terms of salivary preservation [6, 7].
- Lee et al. [8] reviewed 67 patients who underwent IMRT for NPC at the University of California-San Francisco between 1995 and 2000. At a median follow-up of 31 months, the 4-year locoregional progression-free rate was 98 %. Sixteen patients experienced distant metastases. At 24 months, only one of the 41 evaluable patients had grade 2 xerostomia, with the remaining having grade 0 or 1 toxicity. Several other single institutions also published similar results.
- Due to the encouraging locoregional control as well as improved salivary function with IMRT for NPC, the RTOG conducted a phase II multi-institution trial, and the results reproduced the excellent locoregional control rates reported by single institutions, with control rates on the order of 90 % [9].
- The predominant failure pattern in patients treated with IMRT for NPC is distant metastasis. Therefore, the RTOG conducted a phase II trial (RTOG 0615) in which patients with locoregionally advanced NPC were treated with the current standard chemotherapy and IMRT with the addition of the study drug, bevacizumab, a targeted agent directed against the vascular endothelial growth factor, to

test whether this addition will further decrease the rate of distant metastasis with the ultimate goal of improving overall survival [10]. Although addition of bevacizumab did not result in any unusual grade 3–4 events, toxicity was nonetheless substantial and compliance with the protocol suboptimal. Therefore, addition of the biologics to standard therapy should only be done in the context of a clinical trial.

- Efforts to identify patients at high risk of recurrence will help to ensure that future attempts to intensify therapy are done in populations that would derive the most benefit. The NRG is currently conducting a phase II/III trial (NRG-HN001) testing whether the levels of Epstein-Barr virus DNA in the blood of patients who completed standard chemoradiation can be used to identify patients who would benefit from adjuvant chemotherapy.

16.3.2 Oropharynx

16.3.2.1 General Facts

- The oropharynx consists of four subsites: soft palate, palatine tonsillar region (fossa and pillars), lingual tonsil or base of tongue, and posterior and lateral pharyngeal walls.
- The oropharynx has a rich lymphatic network and primarily drains into the subdigastric, upper cervical (II and III), and parapharyngeal lymph nodes (in proximity to cranial nerves IX–XII). Progression of nodal metastases is usually orderly, starting at level II and proceeding inferiorly to levels III and IV. Skip nodal metastases are relatively rare.
- The vast majority of tumors of the oropharynx are squamous cell carcinomas.

16.3.2.2 General Management

- Surgery and adjuvant radiation ± chemotherapy were previously the treatment paradigm.
- The study RTOG 73-03 (Kramer et al. [11]) was the first to suggest that surgery was not necessary as a component of treatment. This study randomized patients to either surgery, preoperative or postoperative radiation therapy or to definitive radiation therapy, reserving surgery for salvage treatment. There was no difference in locoregional control or overall survival, and complications were higher in the surgical arms.
- Parsons et al. [12] compiled results from 11 institutions from 1970 to 2000 using a MEDLINE search to determine if there was a difference in outcomes for patients treated with surgery ± adjuvant radiation versus definitive radiation ± neck dissection. While rates of locoregional control, 5-year overall survival, and 5-year cause-specific survival were similar in the two groups, the rate of significant complications was higher in patients who underwent up-front surgery.
- Fu et al. [13] performed a randomized trial of over 1000 patients with locally advanced head and neck cancer, randomizing them to (a) standard fractionation at 2 Gy once daily to 70 Gy; (b) accelerated fractionation, 1.2 Gy BID to 81.6 Gy; (c) accelerated fractionation with a split-course, 1.6 Gy BID to 38.4 Gy, 2-week break, then to 67.2 Gy; or (d) accelerated fractionation with a concomitant boost, 1.8 Gy daily to 72 Gy, with a boost of 1.5 Gy as a second daily treatment for the last 12 fractions. Arms (b) and (d) had better locoregional control than arms (a) and (c).
- Denis et al. [14] randomized 226 patients with stage III or IV oropharyngeal carcinoma to either (a) radiation alone (70 Gy in 2 Gy fractions) or (b) concomitant chemoradiation with the regimen above and carboplatin (70 mg/m^2) with fluorouracil (600 mg/m^2). Five-year overall survival (22 vs. 16 %), disease-free survival (27 vs. 15 %), and locoregional control (48 vs. 25 %) all favored the chemoradiation arm.
- Pignon et al. [15] performed a meta-analysis that included trials between 1965 and 2000 of patients with carcinoma of the oropharynx, oral cavity, larynx, or hypopharynx; there was an overall survival benefit of approximately 6.5 % in 5 years in favor of concomitant chemoradiotherapy.

16.3.2.3 Target Delineation

- Table 16.4 depicts suggested guidelines for target delineation in oropharyngeal carcinoma.
- Note that the bilateral neck is covered in all oropharyngeal lesions other than T1N0 and small well-lateralized T2N0 tonsillar lesions without soft palate or base-of-tongue involvement.
- Figure 16.2 depicts the delineation of a representative patient from Memorial Sloan-Kettering Cancer Center (MSKCC).

16.3.2.4 IMRT Results

- Chao et al. [16] reviewed 74 patients with squamous cell carcinoma of the oropharynx (all stages) treated with IMRT. Thirty-one received definitive IMRT and the remaining were treated postoperatively. Four-year overall survival and disease-free survival were 87 % and 81 %, respectively. Fifteen patients experienced grade 3 or higher skin toxicity, while 32 experienced grade 3 or higher mucosal toxicity (28 with grade 3). There were no grade 3 or higher late toxicities. The most common late toxicity was xerostomia; there were 32 patients with grade 1 and nine patients with grade 2 late toxicity.

Table 16.4 Suggested target delineation guidelines for oropharyngeal cancer

Site/stage	CTV1	Primary CTV2	Nodal CTV2 (N+ hemineck) or CTV3 (N0 hemineck)
Tonsil/T1–T2N0 (well lateralized)	GTV + 0–5 mm	GTV + minimum 1 cm margin including ipsilateral base of tongue/soft palate/ glossotonsillar sulcus, extending superiorly to pterygoid plate and inferiorly at least 1 cm below the GTV	Ipsilateral levels II–IV[a], RP to C1
Tonsil/T3–T4N0	GTV + 0–5 mm	As above, extending inferiorly to the hyoid	Bilateral levels II–IV[a], RP to C1
Tonsil/T1–T4N+	GTV + 0–5 mm	As above	Bilateral levels IB–V[a] including high level II/retrostyloid space, RP to skull base; consider limiting contralateral N0 neck to II–IV and RP to C1 only
Base of tongue T1–T4N0	GTV + 0–5 mm	GTV + minimum 1 cm including the entire base of tongue anteriorly, tonsillar sulcus, vallecular, pre-epiglottic space, extending superiorly to the tip of the uvula. For tumors involving the epiglottis, consider inclusion of the entire supraglottic larynx	Bilateral levels II–IV[a], RP to C1
Base of tongue T1–T4N+	GTV+ 0–5 mm	As above	Bilateral levels IB–V[a] including high level II/retrostyloid space, RP to skull base; consider limiting contralateral N0 neck to II–IV and RP to C1 only
Soft palate T1–T4N0	GTV+ 0–5 mm	GTV + margin including entire soft palate, superior aspect of tonsillar pillars and fossa, adjacent nasopharynx to pterygoid plate. May need to include pterygopalatine fossa and portion of hard palate	Ipsilateral II–IV, RP to C1
Soft palate T1–T4N+	GTV+ 0–5 mm	As above	Bilateral levels IB–V[a] including high level II/retrostyloid space, RP to skull base; consider limiting contralateral N0 neck to II–IV and RP to C1 only

Note: For all dosing, the treating physician can also decide on whether the N0 nodal CTVs are treated with the CTV2 or CTV3 dose
RP retropharyngeal nodes
[a]At the discretion of the treating physician, can treat levels Ib–V in N0 neck

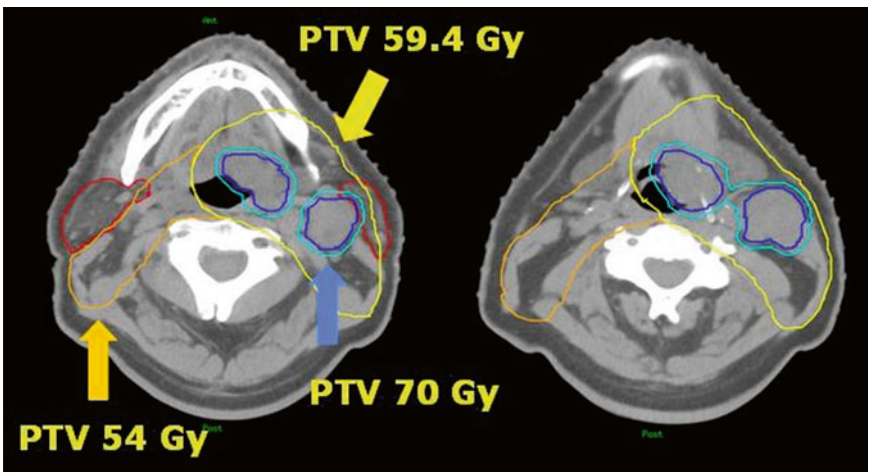

Fig. 16.2 Axial slices of representative slices of an oropharyngeal carcinoma patient undergoing IMRT

- Setton et al. updated the MSKCC experience with IMRT for oropharyngeal carcinoma [17, 18]. Between 1998 and 2009, 442 patients were treated (73 % stage IV disease, 93 % with definitive treatment). Three-year local failure incidence was 5.3 % and overall survival was 84.9 %. Incidence of late dysphagia and xerostomia grade 2 or higher was 11 % and 29 %, respectively.

16.3.3 Hypopharynx

16.3.3.1 General Facts

- The anatomical boundaries of the hypopharynx are as follows: superior, hyoid bone, and inferior, inferior edge of cricoid cartilage. The pyriform sinuses are lateral to the vocal cords, but the apices of the pyriform sinuses extend inferiorly to the vocal cords.
- Superior to the hypopharynx is the oropharynx and inferiorly lies the most superior portion of the esophagus (the cervical esophagus).
- There is significant lymphatic drainage to the hypopharynx. Three main pathways exist: (1) through the internal branch of the superior laryngeal artery to levels II and III, (2) through the paratracheal lymph nodes into level IV and the mediastinal lymph nodes, and (3) to the retropharyngeal lymph nodes.
- The most common site of lymph node metastasis is to level II.
- Almost all hypopharyngeal tumors are squamous cell carcinomas.

16.3.3.2 General Management

- T1–T2N0 disease can be treated with either definitive radiation or surgery.
- Conservative surgery for early-stage disease entails a partial laryngopharyngectomy with ipsilateral neck dissection. Patients with N2C disease undergo a bilateral neck dissection.
- The following are contraindications for conservation surgery: vocal cord paralysis, pyriform sinus apex invasion, cartilage invasion, extralaryngeal extension, and/or arytenoid involvement.
- For locally advanced disease, including T3–T4 or node-positive tumors, surgery with adjuvant radiation ± chemotherapy or concurrent chemoradiotherapy is the treatment of choice.
- The surgery for locally advanced disease is a total laryngectomy and partial pharyngectomy with neck dissection.
- Multiple retrospective studies have demonstrated the efficacy of postoperative radiation therapy for advanced tumors [18–21].
- Randomized studies have shown the added benefit of chemotherapy given concurrently with postoperative radiation therapy in patients with high-risk features, i.e., positive margins or extracapsular extension [22–24].
- In a phase III trial by Lefebvre et al. [25], patients with T2–T4N0-N2b disease were assigned to either (a) immediate laryngectomy with postoperative radiotherapy (50–70 Gy) or (b) induction chemotherapy with cisplatin (100 mg/m^2) and fluorouracil infusion (1000 mg/m^2), followed by either radiation (70 Gy) in the responders or laryngectomy followed by postoperative radiation (50–70 Gy) in the nonresponders. While local failures were approximately the same in the two arms (12 vs. 17 %), there were fewer distant failures in arm b (25 vs. 36 %), and the median overall survival was also greater (44 vs. 25 months). The authors concluded that laryngeal preservation is a feasible approach in patients with locally advanced hypopharyngeal cancer.
- Several randomized trials comparing chemoradiotherapy to radiotherapy alone included hypopharyngeal carcinoma and have shown improved locoregional control, disease-free survival, and overall survival in the combined-modality arm.

16.3.3.3 Target Delineation

- Due to concerns regarding late effects, hypofractionation and/or simultaneous integrated boost is not recommended for treatment of hypopharynx.
- At MSKCC, dose-painting IMRT delivering 70 Gy in 2 Gy fractions to PTV1, 59.5 Gy in 1.7 Gy fractions to PTV2, and 56 Gy in 1.6 Gy fractions to PTV3 is used.
- Extended IMRT plans are recommended to avoid a match line across the primary tumor or involved lymph nodes.
- Table 16.5 depicts suggested target volumes for patients with hypopharyngeal tumors. GTV includes all gross disease and any clinically involved lymph nodes.
- Due to the high likelihood of lymphatic spread, levels II–V should be included in the field along with retropharyngeal nodal regions. Please see Table 16.5 for further details.
- Figure 16.3 depicts representative CT slices from a patient with locally advanced hypopharyngeal carcinoma.

16.3.3.4 IMRT Results

- Lee et al. [26] analyzed 20 patients with laryngeal cancer and 11 patients with hypopharyngeal cancer treated with IMRT and concurrent platinum-based chemotherapy at MSKCC, most of whom had stage IV disease. Two-year locoregional control for the patients with hypopharyngeal tumors was 73 %, and 2-year overall survival was 53 %. Four of the 11 patients were PEG-tube dependent at the time of the analysis, and the 2-year PEG-tube dependency rate was 31 %.

Table 16.5 Suggested target delineation guidelines for hypopharyngeal cancer

Site/stage	CTV1	CTV2 (primary and N+ hemineck) or CTV3 (N0 hemineck)
T1–T4N0	GTV + 0–5 mm	GTV + 1 cm margin, including the entire subsite, bilateral levels II–IV, RP. Consider paratracheal/upper mediastinal coverage for inferior tumors with involvement of postcricoid space
T1–T4N+	GTV + 0–5 mm	GTV + 1 cm margin, including the entire subsite and any tissue that lies between the primary tumor and involved level III–IV nodes. Bilateral levels Ib–V, RP to skull base, may cover contralateral II–V and RP to C1 for N0 side for non-midline primaries. Consider paratracheal/upper mediastinal coverage for inferior tumors with involvement of postcricoid space

RP retropharyngeal nodes

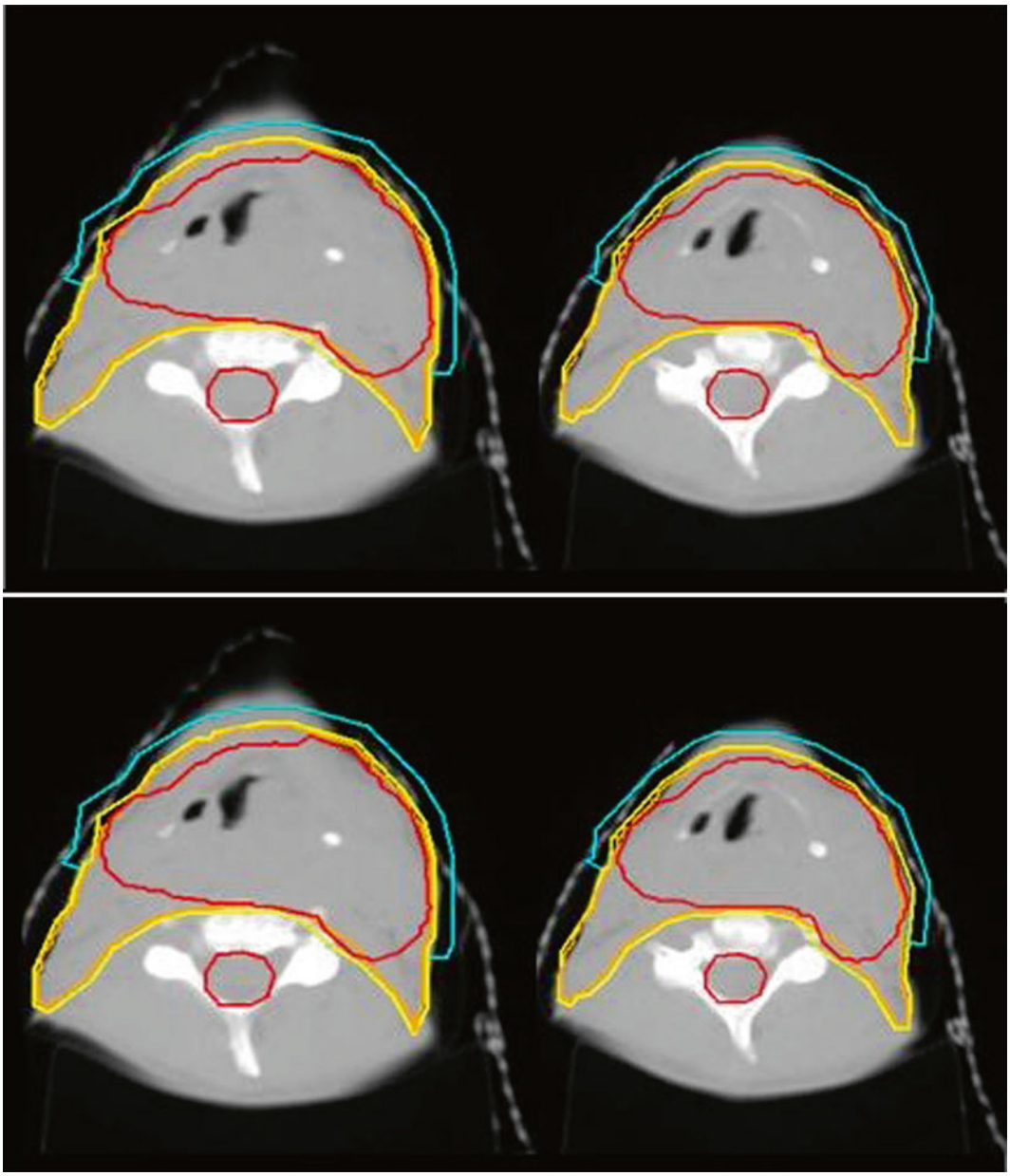

Fig. 16.3 Axial slices of representative slices of a hypopharyngeal carcinoma patient undergoing IMRT

16.3.4 Larynx

16.3.4.1 General Facts

- The larynx is divided into three subsites: the supraglottis, the glottis, and the subglottis.
- The supraglottis contains the following: epiglottis, aryepiglottic folds, arytenoids, and false vocal cords. The supraglottis has a significant amount of lymphatic drainage. Through the thyrohyoid membrane, the lymphatic drainage proceeds to levels II–IV.
- The glottis contains the true vocal cords and the anterior and posterior commissures. There are no lymph nodes that drain from the true vocal cords. Lymph node metastases from tumors of the true vocal cords occur with extension of the tumor to the subglottis or supraglottis.
- The subglottis extends from the lower boundary of the glottis to the inferior aspect of the cricoid cartilage. The subglottis drains to prelaryngeal, lower jugular, pretracheal, and upper mediastinal lymph nodes.
- Greater than 95 % of laryngeal tumors are squamous cell carcinomas.
- One distinct entity of squamous cell carcinoma in laryngeal cancer is verrucous carcinoma, which is well differentiated and exophytic. It has been cited in the past that these tumors undergo transformation to an aggressive phenotype after radiation, but whether or not this truly occurs remains unclear.

16.3.4.2 General Management

- Carcinoma in situ of the vocal cord can be managed by either radiation therapy, local excision, or laser therapy. With vocal cord "stripping" or laser excision, tumors often recur, and such patients should be referred for radiation therapy. Control rates are above 95 % with radiation.
- For early-stage carcinoma of the vocal cord (T1–T2N0M0), surgical excision and radiation therapy have been shown to have comparable results. However, voice quality is generally better preserved with radiation therapy. The typical dose is 2.25 Gy to a total dose of 63 Gy for T1 and 65.25 Gy for T2 lesions.
- To study locally advanced laryngeal cancer, RTOG 9111 [27] randomized 547 patients with stage III or IV laryngeal carcinoma (T1 tumors and large-volume stage IV excluded) to either (a) induction chemotherapy with cisplatin (100 mg/m^2) and fluorouracil (1000 mg/m^2) followed by radiation therapy (70 Gy in 2 Gy fractions), (b) concurrent radiation (70 Gy in 2 Gy fractions) and cisplatin (100 mg/m^2 on days 1, 22, and 43), or (c) radiation alone (70 Gy in 2 Gy fractions). The study found that concurrent chemoradiation provided an increased rate of larynx preservation at 2 years (88 % vs. 75 % and 70 % in arms b vs. arms a and c, respectively), as well as improved disease-free survival.
- Early exophytic lesions of the supraglottis (T1N0) can be treated with either definitive radiation or hemilaryngectomy (supraglottic laryngectomy), which provides voice preservation.
- For intermediate disease (T2NX), definitive chemoradiation and supraglottic laryngectomy offer similar rates of local control. The following are contraindications to supraglottic laryngectomy: bilateral arytenoid involvement, arytenoid fixation, base-of-tongue involvement, invasion of the thyroid or cricoid cartilage, involvement of the postcricoid region, impaired vocal cord mobility, glottic extension, and/or patients at increased risk of aspiration (elderly, patients with lung disease).
- For extensive lesions (T3–T4), either voice preservation with chemoradiation or surgery and postoperative radiation ± chemotherapy are utilized. Note that patients with significant thyroid cartilage invasion are usually referred for surgery. Postoperative chemotherapy should be considered in patients with a positive margin or extracapsular extension.
- Subglottic tumors are rare and are usually diagnosed at an advanced stage. The treatment of choice is typically surgery followed by radiation ± chemotherapy. Alternative treatment consists of concurrent chemoradiotherapy.

16.3.4.3 Target Delineation

- Table 16.6 demonstrates the suggested target delineation for a patient with supraglottic cancer. As noted above, subglottic tumors are rare and treatment should be individualized depending on the clinical situation.
- Laryngeal cancer (other than T1–T2N0 glottic tumors) is generally treated using an "all-in-one" technique. No low anterior neck field is utilized.
- As noted above, in T1–T2N0 tumors the neck is generally not treated. However, in T2N0 tumors that are bulky, or with subglottic extension, the physician can consider treating the bilateral neck, as described for T3–T4N0 tumors.

16.3.4.4 IMRT Results

- In the Lee et al. [28] study cited above, 20 patients with laryngeal cancer (and mainly stage IV disease) were treated with IMRT and concurrent platinum-based chemotherapy. The 2-year rates of locoregional control and overall survival were 90 % and 69 %, respectively, for the patients with laryngeal cancer. One patient developed laryngeal necrosis and one patient had an unusual complication of necrotizing fasciitis. The 2-year PEG-tube dependency rate was 15 %.

Table 16.6 Suggested target delineation guidelines for laryngeal cancer

Site/stage	CTV1	CTV2 (primary and N+ hemineck)	CTV3 (N0 hemineck)
Supraglottic			
T1–T4N0	GTV + 5–10 mm	CTV1 plus entire larynx from the top of the thyroid notch to the bottom of the cricoid cartilage	Bilateral levels II–IV
T1–T4N+	GTV + 5–10 mm	As above and levels Ib–V on the involved N+ neck, including high level II	At least levels II–IV of the uninvolved neck and levels Ib–V for the involved neck, consider covering VI, VII, and RP
Glottic			
T3–T4N0	GTV + 5–10 mm	CTV1 plus entire larynx from the top of the thyroid notch to the bottom of the cricoid cartilage	Bilateral levels II–IV
T1–T4N+	GTV + 5–10 mm	As above and levels Ib–V on the involved N+ neck, including high level II	At least levels II–IV of the uninvolved neck and levels Ib–V for the involved neck, consider covering VI, VII, and RP

Note: RP nodal regions should be covered if there is involvement of the hypopharynx or there are involved cervical lymph nodes. Level VI, including tracheoesophageal nodes, should be covered for primary tumors with subglottic extension, hypopharyngeal involvement, gross level IV adenopathy, emergent tracheostomy, or soft tissue extension from the primary into the neck. Level VII coverage should be considered for subglottic extension or hypopharyngeal involvement
RP retropharyngeal nodes

16.3.5 Oral Cavity

16.3.5.1 General Facts

- The oral cavity is made up of the lips, buccal mucosa, the floor of the mouth, the upper and lower gingiva, the anterior two-thirds of the oral tongue, the hard palate, and the retromolar trigone.
- The upper lips are drained primarily by level IB (submandibular) lymph nodes and less commonly by the periauricular and parotid lymph nodes.
- The lymphatic drainage to the buccal mucosa is primarily to levels IB and II.
- The primary lymphatic drainage of the floor of the mouth is to levels IA and II.
- The primary lymphatic drainage of the upper gingival is to levels IB and II.
- The muscles of the oral tongue are innervated by the hypoglossal nerve, and sensory innervation is through the lingual nerve, which is part of the mandibular branch of the trigeminal nerve (V). Taste sensation is provided by cranial nerve VII. The three most common routes of lymphatic drainage are to levels IB, II, and, less commonly, IA. However, there is also a direct route to level III, and occasionally isolated metastases are found in this region.
- The most common lymphatic metastases of the hard palate are to levels IB and II.
- The retromolar trigone primarily drains to levels IB and II.
- Squamous cell carcinoma accounts for the vast majority of cases.

16.3.5.2 General Management

- Definitive surgery is the preferred treatment of choice for all oral cavity cancers unless there is a contraindication. Postoperative radiation therapy is given to those at high risk for recurrence.
- Chemotherapy has been shown to benefit patients with positive margins or extracapsular extension, as detailed above in the Cooper et al. and Bernier et al. studies [22–24].

16.3.5.3 Target Delineation

- Due to the higher propensity for oral cavity tumors (and in particular floor-of-mouth and oral tongue cancers) to invade lymph node level I, these lymph nodes should be included in the neck volumes. Therefore, in the positive neck, levels I–V should be included. In the node-negative contralateral neck, levels I–IV should be included.
- Coverage for the postoperative bed should be generous as this anatomic site has been surgically violated. This volume should at least include the preoperative GTV.
- One can consider sparing the contralateral neck in early-stage lesions of the buccal mucosa, retromolar trigone, and gingiva; for lesions that are not well lateralized, the bilateral neck should be treated.
- The risk of metastasis to retropharyngeal lymph nodes is low, but these lymph nodes can be treated in locally advanced or midline lesions at the physician's discretion.
- Figure 16.4 demonstrates representative CT slices from a patient with oral tongue cancer treated at MSKCC.

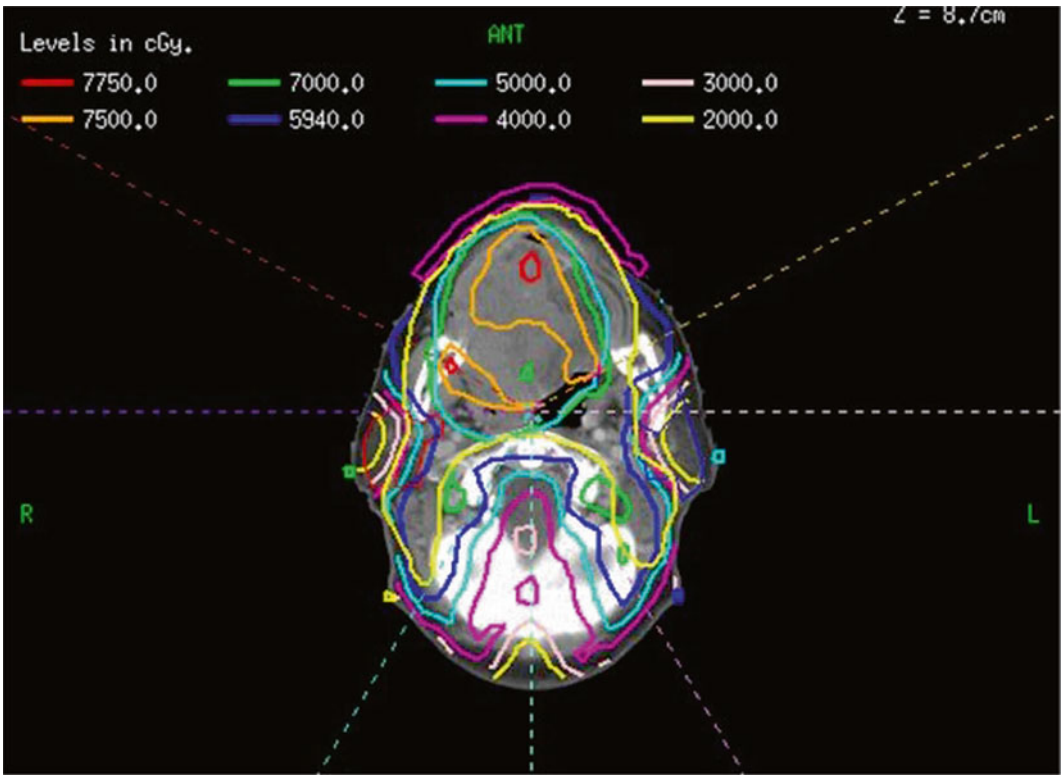

Fig. 16.4 Axial slices of representative slices of an oral cavity patient undergoing IMRT

16.3.5.4 IMRT Results

- Yao et al. [28] recently reported on 55 patients with squamous cell carcinoma of the oral cavity, 91 % of whom had stage III or IV disease. At a median follow-up of 17 months, 2-year disease-free and overall survival rates were 82 % and 68 %, respectively. When examining prognostic factors for locoregional control, the study found that anatomic subsite was predictive, with 2-year rates of locoregional control being 69 % in oral tongue cancer, 100 % for floor-of-mouth cancer, and 83 % for all other groups together. Extracapsular extension was also found to significantly affect locoregional control.
- Studer et al. [29] analyzed 58 patients with oral cavity cancer treated at the University of Zurich. Twenty-eight of these patients were referred for postoperative treatment and the remainder for definitive treatment. Forty patients had T3 or T4 lesions. Patients treated postoperatively had a 92 % rate of local control at 2 years, while those treated with radiation alone had a local control rate of 30–40 %.
- Gomez et al. [30] reported a series of 35 oral cavity patients treated with IMRT ± chemotherapy after definitive surgical resection. All patients had stage III–IV disease. With a median follow-up of 28.1 months, the 2- and 3-year estimates of locoregional progression-free survival were 84 % and 77 %, respectively. The overall survival was 74 %. Late complications included trismus (17 %) and osteoradionecrosis (5 %).

16.3.6 Thyroid

16.3.6.1 General Facts

- The thyroid gland is made up of two lobes. They are joined by the thyroid isthmus. The gland lies posterior to the strap muscles and anterior to the prevertebral muscles, inferior to the thyroid cartilage and with the isthmus overlying the second and third tracheal rings.
- The thyroid gland has a rich vascular and lymphatic supply. The lymphatic drainage is primarily to the surrounding lymph nodes of the trachea and esophagus (level VI), with a secondary route being to the cervical lymph nodes, levels I–V. There is also lymphatic drainage to level VII.

16.3.6.2 General Management

- The mainstay of management for thyroid carcinoma is surgery. Depending on the extent of disease, this resection can entail a near-total thyroidectomy, total thyroidectomy, or wide composite resection to include the surrounding infiltrated tissue.
- External beam radiotherapy is given in select cases where patients are at high risk for local recurrence due to their

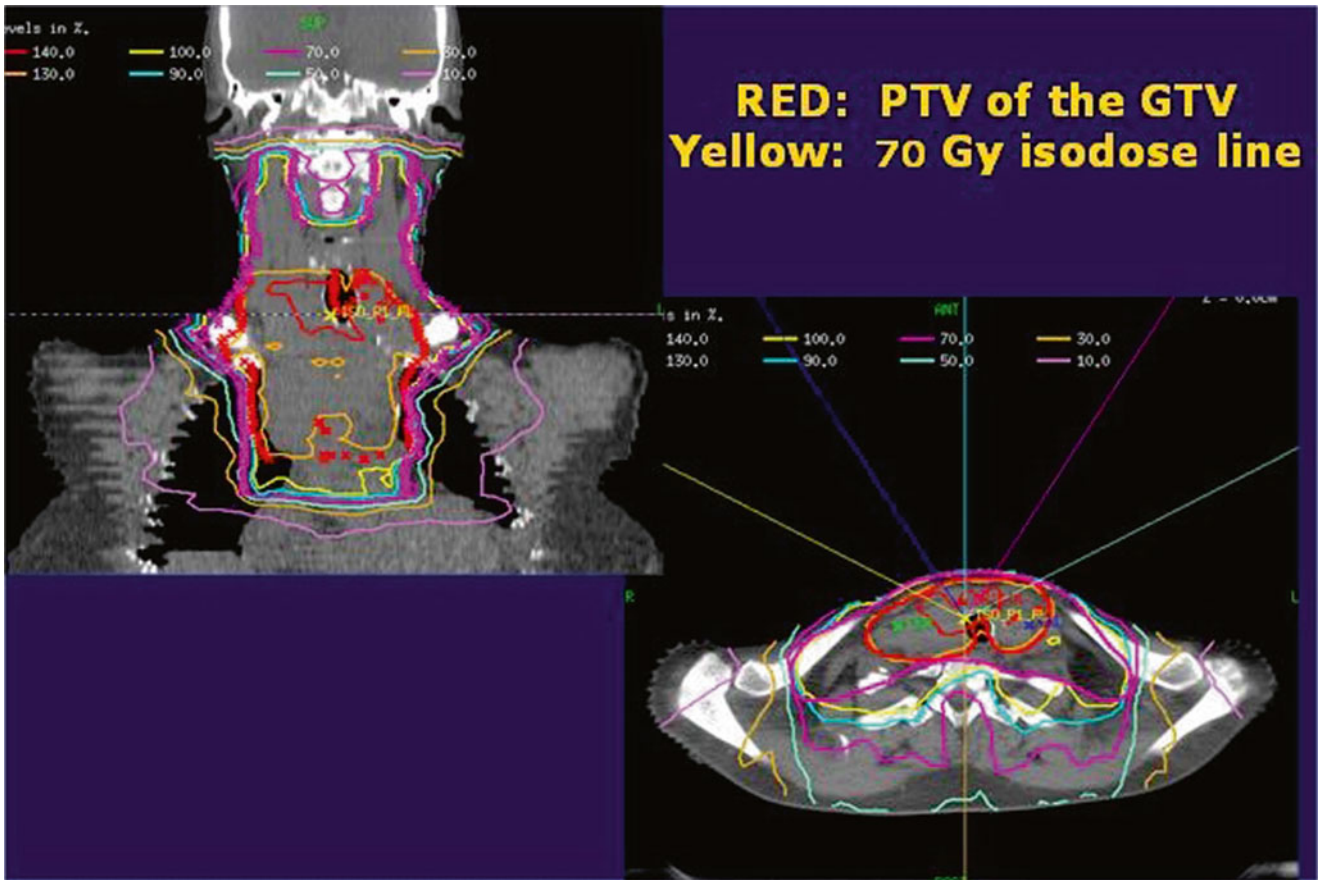

Fig. 16.5 Axial slices of representative slices of a thyroid cancer patient undergoing IMRT

locally aggressive nature, aggressive histology, or unsatisfactory surgery.

16.3.6.3 Target Delineation

- The CTV includes the thyroid bed, tracheoesophageal groove, central compartment, levels II–VII, and the upper mediastinum to the level of the carina.
- Figure 16.5 demonstrates representative CT slices from a patient with thyroid cancer treated with IMRT.

16.3.6.4 IMRT Results

- Rosenbluth et al. [31] examined 20 patients with nonanaplastic thyroid carcinoma treated with IMRT. Seventeen of these patients had T4 disease and 16 patients had N1 disease. The median total radiation dose was 63 Gy ("high-risk" PTV with a total dose of 59.4–63 Gy, positive margins treated to 63–66 Gy). The 2-year local control rate was 85 % and the 2-year overall survival rate was 60 %. Four of the six deaths were due to metastatic disease.
- In terms of toxicity, seven of 20 patients had grade 3 acute mucositis, three of 20 patients developed grade 3 pharyngitis, and two of 20 patients had grade 3 skin toxicity. There was no grade 3 or higher xerostomia.

16.3.7 Cancer of Unknown Primary

16.3.7.1 General Facts

- The most commonly involved lymph nodes in cancer of unknown primary (CUP) of the head and neck are levels II and III. Levels I, IV, and V are less commonly involved.
- The most common primary site for CUP is the oropharynx, which accounts for approximately 80 % of tumors.
- The most common histology of CUP is squamous cell carcinoma, with lymphoma, adenocarcinoma, and poorly differentiated tumors being less common.
- Multiple studies have examined the role of PET scan in detecting the primary tumor, particularly when conventional techniques have not elucidated the origin of disease.

16.3.7.2 General Management

- Patients with N1 disease can be treated with a neck dissection alone if there is no extracapsular extension.

However, a review by the Danish Society for Head and Neck Oncology showed that patients treated with surgery alone had an emerging primary rate of 54 % at 5 years and a neck control rate of 58 % [32].

- Radiation therapy alone is also an option for patients in lieu of neck dissection. In the same study by the Danish Society, the mucosal control rate was 84 % in patients receiving radiation alone and the neck control rate was 50 %.
- Surgery in combination with radiation therapy has appeared to produce the lowest rates of mucosal primary emergence and neck control. The emerging primary rate in the study above for patients receiving surgery with radiation therapy was 15 %.
- Patients are usually treated with a field that encompasses the bilateral cervical lymph nodes, the retropharyngeal lymph nodes, and the comprehensive mucosal membranes. However, studies have also been done that utilized ipsilateral neck radiation, particularly for patients with poorer performance status.

16.3.7.3 Target Delineation

- In addition to lymph node coverage, the mucosal surfaces throughout the head and neck should also be targeted, including the nasopharynx, oropharynx, larynx, and hypopharynx, while the oral cavity is excluded.
- The dosing of the different mucosal sites can differ depending on the likelihood of emergence of primary in that site. For example, a patient with Asian descent should receive a higher total radiation dose to the nasopharynx, while a Caucasian is more likely to have disease involving the oropharynx and hence a higher total dose should be delivered to that site.
- There are situations at the discretion of the treating physician where only the involved neck needs to be treated.

16.3.7.4 IMRT Results

- Klem et al. [33] examined 21 patients treated with IMRT. Fourteen were treated with chemoradiation, and five patients received radiation with definitive intent (rather than in the adjuvant setting). Two-year rates of locoregional survival, distant metastasis-free survival, and overall survival were 90 %, 90 %, and 85 %, respectively.
- In terms of toxicity, at 6 months posttreatment, one patient had greater than grade 1 xerostomia, and grade 3 acute skin and mucosal toxicity were 5 % and 14 %, respectively. PEG-tube placement was required in 13 patients, but at the last follow-up, only one patient was PEG-tube dependent. Three patients experienced esophageal strictures, and all had improvement with dilation.

16.4 Conclusions

IMRT has resulted in clinical improvement quality of life for patients with head and neck cancer. Yet target delineation remains a challenge, due to the complexity of the head and neck anatomy. Improved imaging promises to help improve the delineation of the extent gross disease, but understanding the patterns of spread of disease from the primary tumor site and the nodal drainage is required.

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Stereotactic Radiotherapy in Head and Neck Cancer Patients

17

Thomas Leroy and Eric Lartigau

Abstract

Stereotactic body radiation therapy is rapidly spreading over radiation therapy department. It offers new possibilities of treatment for patients with head and neck tumor.
Preliminary results show excellent results in terms of local control.
High-dose gradient allows decreasing toxicities as dysphagia by sparing critical structures. However due to the high-dose delivery, precautions must be taken to prevent severe toxicity like carotid blowout syndrome.
Main indication up today is reirradiation of tumors in previously irradiated field.
Boost strategies are currently under development and must be validated in clinical trials.
Stereotactic radiation body therapy seems to be very promising and must be considered in multimodal approach for the treatment of head and neck carcinomas.

Keywords

Stereotactic body radiotherapy • Head and neck cancer • Salvage treatment • Reirradiation

List of Abbreviations

3DRT	3D conformal radiotherapy
CBOS	Carotid blowout syndrome
H&N	Head and neck
QOD	Every other day
IMRT	Intensity-modulated radiation therapy
SBRT	Stereotactic body radiation therapy
SCC	Squamous cell carcinoma

17.1 Introduction

Radiotherapy plays a key role in the management of head and neck tumors whether in adjuvant setting after surgery or whether in exclusive setting with or without chemotherapy or targeted therapies. Despite the improvement of multimodal strategies, a local recurrence will occur in approximately 30 % of the patients with a squamous cell carcinoma (SCC).

Stereotactic body radiation therapy (SBRT) has been developed in these last years and seems promising to improve the H&N cancer patient's prognosis especially in the treatment of the previously irradiated recurrences.

We will review here the main current indications, treatment modalities, and future possible indications of SBRT in the management of head and neck tumors.

17.1.1 SBRT Definition

Radiosurgery, which is defined by the use of a single fraction, was initially used to treat brain tumors. Technological and imaging developments have allowed treating extracranial tumors.

Currently, SBRT is defined by a high conformal irradiation in few fractions (usually 3–6) to a limited volume with high "ablative" dose per fraction (6–20 Gy).

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The high conformation of SBRT results in a high-dose gradient and minimal dose to the organ at risk. (Fig. 17.1).

In order to deliver such highly conformal irradiation, it is necessary to know exactly the position of the target with imaged-guided radiotherapy systems and to use a reproducible immobilization system to minimize setup errors. Current SBRT systems can deliver irradiation with an infra-millimetric precision. Some of these systems are dedicated to SBRT (CyberKnife, Novalis), and some can perform other radiation modalities like IMRT or three-dimensional conformal radiotherapy (3DRT). The CyberKnife, for example, is a robotic linear accelerator, dedicated to SBRT, which can follow the target movement. A CyberKnife treatment plan typically uses 80–200 beams, and this explains the high-dose gradient and the high conformation dose (Fig. 17.2).

17.1.2 Radiobiology of SBRT

Conventional fractionation uses doses per fraction of 1.8–2 Gy. The efficacy of this type of radiotherapy is directly linked with the difference between normal and can-

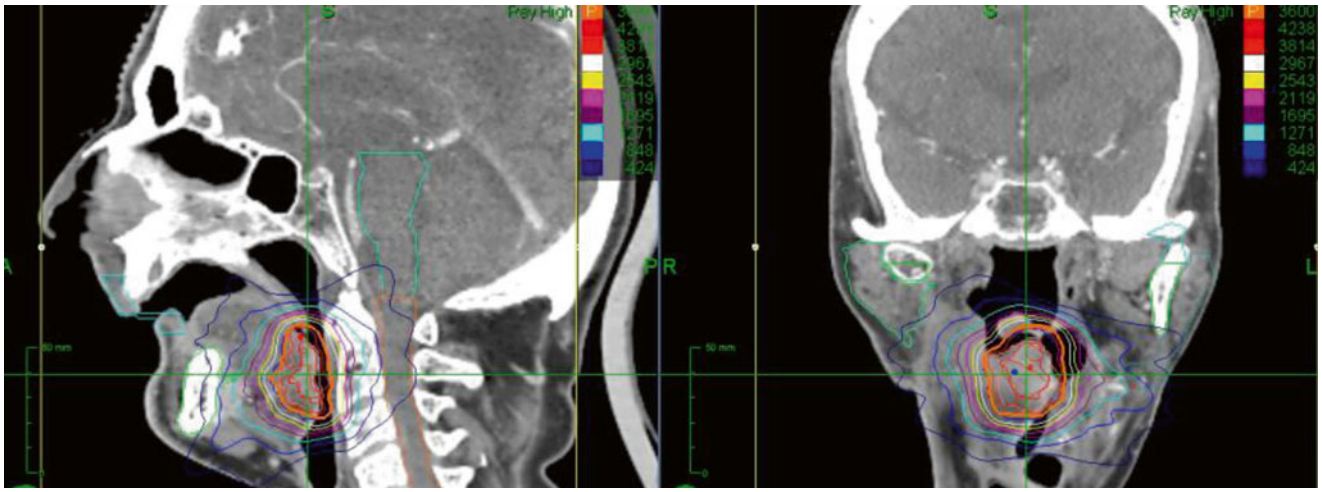

Fig. 17.1 CyberKnife treatment plan for a reirradiation of an oropharynx SCC

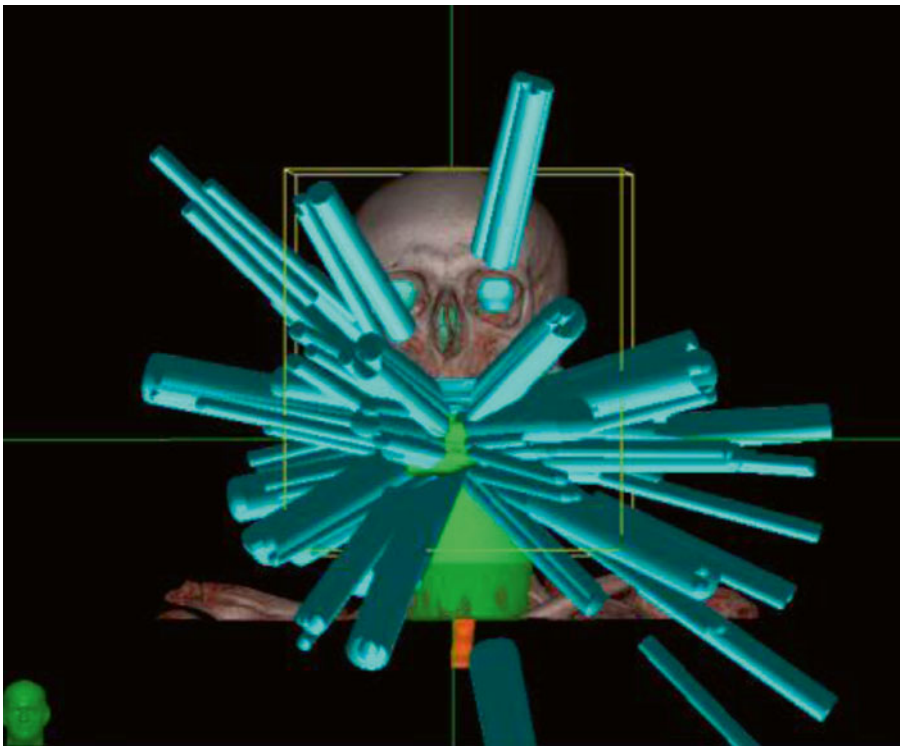

Fig. 17.2 Beam modelization of a CyberKnife treatment plan (same patient as in Fig. 17.1)

cer cells in their capacity to repair DNA lesions: this is called the differential effect.

The biological effect is predicted in conventional fractionation with the linear-quadratic model that derives from survival curves established from cells.

Higher dose per fraction should not be used with 3DRT due to the risk of late side effects. However the high conformation of SBRT allows to spare normal tissue and to deliver higher dose per fraction to the tumor (5–20 Gy).

Radiobiology of SBRT is currently debated, but it seems that the linear-quadratic model can predict biological effect although vascular and immunogenic effects are not assessed.

With such dose level radiation, it is important to consider new organ at risk constraints in the treatment planning. For example, carotid arteries are usually considered as radioresistant, but in hypofractionation setup, some hemorrhage or carotid blowout syndrome were observed.

To prevent severe toxicities, interval between two fractions needs to be longer in SBRT than in 3DRT. Indeed King et al. [1] observed decreased rate of severe rectal toxicity after treatment every other day (QOD) compared with that after treatment over 5 consecutive days (0 vs. 38 %, $p=0.0035$). Although these observations were made in prostate cancer, the phase I dose escalation for head and neck tumor reirradiation used QOD treatment and conclude that up to 44 Gy in five fractions SBRT was well tolerated [2].

17.2 SBRT for Squamous Cell Carcinoma

17.2.1 Reirradiation

Despite multimodal approach, 30–50 % of the patients with SCC will present a local relapse in a previously irradiated region.

Surgery remains the gold standard but is not possible in most of the case.

Taussky et al. [3] have reported on the treatment of 297 patients, 26 % (75 patients) of whom had a local recurrence. Only 17 of the recurrent patients (20 %) were eligible for salvage surgery.

Chemotherapy is a palliative option, which is not satisfactory in case of isolated local recurrence with a median survival of 6–8 months.

3DRT has been investigated with good results in terms of local control but with significant toxicities. Currently Vokes et al. [4] remain the standard of care in case of reirradiation.

A study of 169 patient forms the Gustave Roussy Institute which showed increased toxicities with this protocol: 32 % of grade 3 and 14 % of grade 4 mucositis, 41 % of mucosal necrosis; five patients died of carotid hemorrhage [5].

So SBRT in head and neck tumor seems particularly interesting in the context of previously irradiated patients to increase local control and prevent toxicities.

Several cohorts have been reported with dose delivered ranging from 13 to 50 Gy in 1–7 fractions. We have summarized the main series in Table 17.1.

However, most of them are retrospective and are heterogeneous. They include both SCC and nasopharynx carcinoma. The prescribed doses are also very different in terms of prescription isodose, dose, and fractionation.

In most of the case, the reirradiation is well tolerated, but exceptional severe toxicities like carotid blowout syndrome were observed.

Cengiz et al. [6] published the highest rate of deaths due to CBOS with 15.6 %. They reported that there was a significant risk of CBOS in patients whose carotid arteries were surrounded by the tumor >270° circumferentially. The treatment was in this study delivered every day. The high rate of fatal CBOS leads to a change of fractionation with QOD treatment with a diminution of fatal CBOS to 6.25 %. No CBOS occurred when the dose to the carotid was inferior to 34 Gy [7]. Optimization of the carotid dose to prevent hotspots could be a way to prevent CBOS [8]. In case of tumor which surround the carotid >180°, conventional fractionation should be preferred and can be realized by IMRT or SBRT.

The results in terms of local control are promising. For example, Lartigau et al. [9] conducted a multicenter phase II trial. It included 60 patients, and a dose of 36 Gy was prescribed in six fractions to the 85 % isodose line covering 95 % of the PTV. At 3 months, response rate was 58.4 % (95 % CI: 43.2–72.4 %) and disease control rate was 91.7 % (95 % CI: 80.0–97.7 %). The 1-year OS rate was 47.5 % (95 % CI: 30.8–62.4). Fifty-six patients received concomitant cetuximab. Only one treatment-related death occurs and other toxicities were quite manageable. Until today this is the only prospective phase II trial of stereotactic reirradiation published in H&N SCC.

Tumor volume <25 ml, time to reirradiation >2 years, overall treatment time <14 days, and HPV [10–12] status are prognosis factors reported as associated with a better outcome in retrospective studies. The role of the addition of cetuximab is still debated but was associated with longer survival in a case-match study independently of previous treatment with cetuximab [13]. Nomogram proposed by Tanvetyanon et al. to predict survival after salvage reirradiation appears to be valid after SBRT [14].

Despite good results in terms of local control, it is essential to consider the SBRT impact on quality of life (QoL). Vargo et al. [15] reported a large cohort of 150 patients. They prospectively assessed QoL and showed that there was a small decrease in the first month after reirradiation and then a significant improvement in swallowing, speech, activity, saliva, and recreation.

These results are good in the context of previously irradiated patients but could improve with greater PTV margin, better delineation, or with the help of metabolic imaging.

Table 17.1 Published study of SBRT in reirradiation of head and neck tumors

Author	Study design	Year	*n*	Dose	Number of fractions	Schedule	ORR	Local control rate	Time of local control evaluation	Median OS (months)	OS (%)	Time of OS evaluation	Acute toxicity	Late toxicity	Fatal CBOS
Prospective studies															
Lartigau et al. [9]	Phase II	2013	60	36	6	EOD	58.40 %	91.70 %	3 months	11.8	47.5	1 year	Grade 3 : 16 (27 %)	Grade 3: 1 (2 %)	1 (1.7 %)
Vargo et al. [12]	Cohort	2011	34	30–44	5	EOD	60 %	77 % 59 %	6 months 1 year	11	76 59	6 months 1 year	Grade 3: 15 %	Grade 3: 6 %	None
Heron et al. [2]	Phase I	2008	25	25–44	5	EOD	17 %	NR		6	NR		No grade 3–4	No grade 3/4	None
Retrospective studies															
Comet et al. [38]	Cohort	2012	40	36	6	EOD	79.40 %	NR	NR	13.6	58 % 24 %	1 year 2 years	Grade 3: 10.3 %	None	None
Rwigema et al. [39]	Cohort	2011	96	15–50	2–5	EOD	71.80 %	Dose 40–50 Gy: 69.4 %/57.8 %/41.1 % Dose 15–36 Gy: 51.9 %/31.7 %/15.9 %	1/2/3 years	15	58.9 28.4	1 year 2 years	Grade 3: 5.2 %	Grade 3: 3.1 %	None
Cengiz et al. [6]	Cohort	2011	46	18–35	1–5	ED	56.80 %	81.30 %	NR	11.93	47	1 year	Grade 3: 4.4 %	Grade 3: 4.4 %	7 (15.2 %)
Kodani et al.[a]{Kodani:2011uu}	Cohort	2010	21	19.5–42	3–7	ED	62 %	NR		24	50	2 years	No grade 3–4	6 severe complications (28 %)	2 (9.5 %)
Kawaguchi et al. [40]	Cohort	2010	22	20–42	2–5	ED	50.00 %	45.50 %	2 years	NR	*N*– 78.6 *N*+ 12.5	2 years	Grade 3: 22.7 %	None	None
Unger et al. [41]	Cohort	2010	65	21–35	2–5	ED	71 %	30 %	2 years	12	41	2 years	Grade 5: 1	Grade 4: 9 %	None
Roh et al. [42]	Cohort	2009	36	18–40	3–5	ED	80 %	61 %/52.2 %	1/2 years	16.2	52.1 30.9	1 year 2 years	Grade 3: 36 %	Grade 5:11 bone necrosis 2 soft tissue necrosis	None
Voynov et al. [43]	Cohort	2006	22	10–36	1–8	ED	NR	26 %	2 years	12	22 %	2 years	Grade 3: 1 (4.5 %)	None	None

[a]Only patients treated for a H&N reirradiation were considered, *ORR* Objective response rate, *OS* Overall survival, *CBOS* Carotid blowout syndrome, *NR* Not reported

The team of Pittsburg has indeed analyzed the recurrence after SBRT for previously irradiated SCC of the head and neck. Most of the failures (61.4 %) were overlap or marginal failures. The patients who had a PET planning had better overall failure-free survival and a better combined overlap/marginal failure-free survival than those who did not have a PET-CT planning ($p=0.037$). The authors suggest an increase of the PTV margin to 5 mm or to use PET-CT planning. However an increase of the margin could lead to more toxicity in some case and should be carefully evaluated [16].

In regard to the published series, SBRT for recurrent SCC is feasible and promising in terms of local control and survival but needs appropriate attention to the critical structures to avoid severe toxicities. Several questions are still to be solved: the utility of PET in this setting, the optimal dose fractionation, the concomitant use of new-targeted therapies, etc.

17.2.2 Boost After IMRT or Conformal Radiotherapy

It has been shown that most of the relapse after initial radiotherapy occurs in the high-dose volume [17].

Several hypotheses explained these relapses: hypoxia, stem cells, decreased radiosensitivity, etc.

To prevent these relapses, boost strategies are under development. A boost is a dose escalation in the high-risk volume in order to improve local control since it is generally accepted that a dose-response relationship exists between local control and radiation dose in head and neck tumor.

Such strategies have been developed with brachytherapy for oropharyngeal and oral cavity tumors with excellent results in terms of local control. However the accessibility and the volume of the tumor limit brachytherapy [18]. Boost is not possible with 3DRT because of the risk of severe toxicities. Strategies of simultaneous integrated boost with IMRT are currently investigated. SBRT appears as an attractive option to escalate dose and reduce treatment short time. Overall treatment time has been indeed shown to be especially important in head and neck tumors due to the tumor repopulation.

To our knowledge only four studies of SBRT boost for SCC have been published. The main one is a prospective study from Rotterdam that included 51 patients with oropharynx carcinoma ineligible for a brachytherapy boost [19]. After 46 Gy of IMRT, a boost of 16.5 by SBRT (5.5 Gy three times in a week) was performed. The 2-year actuarial rates of LC, DFS, and OS were 86 %, 80 %, and 82 %, respectively, and the 3-year rates were 70 %, 66 %, and 54 %, respectively. No grade 4 or grade 5 toxicity was reported, and the overall 2-year cumulative incidence of grade ≥2 late toxicity was 28 %.

Similar rates were observed in a recent multicenter Japanese study. PTV volume and initial response to SBRT boost were predictors of good outcome. Patients with PTV ≤20 cm^3 showed better PFS (92 %) and OS (100 %) than those with a PTV > 20 cm^3 (PFS, 61 % and OS, 47 %) [20].

However another study from Lee et al. [21] reported high rates of late complications. SBRT boost volume was a predictor of severe late complications. In this study boost volume ranges from 10 to 25 Gy in 2–5 fractions and was delivered each consecutive day. This can possibly explained why the authors observed these rates of complications.

Teguh et al. [22] showed that there was a dose relationship between the dose in the superior constrictor muscle and the incidence and severity of dysphagia. Lower doses were attainable with brachytherapy or SBRT boost than with IMRT suggesting a benefit in quality of life for the patients.

So SBRT boost is an attractive option for H&N SCC treatment. One the main difficulty may be the definition of the target boost volume and the optimal dose scheme. In this context metabolic imaging should be useful. For example, Jeong et al. [23] investigated the impact of the FDG avidity on the dose required for head and neck radiotherapy local control. FDG-avid tumor requires 10–30 % more dose than FDG-non-avid tumors to reach equal local response. Hypoxia tracers such as FAZA or F-MISO could also be useful in the future to assess the optimal boost volume [24].

Currently SBRT boost cannot be recommended outside clinical trials but seems very promising for the future management in SCC. Clinical trials are needed to assess the optimal dose and volume to boost.

17.2.3 In Adjuvant Setting

As previously said surgery remains the standard of care in case of local recurrence in a previously irradiated field. However, when this surgery is possible, many failures occur. To improve tumor control, adjuvant therapies have been tried. The only phase III trial is from Institute Gustave-Roussy [25]. Patients were randomized after salvage surgery between observation and chemotherapy + reirradiation. DFS was improved but not OS albeit significant toxicities (39 % of grade 3 or 4 late toxicities). In regard to toxicities, adjuvant therapies in the salvage setting are currently very occasionally used.

As already explained SBRT offers the possibility to reduce irradiation doses to normal tissues. Vargo et al. [26] have recently reported a retrospective series of adjuvant SBRT ± cetuximab. The 1-year locoregional control, distant control, disease-free survival, and overall survival were 51 %, 90 %, 49 %, and 64 %, respectively. Rates of acute and late severe (≥grade 3) toxicity were low at 0 % and 8 %, respectively.

Such strategy is not a standard option but should be investigated in regard to these results.

17.2.4 As Primary Treatment

Some patients are not eligible to standard treatment in regard to their toxicities. However their QoL could be altered by the tumor evolution. SBRT offers them a therapeutic option that can delay local symptomatology with minimal side effects.

Vargo et al. [27] investigated SBRT as primary treatment for elderly patients with unresectable H&N SCC. 44 Gy was administered in five fractions. The 1-year actuarial local progression-free survival, distant progression-free survival, progression-free survival, and overall survival were 69 %, 100 %, 69 %, and 64 %, respectively. Two patients experienced grade 3 toxicities (dysphagia and mucositis). There was no degradation of quality of life.

Further investigation and follow-up of SBRT in this indication are needed, but SBRT can be an option for patients ineligible to others treatments.

17.2.5 Oligometastatic Disease

Standard of care for metastatic disease is chemotherapy. Hellman et al. [28] first described the "oligometastatic" state for patients with less than five metastases. In this setting a local treatment of the metastases is an option. SBRT allows treating extracranial lesions like pulmonary or hepatic metastases. The high doses delivered are considered as "ablative" and local control seems the same after surgery. Local control could even be linked with survival in these metastatic patients [29].

However there are currently no studies that assess especially this technique in head and neck oligometastases, but for patients with few metastases, it can be a treatment option.

17.3 SBRT for Nasopharynx Carcinoma

The therapeutic options for nasopharynx carcinoma treatment offered by SBRT are almost the same as for the head and neck SCC. Nasopharynx carcinoma has traditionally a better outcome than SCC. Due to the proximity of critical structures, SBRT has been tested in large series in boost or reirradiation setting. For nasopharynx carcinoma, heterogeneity of structures must be considered, and specific algorithms that consider secondary electron transport must be used for dose calculation and optimization [30].

17.3.1 Planned Boost

Despite being very radiosensitive, local failure of nasopharynx carcinoma occurs up to 17 % even with IMRT use. This is especially true in case of T3/T4 tumor. So there is a rational to escalate dose in order to increase local control. However critical structures like brainstem or optical pathways limit dose escalation with conventional or IMRT techniques. Brachytherapy has been tested with success for T1/T2 tumors but cannot be used for larger tumors [18].

Four retrospective studies have investigated planned boost for nasopharyngeal carcinoma [31–34]. All of them achieved more than 93 % of local control at 3 years. Most of the relapses were distant relapses. Toxicity was quite acceptable. However Hara et al. [31] described ten temporal necroses on 82 patients; two of them were symptomatic (seizures) and nine of the patients had a T4 tumor.

A boost of 11–18 Gy in 1–3 fractions was delivered to achieve these local control rates.

This strategy must be evaluated prospectively but appears very promising to treat T3/T4 tumors of the nasopharynx.

17.3.2 Residual Disease or Recurrence

Standard treatment of nasopharyngeal carcinoma associates chemotherapy and radiotherapy. Despite these multimodal strategies, a residual disease persists in 7–13 % of the case 10 weeks after irradiation. Reirradiation is one of the therapeutic options available in this setting. It has been tested in large series of endemic countries. No randomized study is up to today published.

Liu et al. [35] published the largest study. They treated 136 patients for residual nasopharyngeal carcinoma with SBRT. Before April 2006 they observed major toxicities with eight cranial nerve injury and five massive nasopharyngeal hemorrhages. After April 2006, due to previous toxicity, lower total dose of 10–21 Gy and fractional dose of 2.5–4 Gy (with a BED $\leq$27.3 Gy) were used with the following indications: small tumor volume ($\leq$30 cm^3), residual tumors abutting carotid sheath or invading pharyngeal recess, cavernous sinus, or foramen lacerum, IMRT as primary RT, and short interval between primary RT and FSRT ($\leq$2 months), age <15 or >70, and concurrent chemotherapy. For other patients higher dose was used (15–24 Gy in 3–4 Gy by fraction). No severe toxicities were observed after April 2006. Five-year local failure-free survival (LFFS), freedom from distant metastasis (FFDM), overall survival (OS), and disease-free survival (DFS) rates for all patients were 92.5 %, 77.0 %, 76.2 %, and 73.6 %, respectively.

Chua et al. [36] compared fractionated SBRT (34 Gy in fraction of 4–6 Gy) to single-dose SBRT (12.5 Gy) in a case-match study for residual disease. Fractionated SBRT achieved better local control with fewer complications.

Currently admitted prognosis factors are T stage, age, tumor volume, and time interval from primary radiotherapy. Concomitant chemotherapy actually showed no benefit [35, 36].

SBRT boost for residual nasopharyngeal carcinoma is effective and safe, but precaution is needed in fractionation and dose scheme choice.

17.4 Follow-Up

Follow-up after SBRT head and neck treatment is a difficult question. High doses could in fact cause initial inflammation and make difficult the radiological evaluation. Furthermore SBRT is an asymmetric irradiation and radiologist must advertise that asymmetric reactions could be caused by post-therapeutic reactions.

False-positive of PET-CT could occur even years after SBRT [37].

So the diagnosis of recurrence after SBRT may be difficult and must be done by experienced teams.

Currently no specific recommendation exists for the follow-up of patients after H&N SBRT.

17.5 Conclusion

SBRT is rapidly improving and offers a new therapeutic option to improve the H&N patients' outcome. Reirradiation is currently the main indication of SBRT in H&N tumors, but planned boost is a promising strategy. Preliminary results show excellent local control with little toxicity if fractionated doses and QOD are used. Caution is required for tumors near vascular structures and fractionation must be adjusted.

Prospective studies are currently ongoing to validate SBRT in head and neck cancer management.

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Proton Beam Therapy for Head and Neck Cancer

18

Danielle N. Margalit, Judy A. Adams, Hanne M. Kooy, and Annie W. Chan

Abstract

The goal of multimodality therapy for head and neck cancer is to improve the therapeutic ratio by increasing the tumor control probability and decreasing treatment-related toxicity. Due to the close spatial relationship of head and neck cancers to numerous normal anatomical structures, conventional photon radiation therapy can be associated with significant acute and long-term treatment-related toxicities. The superior dose-localization properties of proton radiation therapy allow smaller volumes of normal tissues to be irradiated than is feasible with any photon technique. Initial clinical experience with proton radiation therapy in the treatment of head and neck cancers is promising. As the number of proton facilities increases worldwide, prospective clinical trials are underway to define the role of proton radiation in the treatment of head and neck cancers.

Keywords

Proton beam therapy • Head and neck cancer • Sinonasal malignancy • Paranasal sinus cancer • Nasopharyngeal cancer • Radiation therapy • Bragg peak • Intensity-modulated proton therapy • Intensity-modulated radiation therapy • Particle therapy

18.1 Introduction

18.1.1 Rationale for Using Proton Beam Therapy for Head and Neck Cancers

The goal of multimodality therapy for head and neck cancer is to improve the therapeutic ratio by increasing the tumor control probability and decreasing treatment-related toxicity. Proton beam therapy is a valuable tool to achieve this goal. A proton beam has similar biological properties to that of photons (X-rays) yet has markedly different physical properties that account for its superior dose distribution. A proton beam delivers most of its dose at a finite range with no dose beyond the target. In contrast, the dose from a photon beam decreases exponentially with depth in tissue resulting in non-essential radiation beyond the target. Therefore, proton beam therapy irradiates a smaller volume of normal tissue both proximal and distal to the tumor than is feasible with any photon technique. The result is that proton therapy decreases the total energy, or, integral dose, deposited in the patient compared with photon therapy.

Cancers of the head and neck present unique challenges for which the benefits of proton beam therapy can be realized. Due to the anatomical location of head and neck and skull base tumors, multimodality therapy can cause significant treatment-related toxicity such as xerostomia, swallowing dysfunction, hearing loss, vision loss, and encephalopathy. By reducing the volume of normal tissue that is irradiated, proton therapy may reduce acute and late toxicities and also improve local control by allowing for dose escalation. Initial

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clinical experiences from single institutions are promising, and clinical trials are underway to define the role of proton radiotherapy in the treatment of head and neck cancers.

18.1.2 History of Proton Beam Therapy

The use of accelerated protons for medical therapy is not a recent proposal. The first published proposal for proton therapy was Robert Wilson's 1946 article, *Radiological use of fast protons* [1]. In 1954, shortly after the construction of the cyclotron at Lawrence Berkeley National Laboratory, the University of California at Berkeley began treating cancer patients. In 1974, investigators at the Massachusetts General Hospital (MGH)/Harvard Cyclotron Laboratory pioneered the use of fractionated proton beam therapy. Rather than deliver a single high-dose fraction, they treated patients with sarcomas of the skull base using 2 Gy (RBE) per fraction to decrease the risk of normal tissue toxicity [2]. In 1990, Loma Linda University opened the first hospital-based proton therapy center with gantry systems. As of November 2014, there were 46 proton beam facilities in operation worldwide, representing major expansion of the number of facilities since early 2008 when there were 29 operational facilities [3]. Statistics from the Proton Therapy Co-Operative Group indicate that 105,743 patients were treated with proton therapy through the end of 2013, almost a doubling of patients treated with protons through 2007 [4]. Smaller and less-costly proton beam delivery units are currently under investigation and may further expand the clinical use of proton beam therapy.

18.1.3 Physical Aspects of Proton Beam Therapy

Protons were first described by Ernest Rutherford in the early 1900s [5] and have a charge of +1 and a mass that is 1800 times that of electrons. Equipment is required to accelerate protons because of their mass. The dose profile for a proton beam is markedly different from that of a photon beam and is the key physical property that accounts for the superior dose distribution achieved with proton therapy. As the proton particles enter the tissue, they slow down and deposit most of their energy just before stopping. This region of maximum dose deposition at the end of the proton range is called the Bragg peak, named after William Henry Bragg who described the phenomenon for α particles in 1903. The location of the Bragg peak is a function of the proton energy and the electron density of the material through which it passes. By modulating the energy of the proton beam and density through which it passes, the precise location of maximum dose deposition (the Bragg peak) can be specified within the tumor. There is no significant radiation dose beyond the Bragg peak [6, 7]. In contrast, the dose from a photon beam decreases exponentially with depth in the irradiated tissues. The physical properties of the proton beam result in less irradiation of normal tissue both proximal and distal to the target compared with photon therapy. This is illustrated in Fig. 18.1 which compares a single photon beam with a single modulated proton beam. Figure 18.2 demonstrates the difference in dose distribution with a single anterior-posterior photon beam (Fig. 18.2a) compared with a single anterior-posterior proton beam (Fig. 18.2b) in the treatment of a patient with a squamous cell carcinoma of the lateral canthus involving the lacrimal gland. There is more radiation to normal tissue distal to the target with the photon beam compared with the proton beam.

There are two general methods for delivering proton radiotherapy: passive scattering and pencil-beam scanning. Most patients have been treated with passively scattered systems. With this technique, a fixed monoenergetic beam is broadened and shaped by a system of scatterers and degraders that determine the desired range of the beam and the area required to cover the target. In order to cover the entire target volume, the depth of the monoenergetic beam is modulated by rotating wheels of different thickness in the beam line. The Bragg peak is pulled closer to the source by the water equivalent thickness of the plastic wheel. This creates a "spread-out" Bragg peak that covers the target volume. Patient-specific hardware must be made for each patient to define the lateral edges of the target and shape the distal edge of the spread-out Bragg peak.

In pencil-beam scanning, magnets are used to steer the positively charged proton beam. Proton beam scanning was first described by Kanai et al. of Chiba, Japan [8], and was

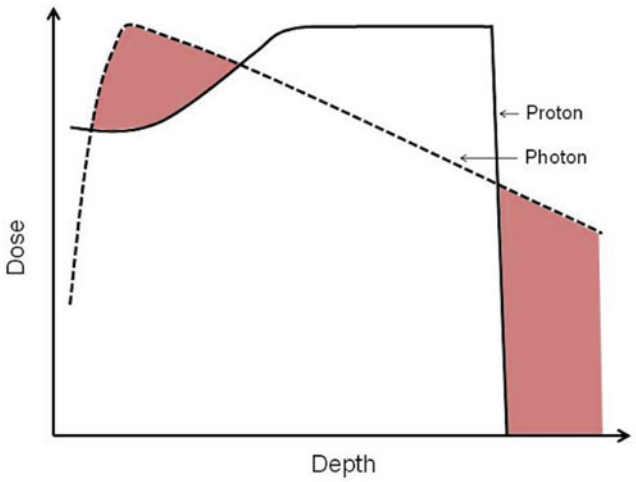

Fig. 18.1 Central axis depth dose of a single high-energy photon beam (*dotted line*) and the spread-out Bragg peak of a single proton beam (*solid line*). The *red* emphasizes the regions to which the photon beam delivers a higher dose than does the proton beam. Note the sharper dose falloff of the proton beam compared with the photon beam

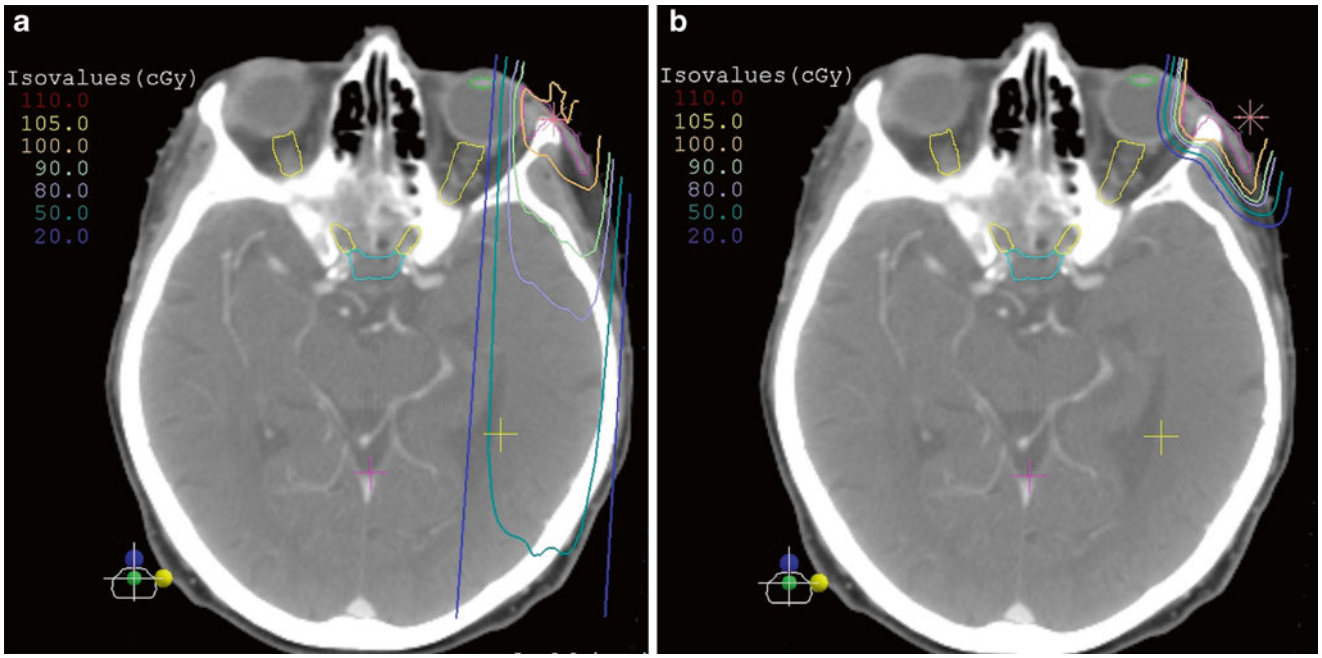

Fig. 18.2 Dosimetric comparison of a single 6 MV photon beam (**a**, *left*) and a single high-energy proton beam (**b**, *right*) in a patient with a squamous cell carcinoma of the lateral canthus involving the lacrimal gland. The *colored isodose lines* represent the percentage of the prescribed dose received by the encompassed tissue. For example, all of the tissue within the *dark-blue line* receives 20 % of the intended dose. With a single photon beam (**a**), there is more normal tissue that receives radiation distal to the target compared to the proton beam (**b**). Abbreviation: *MV* megavoltage

developed for medical use at the Paul Scherer Institute (PSI) in Switzerland. The technology required for beam scanning is more sophisticated and more sensitive to tissue inhomogeneity and organ motion [9, 10] than passive scattering systems. Yet there are several advantages compared with passively scattered delivery. For pencil-beam scanning, there is no patient-specific hardware needed to shape the beam which also results in less neutron contamination to the patient. Intensity-modulated proton therapy is enabled with beam scanning technology, and a steeper lateral dose gradient can be achieved. Despite the potential advantages of active pencil-beam scanning compared with passive scattering systems, most operational facilities use passive scattering systems.

The planning and delivery of proton radiotherapy are currently more complex than that of photon radiotherapy. The estimated tissue density from the planning CT scan must be converted to proton stopping power to determine the range of the beam and the required compensator thickness to ensure that the beam covers the target without overshooting or undershooting. Protons are more sensitive to slight changes in tissue inhomogeneity than photons [11–13]. Therefore, daily error in patient setup and immobilization are less tolerated in proton radiotherapy. In the head and neck, variation in tissue density over the course of treatment fluctuates due to variable aeration of the nasal cavity or paranasal sinuses and can lead to increased uncertainty in the range of the protons with the potential for increased dose to normal organs or decreased dose to the tumor target [14]. Accurate delineation of the target volume is absolutely essential to avoid marginal misses, and appropriate margins must be placed on the target to ensure adequate target coverage. Proton beam delivery requires a high degree of specialized training and quality control for those facilities that deliver proton radiotherapy.

18.1.4 Intensity-Modulated Radiation Therapy Versus Intensity-Modulated Proton Therapy

Intensity-modulated radiation therapy (IMRT) is a technique in which the intensity of the photon (X-ray) radiation varies throughout the treatment field. Compared with traditional external beam therapy, IMRT can create a sharp dose gradient between the target and surrounding nontarget tissue. IMRT is increasingly used for the treatment of head and neck cancers in an effort to decrease morbidity and improve tumor control. The adoption of IMRT is a good example of evidence-based adoption of newer technologies. There are three randomized controlled trials showing the benefit of IMRT compared with conventional radiation techniques in decreasing rates of xerostomia [15–17]. With IMRT, the dose is frequently spread among many beams that enter the patient from different angles. This results in a "dose bath" in which normal tissue receives a low to medium dose of unnecessary

irradiation, which may result in unwanted acute and late side effects.

The intensity of the proton radiation can also be modulated to produce intensity-modulated proton therapy (IMPT). This is achieved by a pencil-beam scanning technique in which a small circular beam, characterized by the beam spot size, is scanned across the defined treatment field with the energy and intensity varying so that the dose in each voxel can be optimized.

The conformality of an IMPT treatment plan has a direct dependence on the spot size and also on the strategy of how spots are placed within the patient. For a "small" spot size (~4 mm) in the head and neck region, the total penumbral spread will be about 5 mm (penumbra can be thought of as the region of tissue receiving radiation at the edge of the radiation beam and outside of the main target: a lower penumbra is desired for minimizing irradiated tissue adjacent to the radiation beam.) In comparison, the current spot size in clinical use in the United States is about 9 mm, and the total penumbral spread is 10 mm. The "apparent" spot size for a scattered field is also about 4 mm, on par with a "small" spot. The spot size is thus an important parameter of the proton beam when using IMPT to minimize radiation dose to the normal tissues.

The spot size can be mitigated, as it is in scattered fields, by the introduction of an aperture in the beam. The aperture minimizes the spot size by the ratio of the distance from the aperture position to the calculation point over the distance from the aperture to the position of the proton beam source. In scattered fields, the source is on the order of 50 mm, and placing the aperture close to the patient can achieve a reduction by a factor of 20. In IMPT, the spot size of 4 mm (or in our case, 9 mm) only requires a minimal reduction.

At the Massachusetts General Hospital, our in-house IMPT treatment planning system has been developed that allows the use of apertures in pencil beam scanning fields and adjusts the pencil-beam spot shape to the constraints of the aperture shape including the effect of the source penumbra. Figures 18.3 and 18.4 are planning examples that demonstrate the dose distribution and relative benefit of decreasing spot size and inclusion of the aperture for treatment of locally advanced nasopharyngeal carcinoma. As expected, IMPT with a 3 mm spot size achieves more sparing of normal structures than IMPT with an 8 mm spot size (b vs. d in Figs. 18.3 and 18.4). Contrary to what is commonly believed, IMPT with 8 mm spot size and without use of aperture (the technique that is currently employed in the United States) does not result in significant sparing of normal tissues or improvement in target conformality when compared to an IMRT plan (b vs. e in Figs. 18.3 and 18.4) or a passively scattered proton plan. Importantly, with the addition of the aperture in IMPT an 8 mm spot size planning, there is significant improvement of normal tissue sparing (b vs. c in Figs. 18.3 and 18.4). Passively scattered proton therapy with the use of apertures and compensators, which has been employed at MGH for more than two decades, provides excellent sparing of normal structures (see Figs. 18.3a and 18.4a). However, passively scattered proton therapy employs a forward-planning approach and is extremely labor intensive and operator dependent. In our department, passively scattered proton therapy will likely be replaced by IMPT with a 3 mm spot size and IMPT with an 8 mm spot size and apertures.

18.1.5 Radiobiology of Proton Beam Therapy

Protons and photons have similar biologic effects; it is the difference in physical characteristics that account for the superiority of dose distributions with protons. The density of ionizations produced by therapeutic radiation as it traverses the tissue is quantified by the linear energy transfer (LET) value. The LET is a calculation of the energy transferred by the radiation along a unit length within the biologic material and is related to the biologic effectiveness of the radiation. The linear energy transfer (LET) value for therapeutic proton beam ranges from 0.2 to 2.0 keV/μm, much lower than carbon or neutron particles which are high-LET radiations.

The International Commission on Radiation Units and Measurements (ICRU) and the International Atomic Energy Agency (IAEA) established the unit of proton dose as "Gy (RBE)" [18]. Protons have a relative biologic effectiveness (RBE) comparable to that of 250 kV X-rays [19] and a generic RBE value of 1.1. That is, the ratio of the dose of ^{60}Co γ-rays relative to that of protons required to produce a defined biologic response is 1.1. The RBE may vary depending on the dose and fractionation, proton energy utilized, and specific tissue irradiated, yet current evidence supports the use of an RBE of 1.1 in dose calculation for treatment planning [20]. There is an increase in RBE over the distal few millimeters of the spread-out Bragg peak (SOBP). The RBE at the terminal SOBP is estimated to be a maximum of 100 keV/μm over a few microns as the particles come to rest [20, 21]. For high-energy protons, this region is so tiny that it is not thought to have any clinical consequence [19]. Therefore, dose adjustments based on variations in RBE in the SOBP are not made. Due to physical and biologic uncertainties at the end of range, the proton beam is not aimed directly at a critical structure when it located in close proximity to the distal edge of the target.

18.2 Clinical Experience

18.2.1 Proton Beam Therapy for Sinonasal Malignancies

For most sinonasal malignancies, a combination of radical surgery and postoperative radiation constitutes standard

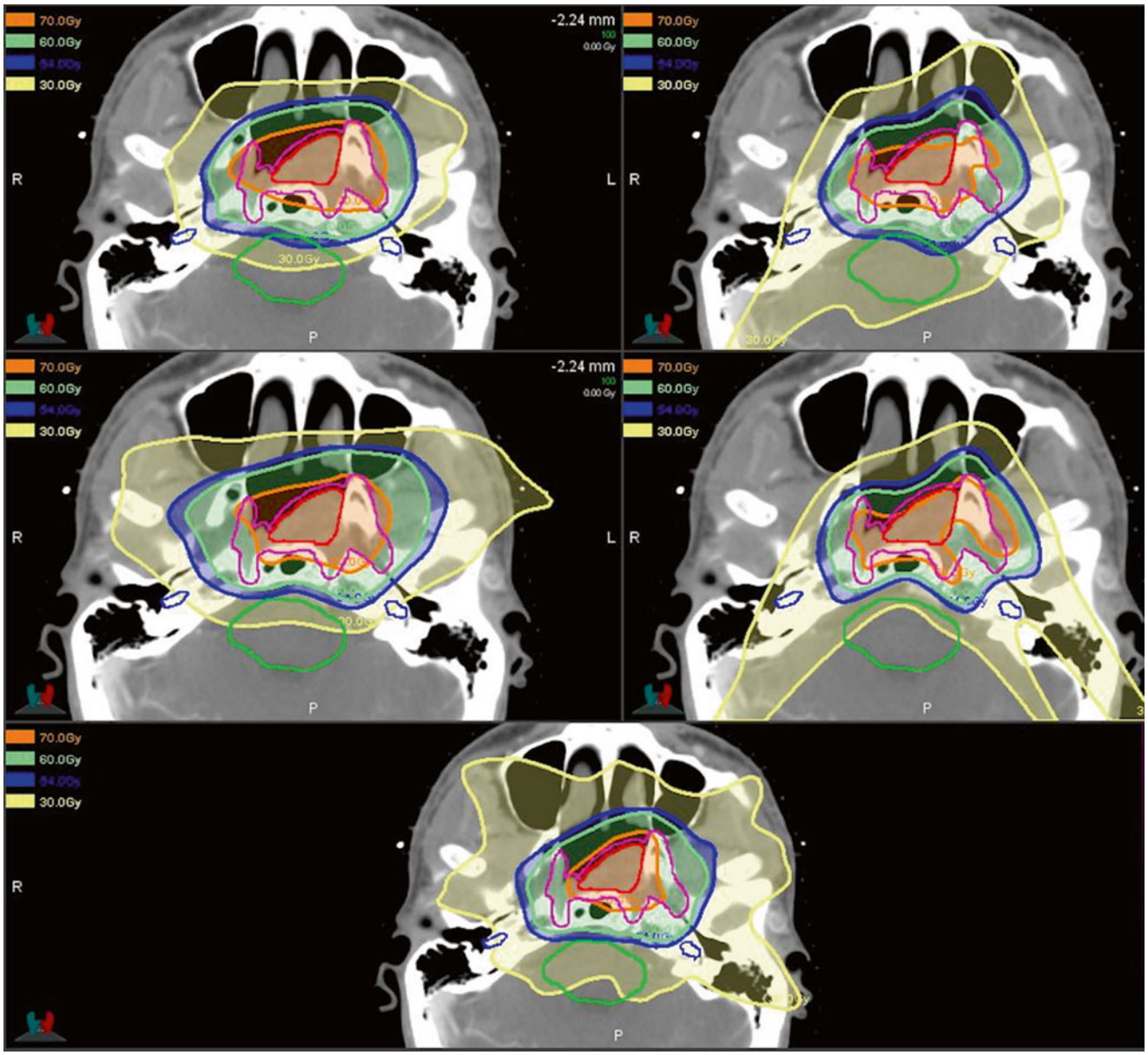

Fig. 18.3 Treatment of the primary site for locally advanced nasopharyngeal carcinoma using intensity-modulated radiation therapy (IMRT) and different intensity-modulated proton therapy (IMPT) techniques. (**a**) (*top*, *left*) passively scattered proton therapy employing apertures and compensators which has been in clinical use at MGH for the past few decades; (**b**) (*top*, *right*) IMPT with the current 8 mm spot size in clinical use in the United States; (**c**) (*middle*, *left*) IMPT with an 8 mm spot size but with the use of apertures; (**d**) (*middle*, *right*) IMPT with 3 mm spot size currently under development at MGH; (**e**) (*bottom*) photon IMRT. Note the best brainstem sparing with IMPT is achieved by the use of the 3 mm spot size. The brainstem sparing is comparable with the use of IMRT (*bottom*) and IMPT with 8 mm spot size (*top*, *right*)

treatment. Despite aggressive therapy, the outcome is poor, with most institutions reporting a 5-year overall survival rate of less than 50 % [22–28]. In advanced tumors that involve the skull base, survival is further reduced. Treatment failure at the primary site is the main pattern of failure for these tumors, ranging from 30 to 100 % [29–32], and local failure is the primary cause of death. Alternative treatment strategies are clearly needed for sinonasal malignancies with skull base involvement.

Higher radiation doses are associated with improved local control [32, 33]. Yet dose escalation is limited because of the adjacent normal tissues of the skull base and optic apparatus. Radiation-induced late ocular and visual toxicity is common. At the University of Florida, 27 % of patients developed unilateral blindness secondary to radiation retinopathy or optic neuropathy, and 5 % developed bilateral blindness due to optic neuropathy [25]. Takeda et al. reported a similar incidence of radiation retinopathy in patients with malignancies

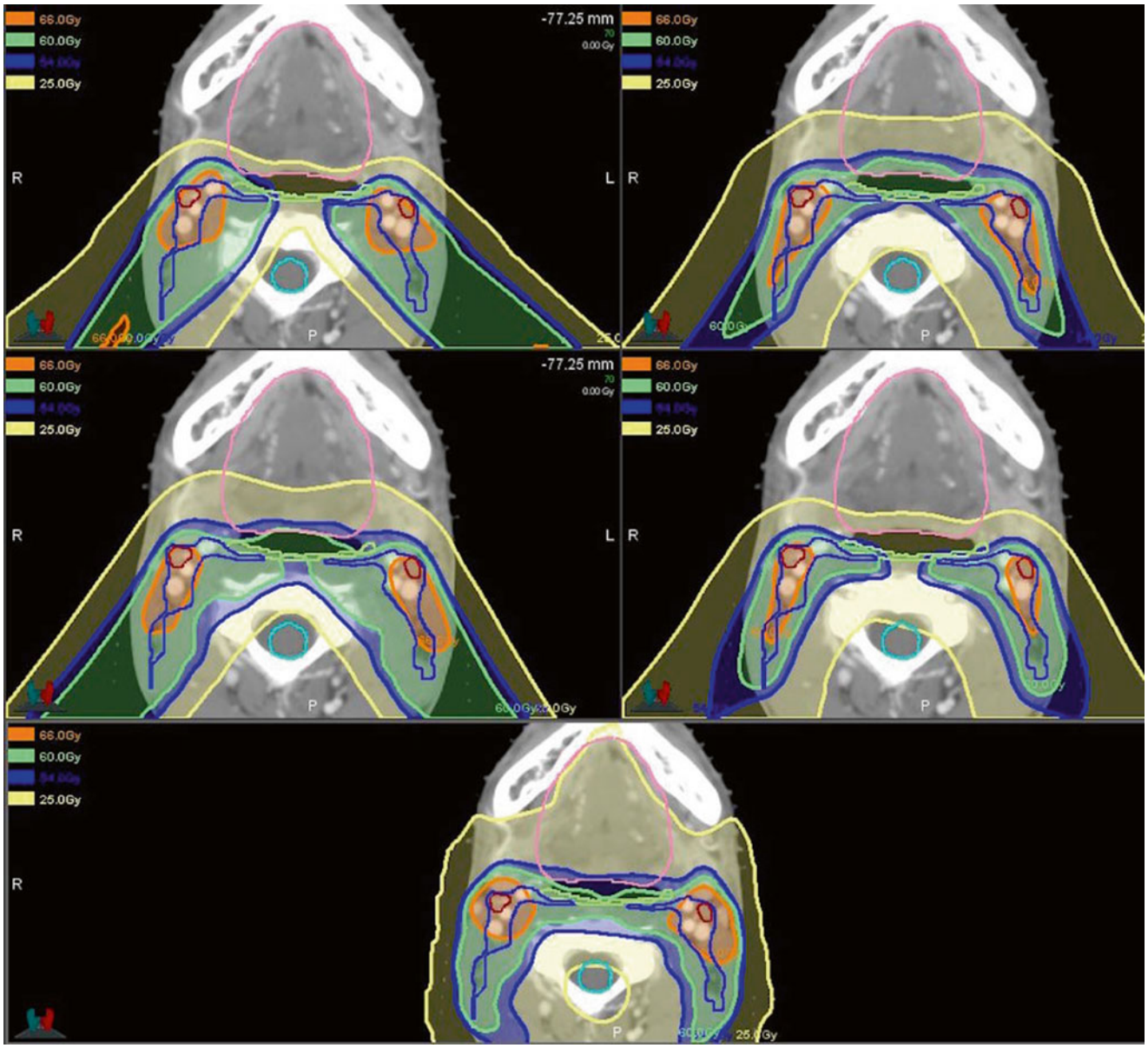

Fig. 18.4 Treatment of the bilateral neck lymph nodes for locally advanced nasopharyngeal carcinoma using intensity-modulated radiation therapy (IMRT) and different intensity-modulated proton therapy (IMPT) techniques. (**a**) (*top*, *left*) passively scattered proton therapy, which employs the use of aperture and compensator, has been in clinical use for the past few decades at MGH; (**b**) (*top*, *right*) IMPT with current spot size (8 mm) that is currently in clinical use in the United States; (**c**) (*middle*, *left*) IMPT with 8 mm spot size but with the use of apertures; (**d**) (*middle*, *right*) IMPT with 3 mm spot size that is currently under development at MGH; (**e**) (*bottom*) photon IMRT. Note the large low-dose bath in the oral cavity with the use of IMRT. Passively scattered proton therapy (*top*, *left*) and IMPT with 3 mm spot size (*middle*, *right*) result in the best oral cavity sparing. The dose conformality around the nodal target is the best with the IMPT-3 mm spot size plan

of the nasal cavity and paranasal sinuses without tumor invasion of the eyes [34]. Waldron et al. reported visual outcomes in patients with ethmoid sinus cancer treated with primary radiation therapy. At a median follow-up of 4 years, 41 % of patients developed unilateral or bilateral blindness and 24 % developed visual impairment [35]. Other radiation-induced ocular/visual toxicities such as neovascular glaucoma, cataract, and dry eye syndrome are also common after treatment with conventional radiation therapy in sinonasal malignancies [34, 36]. The rates of visual toxicity have declined over time with increased use of three-dimensional conformal radiation therapy and IMRT. But these new technologies have not resulted in gains in local control or survival [23, 26, 37].

At Massachusetts General Hospital, 102 patients with advanced sinonasal cancers received proton therapy between 1991 and 2002. There were 33 squamous cell carcinomas, 30 carcinomas with neuroendocrine differentiation, 20 adenoid

cystic carcinomas, 13 soft-tissue sarcomas, and 6 adenocarcinomas. The median dose was 71.6 Gy (RBE) and 20 % of patients underwent complete resection before proton radiation therapy. With a median follow-up of 6.6 years, the 5-year actuarial local control was 86 % [38, 39]. The improvement in local control also shifted the pattern of failure from local to distant. At 45 months, the first site of failure was local for 11 patients and distant for 19 patients. These results compare favorably with that achieved by IMRT or three-dimensional conformal radiation therapy [23, 26, 37]. More recently, the National Cancer Center Hospital East and the Tokyo Medical and Dental University in Japan published their outcomes of proton beam radiation for unresectable T4 nasal cavity and paranasal sinus malignancies. Most patients were treated with a hypofractionated regimen of 2.5 Gy (RBE) per fraction to a total dose of 65 Gy (RBE). The 1-year local control rate of 77.0 % compared favorably to historical series. Retrospectively graded toxicity with the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) showed that five patients (12.8 %) experienced grade 3–5 toxicity including one treatment-related death due to a cerebrospinal fluid leak, two cases of grade 3 decrease in visual acuity, and a case of cranial neuropathy and bone necrosis [40]. Another series from University of Tsukuba, Japan, described that 17 patients with unresectable T4 nasal cavity or paranasal sinus carcinomas treated with protons to a median of 78 Gy (RBE) over 36 fractions showed reasonable rates of retrospectively graded toxicity with two cases of RTOG grade 4 toxicity (there were no grade 5) including one patient with unilateral blindness and one patient with brain necrosis [41]. Prospective study of toxicity is needed to fully understand the toxicity profile of dose escalation or hypofractionation with proton beam for unresectable tumor near the brain, brainstem, and optic structures.

Management of locally advanced adenoid cystic carcinoma with combined modality therapy remains a challenge. For patients with inoperable tumors or gross residual disease, the local control rate ranges from 0 to 43 % [29, 30, 32]. Neutron radiation therapy, though an accepted treatment option for adenoid cystic carcinoma, results in a locoregional control rate of 23 % for patients with base of skull involvement [42]. The Massachusetts General Hospital reported the results of 23 patients with adenoid cystic carcinoma involving the base of skull treated with combined proton and photon radiotherapy from 1991 to 2003 [39]. Only three patients had a gross total resection with positive margins, 11 patients (48 %) received a biopsy alone, and nine (39 %) had a partial resection. With a median dose of 76 Gy (RBE), the 5-year locoregional control rate was 93 %. High-dose conformal proton beam radiation therapy resulted in encouraging local control in advanced adenoid cystic carcinoma with skull base involvement.

Treatment of sphenoid sinus cancer is technically challenging for both the radiation oncologist and surgeon because of the close proximity and relative radiosensitivity of adjacent critical structures including the orbit and central nervous system. Investigators at Massachusetts General Hospital performed a retrospective analysis of oncologic and toxicity outcomes of locally advanced primary sphenoid sinus carcinoma treated with proton radiation therapy [43]. From 1991 to 2005, 20 patients received a median dose of 76 Gy (RBE). With a median follow-up of 27 months, the 2-year local control and regional control rates were each 86 %, and the freedom from distant metastasis rate was 50 %. None of the patients developed grade 3 or higher late ocular or visual toxicity after radiation. This data demonstrated that proton beam therapy can achieve local control and toxicity rates that compare favorably with previously published studies [25, 28].

The Massachusetts General Hospital also reported the long-term ocular and visual toxicity in a group of patients with advanced sinonasal cancers treated with accelerated hyperfractionated proton radiation therapy [44]. The median dose to the gross tumor target was 70 Gy (RBE). All patients had a baseline ophthalmology examination and every 6 months thereafter. At a median follow-up of 52 months, there were only two cases of LENT/CTC grade 3 toxicity. There was no vascular glaucoma, retinal detachment, or optic neuropathy. Proton beam therapy allowed the delivery of tumoricidal doses with minimal ocular/visual complications compared to historical series.

18.2.2 Proton Beam Therapy for Nasopharyngeal Carcinoma

Concurrent chemoradiation became the standard of care for patients with advanced nasopharyngeal carcinoma since the publication of the landmark Intergroup 0099 study [45]. The optimal radiation technique used alone or in combination with chemotherapy, however, still needs to be defined. The therapeutic margin for nasopharyngeal carcinoma is narrow due to the proximity of critical structures. Conformal radiation therapy is associated with ototoxicity, xerostomia, dysphagia, cranial neuropathies, temporal lobe necrosis, endocrinopathy, soft-tissue necrosis, and vision loss [46]. Despite improvements in survival and local control, multimodality therapy with the addition of chemotherapy is associated with increased late toxicity [46, 47]. Two randomized control trials compared parotid-sparing IMRT with two-dimensional radiation therapy in patients with early stage (T1-2b, N0-1) nasopharyngeal carcinoma [15, 16]. Both studies demonstrated significantly better objective measurements of salivary flow at 1 year after IMRT as determined by the stimulated parotid flow rate and stimulated whole saliva

flow rate. One of the studies also showed a significant difference in subjective xerostomia-related symptoms at 1 year [16]. IMRT achieves increased tumor conformality and parotid sparing compared with conventional radiation techniques by increasing the amount of dose delivered to the oral cavity and other structures.

Prospective studies are needed to determine if health-related quality of life improves by reducing the amount of normal tissue receiving radiation. Investigators at the MGH completed the first prospective phase II study of three-dimensional (3D) proton beam therapy for the treatment of nasopharyngeal carcinoma. In addition to assessment of recurrence and survival endpoints, the study aimed to determine the health-related quality of life using both objective measurements and validated quality-of-life instruments. The early results were reported in abstract form and reported on 24 patients with stage III–IV nasopharyngeal carcinoma treated with proton beam and chemotherapy from 2006 to 2011 to a total tumor dose of 70 Gy (RBE). Swallowing function was assessed objectively using videofluoroscopic swallowing studies. With a median follow-up period of 2.3 years, there was one case of nasal regurgitation, no change in duration of upper esophageal sphincter opening, normal pharyngeal residue with all consistencies, and unchanged oropharyngeal transit time for all patients with liquid boluses. The swallowing function after proton beam compared very favorably to historical outcomes especially given the advanced nature of the tumors [48]. Additionally, a case–control study of patients treated with IMPT and IMRT from 2011 to 2013 at the University of Texas MD Anderson Cancer Center and Linkou Chang Gung Memorial Hospital, Taiwan, showed a significantly lower proportion of gastrostomy tube insertion in the IMPT group compared to the IMRT group (23.1 vs. 57.7 %) [49]. Data thus far strongly suggests that proton therapy for nasopharyngeal carcinoma can result in a meaningful reduction in acute toxicity.

18.2.3 Proton Beam Therapy for Oropharyngeal Carcinoma

Gains in tumor control for oropharyngeal carcinoma occurred with the addition of concurrent chemotherapy to radiation therapy and with altered fractionation [50–53]. However, treatment intensification is also associated with increased rates of acute and long-term toxicity. Technological advances in radiation therapy including IMRT and proton therapy may be harnessed to decrease toxicity by increasing conformality of radiation and minimizing dose to normal structures, including the spinal cord, salivary glands, mandible, and pharyngeal muscles. The Radiation Therapy Oncology Group (RTOG) conducted the first multi-institutional prospective phase II study to assess the feasibility of using IMRT with standardized dose and target delineation procedures in patients with early stage (T1-2, N0-1) oropharyngeal carcinoma [54]. Sixty-nine patients received moderately accelerated hypofractionated IMRT to dose of 66 Gy in 2.2 Gy/fraction to the primary tumor and involved nodes and 54–50 Gy/fraction to subclinical target volumes. Patients did not receive concurrent chemotherapy. With a median follow-up time of 2.8 years for surviving patients, the 2-year estimated local–regional failure rate was 9 %, and xerostomia grade ≥ 2 was 55 % at 6 months and decreased to 16 % at 24 months. Both local control and salivary toxicity were improved compared with patients from prior RTOG studies that used conventional or 3D-conformal photon-based radiation therapy.

There are limited published reports describing the use of proton therapy for treatment of oropharyngeal carcinoma. Investigators at Loma Linda University Medical Center (LLUMC) conducted an accelerated hyperfractionation study for stage II–IV oropharyngeal carcinoma using a technique similar to the MD Anderson concomitant boost technique [55]. The LLUMC trial differed from the concomitant boost trial in a number of factors including a higher total dose of 75.9 Gy that was delivered in a shorter overall time of 28 treatment days [51]. The majority of dose was delivered using the opposed lateral photon technique, and protons were used to deliver the boost dose of 25.5 Gy (RBE). The study accrued 29 patients over more than 10 years. All patients completed the prescribed dose without any interruption. With a median follow-up of 28 months, the 2-year locoregional control and disease-free survival rates were 93 % and 81 %, respectively. The 2-year actuarial incidence of late RTOG grade 3 toxicity was 16 %. This small study was performed over a prolonged period of time without the use of chemotherapy and employed proton radiation therapy for only 35 % of the total dose. Further prospective studies of proton beam therapy for oropharyngeal cancer are needed with detailed assessment of toxicity rates in addition to oncologic outcomes. A recent case–control study from the University of Texas MD Anderson Cancer Center matched 26 IMPT cases to 26 IMRT cases of oropharyngeal carcinoma and showed a lower rate of grade 3 dysphagia for IMPT compared with IMRT [56].

Currently, MD Anderson Cancer Center is sponsoring the first randomized trial comparing IMPT versus IMRT to compare the side effects of treatment for oropharyngeal cancer (NCT01893307). The primary outcomes are the rate and severity of late grade 3–5 toxicity, as assessed prospectively and utilizing both patient-reported and clinician assessments as well as objective swallowing assessment with interval modified barium swallow studies.

18.2.4 Proton Beam Therapy and Concerns Regarding Risks of Second Malignancy

Concerns have been raised regarding the risk of second malignancy from neutron contamination during proton delivery [57]

as low doses of neutrons are carcinogenic [58]. Proton collision with a heavy atomic nucleus can cause neutrons to be expelled. During proton radiotherapy, the major source of neutrons comes from proton interactions with the scattering components in the treatment nozzle [59] of which the largest source of neutrons is the final patient-specific brass aperture [60]. Neutrons are also generated internally, within the patient. Measuring neutron dose in tissue is challenging and most methods involve the use of Monte Carlo simulations. Additionally, the biological effectiveness for carcinogenesis for low-dose high-energy neutrons is uncertain especially for very low doses such as during fractionated therapy [61]. Since most contamination comes from the treatment nozzle and patient-specific hardware, if inaccurate or outdated delivery parameters are incorporated into the model, neutron contamination can be overestimated by several orders of magnitude [57, 62, 63]. Spot scanning techniques also reduce the neutron contamination significantly.

Protons result in a lower integral dose to nontarget tissue compared with intensity-modulated therapy, which may actually result in a reduction in the potential risk of secondary cancer. Miralbell et al. [64] estimated at least a twofold reduction in secondary cancers in pediatric patients treated with protons compared with photons (intensity modulated or passively scattered) due to a reduction in the integral dose to nontarget organs. Jarlskog and Paganetti [65] used a Monte Carlo approach to estimate the risk of second malignancy from neutron dose in patients treated for a brain tumor using passive-scattered proton beams. The risk was highest in young patients and was comparable to the risk caused by scattered photon dose with IMRT. A matched retrospective analysis compared second malignancy rates of 503 children treated at the Harvard Cyclotron from 1974 to 2001 with 1591 matched patients treated with photons identified via the Surveillance, Epidemiology, and End Results (SEER) cancer registry. There were 32 (6.4 %) malignancies in the proton group compared with 66 (13.1 %) in the photon group. There was a significantly higher risk of second malignancy in patients treated with photons even after adjustment for gender and age at treatment (adjusted HR 3.01, $p<0.0001$) [66].

Due to the long latency of second malignancies, long-term follow-up is of utmost importance. The contribution of secondary neutron dose to second malignancy is "a charged issue" [60], and any potential risk of secondary cancer from externally generated neutrons can be lowered with the use of active scanning proton beams.

18.2.5 Prospective Studies on Proton Beam Therapy

There continues to be a debate regarding the necessity of randomized control trials to evaluate the efficacy of new technology, and proton beam therapy has received much attention [67–71]. There are no completed randomized control trials comparing proton and photon radiotherapy. Currently, a phase II/III randomized trial sponsored by the University of Texas MD Anderson Cancer Center is accruing and will compare intensity-modulated proton beam therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for oropharyngeal cancer with a primary outcome of toxicity (NCT01893307). Protons have unique physical characteristics that account for the superior dose distribution compared with photons. Those in favor of requiring randomized control trials state that dosimetric studies may not translate to clinical benefits. Others argue that there can be no benefit to irradiating normal tissue and question the presence of equipoise when considering such randomized control trials [67].

The cost of proton therapy is also a key issue when considering future prospective trials. Some argue that if it were not for the increased cost of proton therapy relative to standard photons and electrons, the necessity for randomized control trials would not be as fervently debated [67]. Others argue that clinical trials are needed to justify the high costs of therapy [72]. A cost analysis performed by Goitein and Jermann [73] estimated the cost of protons to be 2.4-fold greater than for X-ray therapy, largely due to the high initial investment in facility construction. If the operating costs did not need to repay the initial investment, they estimated a reduction in the cost ratio to approximately 1.6. Under the current reimbursement model in the United States in 2014, it is estimated that the increased number of proton facilities is not sustainable due to limitations in per-patient reimbursement [74]. Additional cost-effectiveness analyses are needed that take into account current costs of implementing and operating proton facilities as well as the costs associated with acute and late toxicity that may be spared with the use of protons.

In the absence of randomized data comparing proton and photon-based therapy, several groups have created models and algorithms to identify appropriate candidates for proton therapy and which may be used to justify insurance coverage for this still costly resource. For example, investigators from the Netherlands developed a model-based approach using normal tissue complication probability (NTCP) rates based on estimates of dose to organs such as the parotid glands or swallowing muscles using either photon or proton plans. The patient is considered to benefit from proton therapy when the use of proton therapy is modeled to result in a reduction in NTCP compared with photons that exceeds a predefined threshold. This model was adopted by the Dutch Health Council and the Dutch Health Care Insurance Board to determine who may be eligible for reimbursement for this costly technology [75]. The same group performed a comparative effective analysis based on NTCP models and planning studies in effort to determine methodology for selecting patients for whom IMPT is cost-effective [76].

18.2.6 Future Directions

Proton beam therapy results in decreased radiation dose to normal tissue. The potential benefits of proton therapy can be fully exploited with active beam scanning technology which also allows for intensity-modulated proton therapy (IMPT), a powerful delivery technique with an improved dose distribution compared to that of intensity-modulated radiation therapy (IMRT). Yet the current IMPT technique in clinical use in the United States is suboptimal for the treatment of head and neck and skull base malignancies as it employs a large spot size. Refinement of current IMPT delivery with smaller spot sizes and the additional use of apertures allow sharpening of the penumbra and improvement of target conformality. Proton beam therapy is less tolerant than photon radiotherapy of uncertainty in treatment planning and delivery, requiring a high degree of specialized training and quality control for those facilities that deliver proton radiotherapy. Accurate delineation of the target structures and careful avoidance planning of normal tissue is essential.

Currently, we recommend proton beam therapy for cancers of the head and neck that are in close proximity to critical structures of the central nervous system, spinal cord, optic apparatus, and base of skull, for which photon-based therapy will exceed the dose-limiting constraints of these critical structures. Cancers of the nasopharynx, paranasal sinuses, nasal cavity, and periorbital skin cancers with orbital invasion are particularly suited to realize the benefits of proton therapy. Well-designed studies are needed and are currently underway to determine if the well-demonstrated dosimetric benefits translate to decreased acute and long-term toxicity and improved local control in the context of multimodality therapy.

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Principles of Systemic Chemotherapy for Squamous Cell Head and Neck Cancer

19

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Abstract

Head and neck squamous cell carcinomas are a group of malignancies that are sensitive to systemic therapy, in part due to the complexity of the molecular aberrations in these malignancies that impair DNA repair mechanisms. Administration of chemotherapy in the treatment of head and neck cancers is guided by treatment goals and patient factors unique to this patient population. The known radiation-sensitizing properties of chemotherapy and its ability to impact rates of distant failure have established concurrent chemoradiation as a standard definitive and adjuvant therapy for locally advanced disease. Although known to produce tumor responses, chemotherapy given in the metastatic setting has not been consistently demonstrated to improve overall survival. The combination of chemotherapy with targeted monoclonal antibodies has shown promising results. The emergence of the distinct HPV(+) oropharynx cancer population has had a significant impact on the design of current clinical investigation for this disease. Further investigation of the role of nonoperative treatments in this disease will likely focus on efforts to decrease late treatment-induced morbidity, exploration of reirradiation with concurrent chemotherapy as a salvage therapy, and further integration of chemotherapy, radiation, and targeted therapies in both definitive and palliative management.

Keywords

Squamous cell carcinoma of the head and neck • Systemic therapy • Chemotherapy • Medical oncology

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19.1 Introduction

Historically, the use of systemic treatments in squamous cell head and neck cancer has required an entirely different approach than that taken by the radiation therapist and surgeon. For the medical oncologist, the anatomic distinctions so critical for locoregional disease management are of considerably less importance than the commonalities that head and neck cancers share. These include the common risk factors of tobacco and alcohol abuse and the associated comorbidity. In addition, these tumors are histologically similar and tend to be locoregionally aggressive with only a limited metastatic potential. The most important similarity, however, has been the relatively uniform response of head and neck cancers to systemic chemotherapy. Indeed, previously untreated squamous cell head and neck cancer is remarkably sensitive to systemic treatments, particularly when compared to most other common solid tumors [1].

19.2 Oncogenesis and the Progression from Benign to Malignant Epithelium

The complex process that transforms normal epithelium to invasive squamous cell carcinoma is incompletely understood, and the intense scientific inquiry focused on these events has paved the way for development of effective systemic agents for this disease. Malignant transformation is a multistep process that is thought to involve an accumulation of genetic defects and interplay between carcinogen exposure, genetic predisposition, and, more recently, viral infection.

Tobacco and alcohol are well-established risk factors for head and neck cancer. "Field cancerization" is used to describe the predisposition to malignant transformation along the entire upper aerodigestive tract epithelium as a result of carcinogen exposure [2]. Molecular abnormalities known to occur early in oncogenesis are often observed not only in the premalignant lesions themselves but the surrounding normal epithelium. Synchronous premalignant and malignant lesions in different areas of the aerodigestive tract have been noted to harbor similar molecular abnormalities. This process is felt to be responsible for the clinical observation of second or third primary upper aerodigestive tract malignancies in patients with heavy alcohol and tobacco exposure successfully treated for their index head and neck squamous cell cancer [3].

The stepwise progression to malignancy is somewhat similar to the colon cancer model of carcinogenesis. One of the first observations supporting this was the reproducible cytogenetic abnormalities identified in hyperplasia, dysplasia, carcinoma in situ, and invasive malignancy [4, 5]. For instance, loss of heterozygosity at the 3p and 9p loci has been frequently observed in early premalignant hyperplastic head and neck mucosal lesions. The transition from hyperplastic to dysplastic epithelium is often characterized by loss of heterozygosity at 17p and gains in the 11q23 region. With more sophisticated molecular techniques, these chromosomal changes have been found to correspond to genes that play critical roles in cell cycle regulation, specifically the tumor suppressor genes p53, Rb, p16, and cyclin D1.

It is becoming increasingly apparent that neoplastic transformation is mediated by a far more complex interaction of factors than genetic mutations in proteins regulating the cell cycle. Gene silencing through epigenetic phenomena, such as hypermethylation of promoter regions of tumor suppressor genes, has been observed [6]. The role of overexpressed cell surface receptors such as EGFR and its downstream signaling cascade mediating cellular immortalization and invasion has been recognized [7]. The influence of genes and proteins responsible for cellular adhesion, such as E-cadherin [8], and matrix metalloproteinases [9], has also been implicated. Furthermore, the critical role of the tumor microenvironment and nonmalignant cellular components within tumors (such as immune and stromal cells) in tumor propagation and immune evasion is rapidly being elucidated [10]. These more recently identified pathways represent therapeutic targets and avenues for drug development [11].

The role of viral infection in carcinogenesis in head and neck cancer was first recognized in nasopharyngeal cancer. Virtually all cases of endemic undifferentiated nasopharyngeal carcinoma are found to harbor the Epstein–Barr virus. The viral proteins LMP1 and LMP2a are thought to exert transforming effects through intracellular signaling cascades promoting cellular immortalization [12]. These cancers behave differently from head and neck cancer of other subsites, with a predilection for early distant spread but otherwise superior treatment outcomes after therapy for local disease.

There has also been increasing recent awareness of a distinct patient population with oropharyngeal cancer harboring high-risk human papillomavirus (HPV) subtypes [13]. These patients may not have a prior exposure to tobacco and alcohol, an observation that has challenged the applicability of the field cancerization theory and the multistep carcinogenesis model to all head and neck cancers. These HPV-associated tumors often contain wild-type p53 and Rb, which are functionally inactivated by viral proteins [14]. Not only are these HPV-positive tumors molecularly distinct, but they also appear to have clinically distinct behavior with significantly better prognosis in both the locally advanced and recurrent/metastatic settings [15, 16]. Of interest, there also appear to be patient factors which modify prognosis within this distinct group, such as tobacco exposure [16] with better outcomes observed in patients with minimal or no smoking history. Investigation into the optimal therapeutic approach for this unique subset is ongoing.

19.3 Treatment Goals and Efficacy End Points

When defining the management for any patient with cancer, it is critical that a clear treatment goal be identified. If the treatment goal is cure, considerable short- and long-term treatment-induced morbidity may be considered acceptable. Aggressive treatment approaches may still be justified when survival prolongation is possible, even if the disease cannot be cured. When the patient can only be palliated, however, considerable discretion must be exercised in the choice of treatment, and the toxicity considered acceptable. Thus, the risk/benefit ratio varies greatly depending on the goal of the treatment and the anticipated outcome. What might be considered to be acceptable risk and toxicity for a potentially curable patient may be entirely unacceptable for a patient treated with palliative intent.

Multiple efficacy end points are used in assessing the success of any cancer treatment [17]. The gold standard end point and the end point which is easiest to measure in a clinical trial have always been overall survival. In patients with head and neck cancer, however, survival is not only impacted by the disease itself but by the frequent underlying cardiopulmonary comorbidity and by the significant incidence of second primary malignancy.

In patients with advanced disease, an improvement in survival may be difficult to demonstrate and may not be a prerequisite for symptomatic palliation. Tumor response, i.e., a measurable shrinkage in tumor volume, has always been considered to be an accurate reflection of antineoplastic activity [17]. Clear definitions of what actually constitutes a meaningful response are critically important in determining which chemotherapeutic agents might be of value in drug combinations, or in definitive multimodality treatment. These definitions have evolved over time but have been recently standardized as the Response Evaluation Criteria in Solid Tumors (RECIST) [18]. Further refinement in these criteria has led to RECIST 1.1 [19], to the development of PET scan-based response criteria (PERCIST) [20], and to response criteria specific to immunotherapeutics [21]. Although these criteria are important in allowing investigators to assess the efficacy of chemotherapy drugs and combinations, it should also be recognized that achievement of a formal response may not be necessary for a patient to achieve symptomatic benefit.

There has been recent discussion about the value of "stable disease" as an end point of palliative systemic therapy [22]. Historically if a chemotherapeutic drug was unable to produce actual tumor shrinkage, it was considered inactive, and the toxicity produced was not felt to be justified. With the recent proliferation of newer and better tolerated targeted therapies, this has been called into question [23]. Many patients treated with these agents achieve disease stability without significant tumor shrinkage and appear to benefit from continued treatment with a possible impact on survival. Thus, the concept of "clinical benefit" (i.e., disease response and disease stability after treatment) has been legitimized as a meaningful end point in palliative management.

For patients being treated with curative intent, additional, more sophisticated end points are often chosen, including progression-free survival, disease-free survival, event-free survival, or disease-specific survival [24, 25]. Although these functions may be more reflective of the effect of treatment than the overall survival, they are often variably defined and difficult to interpret. Standard definitions have been proposed. When reporting the efficacy of local or regional treatment modalities, investigators have often chosen such end points as local or locoregional control [25]. While somewhat reflective of overall outcome, such assessments ignore the relationship between local, regional, and distant disease and do not fully address the overall impact of the disease on the patient. When measuring the effect of a systemic treatment, distant disease control is also a common end point. Once again, however, this function is not independent of locoregional control. Furthermore, distant metastases are a relatively infrequent cause of treatment failure in head and neck cancer.

Even these end points may not be the most important outcome from the patient's perspective. Cancers in the head and neck and their treatments may significantly compromise several major human functions including speech, swallowing, and non-stomal breathing. Preservation of these functions may be more important to a patient than survival. While organ preservation, i.e., the avoidance of surgical resection of the organ, is easy to measure, it is only a crude estimate of functional preservation, a more difficult end point to assess, particularly for any given patient [26].

Moreover, the acceptability of functional compromise will vary between patients, and functional restoration is often possible even after organ removal. Non-laryngeal speech with preservation of swallowing may or may not be a preferable outcome to speech preservation with feeding tube dependence for any given patient.

List and colleagues from the University of Chicago have explored these kinds of patient-defined goals after head and neck cancer treatment in some detail [27]. When patients were asked to rank the relative importance of several treatment outcomes, cure and longer survival were consistently most important. There was considerable variability in the relative importance of other functional and cosmetic treatment priorities, including those goals related to pain, energy, voice, swallowing, and appearance. This is a message that we, as physicians, must remember when discussing treatments with our patients.

A number of validated quality of life instruments have also been developed in an attempt to better assess the impact of treatment and disease from the patient's perspective. Several of these tools have been widely employed including the Performance Status Scale for Head and Neck Cancer [28], the Functional Assessment of Cancer Therapy (FACT) scale [29], the EORTC quality of life questionnaire [30], and the University of Washington scale [31]. Thus far, however, the results and importance of these measurements are not entirely clear.

When using chemotherapy as palliative treatment in patients with incurable disease, the acceptability of the acute toxicities is the major determinant of the risk/benefit ratio of the treatment. However, when chemotherapy is being used as part of a curative multimodality treatment approach, the acute toxicities, while important, are of less concern than any late or long-term morbidity. Fortunately, except for a small risk of sterility or of a second malignancy, late morbidity from chemotherapy is uncommon. It is clear, however, that the combination of chemotherapy and radiation increases the likelihood and severity of the long-term morbidities commonly associated with radiation, an interaction which must also be considered when choosing treatments [32].

The escalating costs of antineoplastic agents and drug administration have long been regarded as unsustainable in developed countries with the health-care system in the United States serving as the prime example. Coupled with the often perceived minute increments in outcome improvement, a new set of end points gaining relevance are those that explore cost-effectiveness and value, of both diagnostic testing and therapeutic interventions [33, 34]. Related to this is the recognition of the adverse economic impact of cancer therapy on individuals, their families, and their community [35]. The term "financial toxicity" is a relatively new end point being studied as an outcome measure in the cancer population.

19.4 General Considerations in the Use of Chemotherapy

Most drugs used for systemic therapy in malignant disease exploit cancer cells' innate inability to repair genetic damage. Because normal cells in various tissues are vulnerable to these drug effects, chemotherapeutic agents are a class with a narrow therapeutic window. Preclinical models have demonstrated the steep dose–response curves after the administration of chemotherapy [36]. With any dose reduction of therapy, there is a consequent significant decrement in the degree of cancer cell kill and a resultant compromise in the ability to eliminate the malignant clone. The challenge in the delivery of chemotherapy is remaining within the therapeutic window, that is, being able to administer maximal drug doses while avoiding lethal injury to normal tissues.

Chemotherapy is usually administered intermittently, but at regular time intervals so as to allow normal tissue (usually bone marrow) recovery from drug-related toxicity and enable administration of adequate drug dose over time. As many chemotherapeutic agents are cell cycle specific, at any given time, a certain proportion of cancer cells are not in the chemotherapy sensitive phase of the cell cycle. Apart from limiting toxicity, repeated drug exposure over time allows for surviving cancer cells to enter the specific cell cycle phase during which an agent exerts its antitumor effects.

Due to consequences of the lifestyle that predisposes to head and neck cancer, cardiac, pulmonary, and renal comorbidity, in addition to suboptimal compliance, complicates treatment planning in this subset of patients. Tailoring the choice of drug and treatment modality to patient factors is critical to optimizing treatment outcomes. The considerable acute toxicity of chemotherapy can result in significant morbidity and even mortality in patients who are poor candidates for aggressive therapy.

Pharmacokinetic considerations for this patient population also have to be taken into account when selecting the appropriate chemotherapeutic regimen. The oral route is often compromised in patients with advanced tumors of the head and neck, and the delivery and absorption of active orally administered drugs such as hydroxyurea may be impaired. Most chemotherapeutic drugs active in this disease are metabolized in the liver and excreted through the biliary or renal route. Renal dysfunction, hepatic impairment, preexisting cardiovascular disease, and the frequency of considerable alcohol exposure are all important considerations in the choice of chemotherapy.

It is well recognized that previously untreated malignancies are more responsive to therapy than is persistent or recurrent local, regional, or distant disease after initial therapy. Certain molecular characteristics have been reported to predict for relapse after chemotherapy and radiation [37–39]. In addition to intrinsic variations in gene expression, persistent or recurrent head and neck cancers often acquire molecular aberrations from prior exposure to pharmacologic agents that render them more resistant to chemotherapy compared to treatment naïve tumors [40, 41]. Changes in tumor vasculature from previous surgery or radiation and increased expression of genes that promote hypoxic tumor growth are thought to contribute to radiation insensitivity [42]. These, in addition to the significant symptom burden of recurrent disease and prior therapy, magnify the difficulty of administering effective systemic therapy in this compromised patient population.

19.5 Single Agents: Mechanisms of Action, Toxicities, and Metabolism

The most frequently used agents in the treatment of both locally advanced and metastatic squamous cell head and neck cancer have been the platinum compounds, methotrexate, 5-fluorouracil, and the taxanes. All four drug classes have single-agent activity, have differing mechanisms of action and toxicity, and can be administered concurrent with radiation as radiation sensitizers. Although many other antineoplastic drugs have known activity, the following section will focus on these four classes (Table 19.1).

Cisplatin was the first platinum compound noted to have antitumor activity in head and neck cancer [43]. The mechanism of action is believed to be drug incorporation into DNA, forming DNA adducts which distort the normal DNA helical structure. This triggers cellular recognition of DNA damage and subsequent apoptosis. Increased intracellular cisplatin doses are noted when the drug is given with radiation. The systemic toxicity of cisplatin can be significant and involves multiple organ systems. It is a highly emetogenic compound, which can cause both early and delayed chemotherapy-induced nausea and vomiting, now more easily controlled with modern effective antiemetic regimens. Nephrotoxicity through glomerular and renal tubular damage with resultant salt wasting can be a consequence of treatment. This can often be prevented and ameliorated by aggressive hydration. Peripheral neuropathy and irreversible ototoxicity (in the form of high frequency hearing loss) can also result from cumulative drug exposure. Carboplatin is an analog of cisplatin, whose properties render it less nephro- and neurotoxic, but more myelotoxic than cisplatin. The chemical structure of carboplatin results in delayed drug conversion and excretion, resulting in a longer half-life than cisplatin. Both of these drugs are excreted primarily through the kidney [44].

The antifolates, like methotrexate, exert antitumor effects by impairing the cancer cell's ability to generate precursors for DNA synthesis [45]. Methotrexate was approved for head and squamous cell cancer treatment in 1953. This drug inhibits dihydrofolate reductase, which maintains the intracellular supply of reduced folate essential for purine synthesis. Methotrexate has a wide range of systemic side effects; the most commonly observed are myelosuppression and gastrointestinal toxicity. Interstitial pneumonitis, hepatic transaminase elevation, and renal dysfunction from drug precipitation in the renal tubules are also recognized side effects. The majority of this drug is eliminated through the kidneys, with a small proportion, about 10 %, excreted through the bile.

5-Fluorouracil is a uracil analog that impairs both DNA and RNA synthesis [46]. It is intracellularly converted to its active form, 5FdUMP, which inhibits the enzyme thymidylate synthetase, depleting thymidylate and arresting DNA synthesis. The drug can also be intracellularly converted into 5-FUTP which, when incorporated into RNA, results in cell death. The drug has a short half-life lasting minutes and can be administered as a bolus or infusion. Like methotrexate, 5-fluorouracil results in myelosuppression and gastrointestinal toxicity. Nausea, stomatitis, mucositis, and diarrhea are common manifestations. Coronary vasospasm resulting in myocardial infarction is a rare but reported side effect. This drug is degraded by the enzyme dihydropyrimidine dehydrogenase, which is present in most tissues. The inactive metabolites are excreted in the urine [47].

The taxanes, paclitaxel and docetaxel, are a pharmacologic class of agents that induce cell death by stabilizing microtubule formation [48]. Subsequent metaphase arrest results in apoptosis. Both paclitaxel and docetaxel are primarily metabolized by the liver and excreted in the bile, thus appropriate dosage adjustments may be necessary in the setting of hepatic dysfunction [49]. Hypersensitivity reactions to paclitaxel are the most common acute toxicity; myalgias and arthralgias after drug administration are also common. Peripheral neuropathy is a cumulative side effect of both drugs. Docetaxel can result in fluid retention or skin toxicity.

Table 19.1 Commonly used chemotherapeutic agents in the management of head and neck cancer

Class	Agents	Mechanism of action	Clearance	Toxicity
Platinum agents	Cisplatin Carboplatin	DNA adduct formation	Renal	Nausea Nephro- and neurotoxicity Myelosuppression
Antifolates	Methotrexate	Depletion of precursors for purine synthesis	Renal	Myelosuppression Gastrointestinal toxicity
Antimetabolites	5-Fluorouracil	Depletion of precursors for DNA synthesis Incorporation into RNA	Renal (inactive drug)	Gastrointestinal toxicity Myelosuppression
Taxanes	Paclitaxel Docetaxel	Mitotic arrest by microtubule stabilization	Hepatobiliary	Hypersensitivity Peripheral neuropathy

19.6 Combination Chemotherapy: Rationale and Principles

When single agents prove active in the management of a malignancy, the next step has always been an attempt to use these drugs in combination. The use of combination chemotherapy, however, is based on several clear principles [50] (Table 19.2). The first is that for a drug to be useful in a combination chemotherapy regimen, it must have single-agent antineoplastic activity. It makes little sense to include an ineffective chemotherapeutic agent in a drug combination, with the hope that it will suddenly prove to kill cancer cells. It should be noted, however, that experience using some of the targeted agents, most notably bevacizumab, has suggested that this caveat does not always hold true. Bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, is a relatively ineffective antineoplastic agent when used alone. When used in combination with other chemotherapeutic drugs, however, it has a demonstrated benefit in several disease sites [51, 52]. The second general principle in the use of combination chemotherapy is the importance of using drugs in full therapeutic doses. There has been general recognition of a dose–response curve for most systemic chemotherapeutic agents. Larger doses tend to produce larger, if not exponentially larger, responses, and suboptimal dosing of multiple agents would be unlikely to produce a better result than the full therapeutic dose of a single drug.

Third, drugs used in combination should have nonoverlapping mechanisms of action. There are a number of defined classes of chemotherapeutic agents, often with several different, but similar members. Rarely has the use of two drugs from the same class (e.g., two alkylating agents or two vinca alkaloids) been of any benefit. Finally, drugs, when used in combination, should not have overlapping toxicities. In view of the steep dose–response curve for most chemotherapeutic agents, the optimal dosing for each drug is usually defined by its dose-limiting toxicity. Two drugs, with the same dose-limiting toxicity (e.g., myelosuppression), if used at their maximally tolerated dose, will undoubtedly produce significant and perhaps intolerable toxicity and would be a poor combination.

Despite the soundness of the rationale for combining chemotherapeutic agents, many of the common drug combinations used in this disease and others violate one or several of these principles. Thus, careful phase I and II testing for both toxicity and efficacy is important before widespread adoption of any chemotherapy combination.

Table 19.2 Principles of combination chemotherapy

1. Drugs used in combination should have single-agent activity
2. Drugs used in combination should be used in full therapeutic doses
3. Drugs used in combination should have nonoverlapping mechanisms of action
4. Drugs used in combination should have nonoverlapping toxicities

19.7 Systemic Chemotherapy in Palliative Management

Patients with persistent or recurrent disease not amenable to local therapy such as radiation or salvage surgery or patients who develop or present with systemic metastasis are incurable. The prognosis for patients in this situation is dismal, and there is little evidence suggesting that chemotherapy is superior to best supportive care. Survival in this patient group, even when palliative chemotherapy is administered, uniformly ranges from 6 to 10 months. In this situation when cure and survival prolongation are not possible, the treatment goal is to palliate symptoms and improve quality of life.

Quality of life can be adversely impacted by the local effects of tumors at both the primary site and the sites of metastasis. Local effects of the primary site tumor include pain and impairment or loss of important functions such as speech, swallowing, smell, hearing, and even vision. Cosmetic deformity in addition to functional compromise can cause significant body image issues and depression. Distant disease most often involves the lung and less commonly bone. This can result in cough, hemoptysis, painful bone lesions, pathologic fractures, and nerve or spinal cord impingement. Palliative care to address these symptoms should be carried out by a multidisciplinary team. Modalities such as radiation therapy to painful sites and adequate pain control contribute to palliation in the metastatic setting.

Systemic chemotherapy is a widely used tool for reducing tumor burden, with the assumption that this leads to alleviation of tumor-related symptoms [53]. Active chemotherapy drugs when given as single agents often result in modest response rates ranging from 10 to 30 % depending on previous treatment [54–56]. Several well-designed clinical trials have been done to compare various single- and multiple-drug regimens [57–59]. Although multiagent chemotherapy does produce a consistent increase in response rates, with only one exception, no significant prolongation of median survival has been observed. One of the more important observations has been the reproducible increase in treatment-related toxicity that accompanies combination drug therapy.

This observation introduces a significant conflict with the palliative goals of care in a patient population with incurable disease and significant comorbidity. Certainly the toxicity of chemotherapy would only be acceptable if it ultimately resulted in some alleviation of tumor-related symptoms. With little convincing evidence of a survival advantage with chemotherapy combinations, great care must be taken to appropriately select patients who are good candidates for combination treatment. In a patient with a

compromised performance status, for example, combination chemotherapy may adversely impact quality of life rather than palliate symptoms.

Phase III clinical trials using chemotherapy for patients with incurable disease carried out in the last two decades have focused on examining the end points of toxicity, survival, and response rates. Little has been done to incorporate validated measurements of quality of life in these studies. The recognition that response rates may not accurately translate to improved symptom control, along with the introduction of a new class of "targeted agents" believed to have a more tolerable side effect profile, has led to the integration of more accurate quality of life measurements in the design of clinical trials.

In general, among most solid tumors, the integration of new pharmacologic agents into curative intent therapy is initiated by observed drug activity in patients with recurrent, pretreated, or metastatic disease. Some examples of these emerging drugs showing antitumor effects in the metastatic setting are newer-generation nucleoside analogs, antifolates, and topoisomerase inhibitors. Gemcitabine is a novel synthetic pyrimidine analog which is activated through intracellular phosphorylation. In its activated form, it is incorporated into DNA and RNA and arrests their synthesis; it also inhibits its own inactivating enzyme, increasing intracellular concentrations [60]. The new-generation antifolate pemetrexed inhibits several enzymes involved in the maintenance of reduced folate pools essential for the production of DNA precursors. Its property of rapid entry into the cellular environment through several transport mechanisms is known to overcome cellular resistance that often hampers the efficacy of older-generation antifolates [61]. Irinotecan is a partly synthetic camptothecin, which inhibits topoisomerase I, causing supercoiling of DNA during replication and growth arrest [62]. These drugs have been shown to possess radiation-sensitizing properties, and their assimilation into curative treatment strategies awaits further investigation.

The epidermal growth factor receptor and its demonstrated synergistic activity with both chemotherapy and radiation resulted in studies using the EGFR inhibitor in the metastatic setting. When compared to single-agent methotrexate, EGFR inhibitors used alone have had disappointing response rates and no demonstrable impact on survival [63]. However, recently published data on the combination of platinum-based chemotherapy and EGFR inhibition has shown an unprecedented albeit modest improvement in survival [64]. The combination of chemotherapy with targeted agents has demonstrated a similar survival advantage in other epithelial malignancies and may represent the future paradigm for investigating and treating metastatic disease.

19.8 Systemic Chemotherapy in Definitive Management

In the curative management of solid tumors, single-modality chemotherapy is rarely sufficient. For most neoplasms, and in particular head and neck cancers, chemotherapy is only effective when used in combination with definitive radiation therapy and/or surgery. Chemotherapy must be considered adjunctive not curative, and its use in multimodality treatment regimens must not compromise the delivery of the definitive locoregional treatment. While considerable morbidity may be acceptable from aggressive curative treatment regimens, the toxicity produced by the addition of chemotherapy cannot be allowed to interfere with the required radiation or surgery.

A number of multimodality treatment approaches have been explored (Table 19.3). All have been based on the recognized chemosensitivity of head and neck cancer. Previously untreated patients with squamous cell head and neck cancer can be expected to respond to systemic combination chemotherapy up to 90 % of the time, with complete responses described in between 30 % and 50 % of patients. These excellent responses are rarely durable however, and disease regrowth is the rule. The question then becomes how best to exploit this antineoplastic activity in conjunction with definitive radiation and surgery.

Induction chemotherapy was the first treatment strategy developed. The rationale for induction chemotherapy was that given the increased chemotherapy responsiveness in the previously untreated patient, the optimal time to use chemotherapy would be prior to any locoregional intervention. It was reasoned that if significant tumor shrinkage

Table 19.3 Multimodality treatment approaches using chemotherapy

Induction chemotherapy	The use of chemotherapy prior to definitive locoregional management
Adjuvant chemotherapy	The use of chemotherapy after definitive locoregional management
Concurrent chemoradiotherapy	
Definitive chemoradiotherapy	The use of concomitant chemotherapy and radiation as definitive management
Adjuvant chemoradiotherapy	The use of concomitant chemotherapy and radiation after definitive locoregional management
Sequential treatment	The use of induction chemotherapy followed by definitive concomitant chemotherapy and radiation

could be achieved, there might, as well, be an improvement in locoregional control, a decrease in distant metastasis, and an overall survival improvement. The potential for surgical modification or organ preservation after chemotherapy-induced tumor shrinkage was also suggested.

An alternative strategy is the use of adjuvant or postoperative chemotherapy. Adjuvant chemotherapy strategies are meant to address concern about disease recurrence and are optimal for those patients likely to develop distant metastasis even after achieving locoregional control. Thus, a patient identified as being at high risk for distant disease recurrence after definitive surgery and/or radiation might be appropriate for further systemic chemotherapy. Not surprisingly given the limited risk for distant metastases in this disease, single-modality adjuvant chemotherapy has not been of major benefit.

Several observations emerged from these kinds of sequential treatment approaches, however. The first was the recognition that chemotherapy responsiveness was predictive for responsiveness to radiation therapy [65]. This suggested the potential that chemotherapy might serve as a selection tool to identify those patients most likely to benefit from radiotherapeutic (i.e., nonoperative) intervention [66]. Chemotherapy was also found to decrease the risk of distant metastases, an achievement with a limited survival impact in a disease with such a small risk for distant disease [67–69]. It was also unfortunately recognized that treatment compliance could be compromised by successful induction chemotherapy. The dramatic response to systemic chemotherapy often experienced by these patients on occasion led to a motivational interference with completion of definitive treatment.

The observation was also made that those patients who respond to systemic chemotherapy live longer than those patients who do not. This has been suggested by some as a justification for the use of systemic chemotherapy. It must be recognized, however, that a response to chemotherapy is more common in those patients with a better performance status and smaller disease burden. These are also the patients with a better prognosis irrespective of the treatment utilized [70].

An alternative to the sequential use of single-treatment modalities has been the concurrent use of chemotherapy and radiation. The rationale for this approach has been the recognition that both chemotherapy and radiation therapy are independently active treatment modalities and that chemotherapy may potentiate radiation, improve locoregional control, and decrease the impact of distant micrometastatic disease. In addition, the use of these two treatment modalities together, rather than sequentially, will shorten the overall treatment duration and in theory improve compliance. Preclinical data support a synergistic role of chemotherapy and radiation therapy through various postulated mechanisms. The enhanced cell kill from simultaneous exposure to systemic chemotherapy and radiation has been attributed to increased cellular cytotoxic drug uptake during radiation, chemotherapy-induced impairment of DNA repair mechanisms in response to radiation-induced damage, and chemotherapy-induced cell cycle shift resulting in increased radiation sensitivity.

There are also several disadvantages to the concomitant use of chemotherapy and radiation. Clearly the concurrent use of two treatment modalities will produce greater toxicity than the use of either treatment modality alone. This toxicity may then result in a compromise of dose intensity and efficacy, such as single agent rather than combination chemotherapy, split rather than continuous course radiation, or a reduction of the chemotherapy doses used. Nonetheless, the concurrent use of chemotherapy and radiation has been intensively explored in this disease both as definitive management and as a postoperative adjuvant. Both locoregional control and survival have been improved with this approach although the treatment has been associated with significant acute and late toxicity [71].

Along with this improvement in locoregional control has been the recognition of a relative increase in the frequency of distant metastases, a change in the natural history of this disease [72, 73]. Given the apparent benefit achieved by induction chemotherapy in reducing the risk of distant metastasis, it has been suggested that a sequential treatment approach of induction chemotherapy followed by concurrent chemoradiotherapy might be advantageous [74]. The induction chemotherapy would address the risk of distant metastasis and the concurrent chemoradiotherapy would deal with the locoregional disease. Despite this seemingly sound rationale, randomized trials thus far have failed to show a survival advantage to induction chemotherapy followed by concurrent chemoradiation compared to concurrent chemoradiation alone [75, 76].

Critical to the use of systemic chemotherapy, both with and without radiation, has been the integration with surgery. Optimal management of the primary site and of the neck requires the definition of careful treatment algorithms. Patients with persistent or recurrent primary site disease after chemoradiotherapy will require some kind of surgical salvage. Patients presenting with large neck nodes at diagnosis, or with neck nodes that only incompletely respond to nonoperative intervention, will require subsequent neck dissection with curative intent [77]. Given the potential for cure after such surgical salvage, it would seem important that we be able to identify those patients likely to fail in the neck or at the primary site after nonoperative intervention.

The development of organ preservation strategies has been somewhat unique to this field. The rationale for organ preservation is the hope that the substitution of radiation, with or without chemotherapy, for surgery might not compromise survival and yet preserve organ

integrity and function. The goal of treatment is no longer one of an improved survival. Instead, it is the hope that survival will not be compromised, but that there will be more organ (usually larynx) preservation. Again it is important to point out the difference between organ preservation and organ function preservation [26]. Preservation of a nonfunctional larynx is of little benefit to a patient despite maintenance of its anatomic integrity. Studies of both induction and concurrent chemotherapy and radiation schedules have been conducted with some success. However, recent data has raised the possibility that current organ preservation practices may have compromised overall survival in larynx cancer [78, 79]. Thus, for any given patient, the debate about the relative importance of organ preservation versus survival continues.

19.9 Emerging Issues

Increasing understanding of the molecular processes underlying head and neck squamous cell cancers, the discovery of new therapeutic targets, and the changing disease epidemiology has had a great impact on current scientific inquiry into the role of chemotherapy in improving patient outcomes.

The decreasing popularity of tobacco use has resulted in a plateau and decline of most tobacco-related malignancies of the upper aerodigestive tract [80]. Among head and neck cancers, a distinct clinical entity of high-risk HPV-positive oropharyngeal head and neck cancers in a patient population without exposure to tobacco or alcohol has surfaced. These tumors have a different molecular profile and have improved prognosis compared to non-HPV-related squamous cell malignancies of the head and neck [15, 81]. These patients are younger with less comorbid conditions and respond to definitive therapy with excellent local and distant control rates. The applicability of previously established therapies for head and neck cancer to this previously unrecognized clinical entity has been called into question, and a reduction of the intensity of therapy to spare patients from the attendant toxicity of chemotherapy and radiation combinations has been proposed for this patient population. Contemporary clinical studies are now moving toward studying HPV-positive and HPV-negative head and neck cancers separately, to further define the appropriate therapy for these two distinct subsets of patients. In particular, among good prognosis HPV-positive oropharynx cancers, ongoing clinical trials are focused on de-escalation of treatment through the following strategies: comparing non-platinum agents to platinum-based concurrent radiation therapy, de-escalation of radiation therapy doses, highly conformal radiation treatment approaches, and reexamining the role of minimally invasive surgical resection such as transoral robotic or laser microsurgical approaches.

Since the discovery that inhibiting the bcr-abl tyrosine kinase results in dramatic responses in patients with CML, numerous molecular markers have been identified as therapeutic targets in head and neck cancer. Inhibiting the epidermal growth factor receptor has been shown to result in synergistic cell kill when used with radiation and chemotherapy [82]. The combination of the monoclonal antibody cetuximab with definitive radiation in locally advanced head and neck squamous cell carcinomas has been shown to be superior to radiation alone in a large phase III clinical trial, with no significant increase in treatment-related toxicity [83]. Another phase III trial comparing combination chemotherapy to the same chemotherapy with cetuximab in patients with recurrent or metastatic head and neck cancer demonstrated a modest survival advantage, an observation never before made in clinical trials using chemotherapy combinations alone [64]. The generally more favorable toxicity profile of these agents makes them attractive prospects for integration into definitive and palliative therapy and is currently under study.

Another emerging role for systemic therapy is in salvage treatment for recurrent or persistent disease. Historically, when a patient experiences locoregional failure after definitive chemotherapy and radiation, surgery, when possible, was the only potentially curative option for salvage therapy. With the advent of more sophisticated radiation therapy techniques, reirradiation has been shown to be a feasible and successful in a highly select group of patients. Because of the dose and field limitations imposed by prior radiation therapy, reirradiation with the addition of systemic therapy for radiation sensitization is an attractive prospect. Several phase II studies have demonstrated the tolerability and efficacy of this approach [84, 85].

Sensitivity to chemotherapy is generally thought to identify disease with a more favorable disease biology. Complete responses to systemic therapy in most solid tumor malignancies are almost always associated with improved outcomes. Because the acute and long-term toxicities of surgery and chemoradiation are substantial, the possibility of using chemotherapy alone to select and cure local disease has been investigated. Single-institution clinical studies have explored the use of chemotherapy alone for nonmetastatic laryngeal carcinoma and demonstrated long-term disease remission in a subset of patients [86, 87]. Results of further studies will be required before this strategy becomes applicable to clinical practice.

The development of technology that can both comprehensively and rapidly sequence the tumor genome is leading to unprecedented insights into the molecular alterations that may hold therapeutic relevance in various malignancies. One such federally funded effort in the United States is the Cancer Genome Atlas. These efforts have been instrumental in identifying molecular targets such as PI3 kinase mutations, and

FGFr aberrations, that hold promise expanding the therapeutic armamentarium in head and neck malignancies [88, 89]. Clinical trials exploring such individualized and targeted treatments are currently underway.

Finally, insight into mechanisms involving immune evasion by malignant cells has resulted the expansion of immunotherapy into head and neck malignancies. Encouraging early phase clinical activity with immune check point inhibitors such as those inhibiting PDL-1 [90] has led to further testing of these and related agents in squamous cell carcinomas of the head and neck.

19.10 Conclusion

The current role of chemotherapy in the definitive management of head and neck cancer has been established by extensive scientific investigation over many decades. The benefits and toxicities of these agents have been well defined. The identification of molecular therapeutic targets, the development of novel active agents, and the changing epidemiology and treatment failure patterns of head and neck cancer are providing avenues for expanding the application of systemic therapy to improve outcomes in both local and metastatic disease.

19.11 Key Points

- Systemic therapy administration in squamous cell carcinomas of the head and neck is guided by therapeutic goals and patient factors.
- Chemotherapy is often a component of curative intent multimodality therapeutic approaches in locally advanced disease. In scenarios where symptom palliation is desired, systemic therapy as single modality is often utilized.
- Systemic treatment options are being expanded by scientific inquiry involving novel targeted agents in both the curative and palliative treatment settings.

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Molecular Targeted Therapies in Head and Neck Cancer

20

Zachary S. Morris, Anne M. Traynor, and Paul M. Harari

Abstract

Molecular targeted therapies for head and neck cancer offer promising opportunities to improve on the clinical outcomes of conventional treatments. The toxicity profiles of these agents are unique, reflecting their distinct mechanisms of action, and generally do not directly overlap the toxicities of conventional treatment modalities. In this chapter, we review the role of specific molecular targets in head and neck cancer and discuss the development and clinical testing of therapeutics that specifically target these molecules. We focus particularly on the epidermal growth factor receptor (EGFR) and explore the phase III clinical trial data demonstrating a survival benefit with the use of the anti-EGFR antibody, cetuximab, in locally advanced and recurrent/metastatic head and neck cancer. We further discuss the clinical investigation of small-molecule inhibitors of EGFR and other tyrosine kinases as well as current approaches to modulating angiogenesis for therapeutic effect in the context of head and neck cancer. We evaluate novel toxicities associated with molecular targeted therapies that have entered clinical practice and discuss next-generation approaches to molecular targeting. This chapter highlights the promise of molecular targeted therapeutics in head and neck cancer and the potential clinical rewards to be gained from continued investment in the preclinical and clinical investigation of these agents.

Keywords

Targeted therapies • EGFR • Head and neck cancer • Cetuximab • Tyrosine kinase inhibitors • HPV • Antibody • Small molecule

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Abbreviations

EGFR	Epidermal growth factor receptor
FDA	Food and Drug Administration
HNSCC	Head and neck squamous cell carcinoma
HER2	Human epidermal growth factor receptor 2
VEGF	Vascular endothelial growth factor
HPV	Human papillomavirus
IGFR	Insulin-dependent growth factor receptor
HGF	Hepatocyte growth factor
ECOG	Eastern Cooperative Oncology Group
RTOG	Radiation Therapy Oncology Group
FcγR	Fcγ receptor
ADCC	Antibody-dependent cell-mediated cytotoxicity
HDAC	Histone deacetylase
PDK	Pyruvate dehydrogenase kinase
TCR	T-cell receptor
PD-1	Programmed cell death-1

20.1 Introduction

Among the most notable advances in oncology over the last 20 years has been the emergence of molecular targeted therapeutics. Although initially defined by the US Food and Drug Administration (FDA) as agents approved together with a prerequisite diagnostic molecular test, molecular targeted therapies are more broadly defined by their specificity to aberrant cellular processes or molecular characteristics of tumors they are designed to treat. In this conceptualization, molecular targeted agents commonly include antibodies and small molecules intended to target a well-defined molecule or pathway resulting in tumor growth inhibition or destruction. While cytotoxic chemotherapeutics commonly target important molecules (e.g., DNA), molecular targeted agents modify specific molecular and cellular functions critical to tumor cell progression rather than generic processes of cell division. Because of this specificity, molecular targeted agents may cause a reduced toxicity profile compared to that with conventional cytotoxic agents. In the setting of locally advanced disease, where multimodality treatment is commonly delivered with curative intent, molecular targeted therapeutics may augment the effect of conventional cancer treatment modalities and enable patients with modest performance status or compromised chemotherapy tolerance to achieve improved outcomes. In this chapter, we review the development and clinical investigation of molecular targeted therapeutics in head and neck squamous cell carcinoma (HNSCC). For the purpose of this chapter, we focus primarily on antibody and small-molecule therapeutic platforms, with hypoxia-directed and drug-conjugated agents beyond the scope of consideration.

During the early twentieth century, Paul Ehrlich conceptualized molecular targeted therapeutics by postulating the existence of selective receptors on microorganisms that could be targeted by organic molecules for therapeutic effect. A half century later, the earliest broad-spectrum cytotoxic chemotherapies including nitrogen mustard and aminopterin were pursued with the intent of targeting molecules such as DNA or the pathway of folic acid synthesis [1]. However, early examples of what would now be considered molecular targeted agents were not formally developed until the introduction of monoclonal antibodies as a therapeutic platform by Levy and colleagues in 1981 [2]. This targeting strategy rapidly expanded with the development of antibodies targeting cell surface receptors critical to signal transduction pathways such as the epidermal growth factor receptor (EGFR or HER1) and the related human epidermal growth factor receptor 2 (HER2). A further platform of targeted therapeutics was established in the 1990s with the development of small-molecule inhibitors of specific or multiple kinases, tumor-specific fusion proteins, and various other proteins critical to tumor cell survival. During the last 20 years, the number of promising molecular targets and molecular targeted agents has rapidly expanded reflecting a tremendous public and private investment in the advancement of molecular cancer research.

The current era of molecular targeting in oncology has followed from the early clinical success of the anti-HER2 antibody, trastuzumab, and the small-molecule inhibitor of the BCR-ABL fusion protein, imatinib. Subsequent clinical studies have demonstrated therapeutic efficacy for a variety of additional agents including antibodies targeting EGFR family receptors, vascular endothelial growth factor (VEGF), markers of immune cell lineages, and receptors regulating immune cell activation. Small-molecule inhibitors of histone deacetylases, proteasomes, specific kinase domains, and other distinct signaling pathways have also entered clinical practice. Critical to the rational identification and successful development of targeted agents is selectivity for a tumor-specific marker, pathway, or process.

20.2 Molecular Targets in HNSCC

Identification of viable molecular targets in oncology fundamentally rests upon the accumulated understanding of cancer cell biology and tumorigenesis achieved through advances in basic and preclinical science. Perhaps most notable among recent efforts in this regard for HNSCC has been the identification of distinct molecular profiles, pathways to tumorigenesis, and prognosis for human papillomavirus (HPV)-positive and HPV-negative tumors. In the oropharynx, HPV has been well established as an etiologic agent [3–5]. HPV infection has been identified in other

subsites of HNSCC; however, a causal relationship appears to be much less common than in the oropharynx. HPV-associated HNSCC tends to present at earlier primary tumor stage but frequently with advanced lymph node involvement by poorly differentiated tumors in patients who are slightly younger and have a lesser history of tobacco or alcohol use [6]. When controlling for such differences, patients with HPV-associated oropharyngeal HNSCC have a 60–80 % reduced risk of death from their cancer as compared to patients with HPV-negative tumors [7, 8]. These differences, as well as clear molecular and genetic profile differences [9–11], identify HPV-positive and HPV-negative HNSCC as distinct diseases with most contemporary studies now examining them separately.

Our rapidly advancing recognition of HPV infection in HNSCC arises in the context of many years of investigation into the molecular and cellular underpinnings of HNSCC. As with all complex solid tumors, efforts to identify "driver" mutations that not only characterize but also play essential roles in tumor development and perpetuation have been undertaken. The most well studied of these in HNSCC are the tyrosine kinase signaling pathways, of which those involving EGFR have had the greatest clinical impact in HNSCC to date. Prior clinical studies demonstrate that EGFR is overexpressed or mutated in 80–90 % of HNSCC tumors [12–14]. A number of mechanisms may contribute to the role of EGFR in initiating or exacerbating the malignant behavior of HNSCC (Fig. 20.1). Included among these are the activation of cell signaling pathways that regulate cellular transformation, cell survival, cell cycle progression, proliferation, differentiation, apoptosis, cell-matrix interactions, cell motility, and metastasis. In addition, EGFR and downstream signaling pathways are activated following exposure to ionizing radiation even in the absence of ligand binding

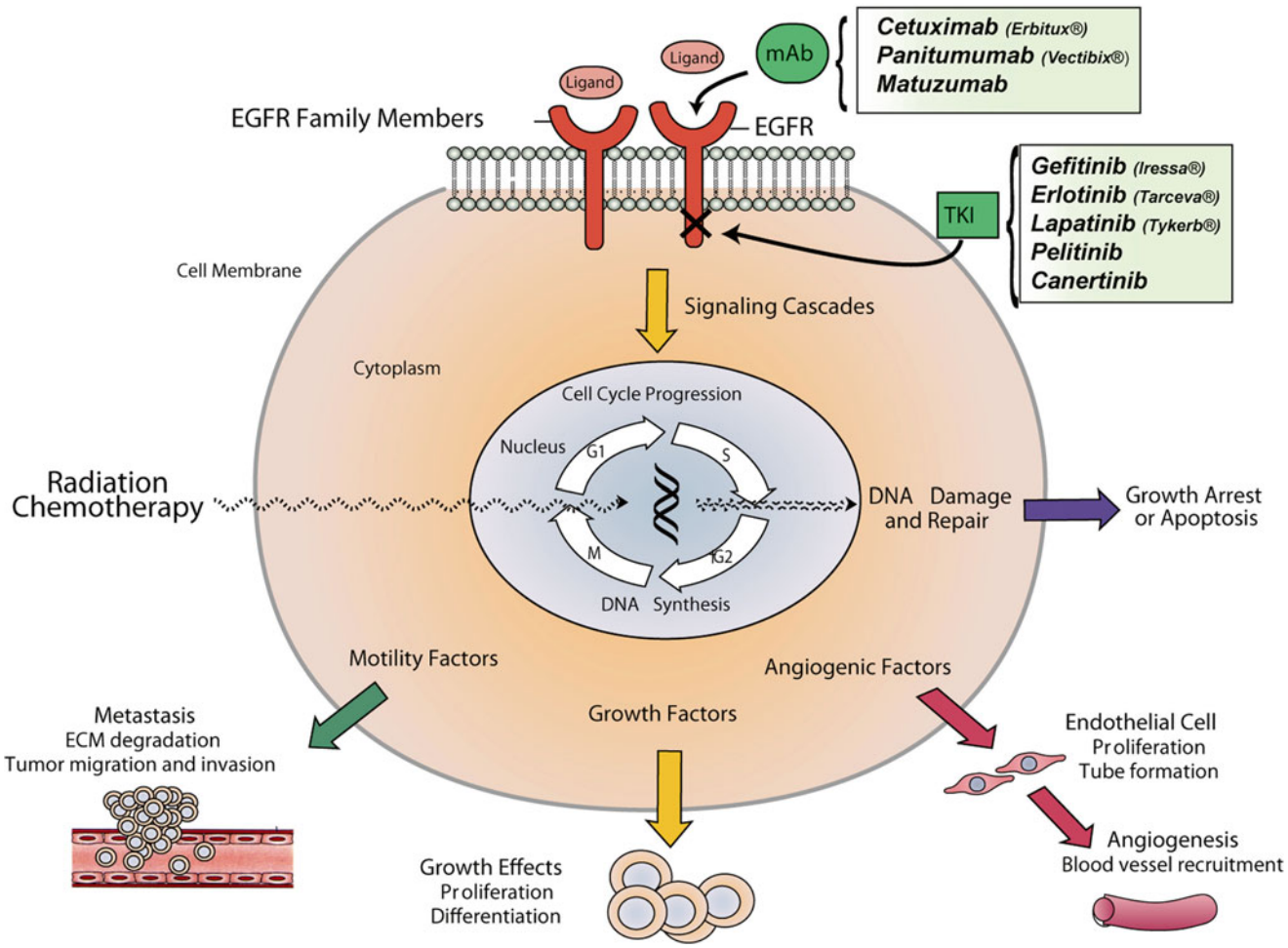

Fig. 20.1 Simplified schematic illustration of the EGFR pathway highlighting potential downstream cellular and tissue effects of EGFR signaling inhibition. The action site for EGFR inhibitors is depicted for mAbs and TKIs. Reprinted from Harari PM, Huang SM. Searching for reliable epidermal growth factor receptor response predictors: commentary re M. K. Nyati et al., Radiosensitization by pan-ErbB inhibitor CI-1033 in vitro and in vivo. Clin. Cancer Res., 10: 691–700, 2004. Clinical cancer research. 2004 Jan 15;10(2):428–32. With permission from American Association for Cancer Research

[15, 16], and overexpression of EGFR is associated with decreased response to radiotherapy and poorer clinical outcome [17, 18]. Preclinical studies from the late 1990s suggested potential for therapeutic efficacy in combining EGFR inhibition and radiation [19–21]. These studies indicated that inhibition of EGFR signaling could modulate cellular sensitivity to radiation and enhance tumor cell response to radiation in vitro and in animal model systems through effects on cell cycle distribution, attenuated DNA damage response, inhibition of accelerated repopulation, and enhancement of radiation-induced apoptosis.

Basic and preclinical research indicates that the varied effects of EGFR in HNSCC tumor cells are mediated principally through activation of downstream mitogenic signaling cascades including the Ras/Raf/MEK/ERK, PI3K/Akt/mTOR, JAK/STAT, Src, and PLC/PKC pathways. Collective evidence suggests that these varied signaling pathways contribute to tumorigenesis and tumor progression [22, 23]. Tumor cells overexpressing EGFR may exhibit aberrant activation of some or all of these pathways, and this may be modulated following EGFR inhibition resulting in therapeutic effect and possibly tumor cell killing in the context of oncogene addiction [24]. Yet the redundancy and interconnected nature of mitogenic signaling pathways also confer potential for resistance mechanisms, and these may involve compensatory activation of other receptor tyrosine kinases, including the insulin-dependent growth factor receptor (IGFR) and mesenchymal–epithelial transition factor (MET) [25]. Notably, MET and its ligand, hepatocyte growth factor (HGF), are overexpressed in 80 % of HNSCC, and this is associated with reduced disease-free and overall survival in HPV-negative HNSCC [26–29]. Ongoing research efforts continue to explore opportunities to simultaneously target such resistance pathways using novel molecular inhibitors and next-generation approaches to targeting EGFR in HNSCC (Table 20.1).

In addition to the activation of oncogenic signaling pathways, inactivation of tumor suppressor pathways is critical to tumorigenesis in HNSCC. The tumor suppressor, TP53, among the most commonly mutated genes in HNSCC, is disrupted in 40–80 % of such tumors [9, 30–33]. The observation of p53 mutations in premalignant lesions and at surgical resection margins suggests that this may be an early step in malignant transformation [30, 34]. The rate of p53 mutation is increased in association with tobacco and alcohol use, suggesting a prominent role in HPV-negative tumor development [35]. Not surprisingly, given the stratification of clinical outcomes by HPV status, p53 mutation is predictive of poor clinical outcomes following treatment with radiation or cytotoxic chemotherapies [36, 37]. On the other hand, wild-type p53 is a principal target of HPV-mediated tumorigenesis and is selectively degraded via the ubiquitin–proteasome pathway upon association with the viral E6 oncoprotein and E6-associated protein (Fig. 20.2) [38, 39]. Similarly, the pRb tumor suppressor is indirectly targeted early in the development of 20–40 % of HNSCC through mutation or copy number loss of the CDKN2A gene [9, 10]. Wild-type pRB, on the other hand, is inactivated in HPV-positive tumors by the viral oncoprotein E7, which competitively displaces the E2F transcription factor promoting G1- to S-phase cell cycle progression and a characteristic upregulation of p16 (Fig. 20.2) [40, 41].

In addition to cell signaling pathways and tumorigenic mutations, certain physiologic processes may afford opportunities for drug development and tumor specificity. Angiogenesis is a process whereby new blood vessels are formed [42]. Preclinical data suggests that solid tumors will not grow larger than several millimeters or generate metastases in the absence of angiogenesis [43–45], and this may represent a rate-limiting step in tumor progression [46]. Triggers of angiogenesis include hypoxia, which may manifest as a tumor outgrows its blood supply. One of the prime angiogenic targets, VEGF, is thought to play a critical role in HNSCC [47–49]. VEGF binds to its transmembrane tyrosine kinase receptor VEGFR-2 and stimulates vascular endothelial cell proliferation and survival and secretion of proteolytic enzymes to break down extracellular matrix [45, 50]. In the context of a tumor, the net product of aberrant angiogenesis is the generation of structurally abnormal vessels that are “leaky” and inefficient in their ability to deliver blood, oxygen, and nutrients resulting in further hypoxia and a feedback loop of perpetually activated angiogenesis (Fig. 20.3) [51]. VEGF and VEGFR are expressed in 90 % of HNSCC tumor samples [52, 53], and VEGF expression in HNSCC tumor samples or patient serum is associated with increased risk of tumor growth, metastasis, treatment failure, and death [54–58]. In preclinical HNSCC models, inhibition of the VEGF signaling pathway has markedly decreased angiogenesis, inhibited tumor growth, and augmented radiation response, the latter perhaps reflecting tumor vascular normalization and reduced hypoxia following VEGF blockade [59–61].

20.3 Clinical Investigation of Molecular Targeted Agents in HNSCC

20.3.1 The Role of EGFR-Targeted Therapeutics in the Treatment of Early-Stage and Locally Advanced HNSCC

EGFR was first identified in the early 1980s as a viable molecular target for functional inhibition with a monoclonal antibody by Sato and Mendelsohn [62]. After extensive preclinical validation, early-phase clinical studies demonstrated safety and disease response from inhibition of EGFR with a mouse–human chimeric anti-EGFR antibody, cetuximab. The initial

Table 20.1 Targeted therapies in HNSCC

Type of drug	Drug	Target	Stage of development	NCT number
Adenovirus gene therapy	Advexin	p53	Phase III	NCT00064103
	ONYX-015	p53	Approved in China	N/A
CDK inhibitor	P276-00	pRb	Phase II	NCT0089954
Monoclonal antibody	Cetuximab	EGFR	In clinical use	N/A
	Panitumumab		Phase II	NCT00756444
				NCT00454779
				NCT00820248
	Zalutumumab		Phase III	NCT00496652
	Nimotuzumab		Phase III	NCT00957086
	Bevacizumab	VEGFR	Phase II	NCT01588431
Tyrosine kinase inhibitor	Gefitinib	EGFR	Phase III	NCT00206219
				NCT00684385
	Erlotinib	EGFR	Phase II	NCT01064479
	Lapatinib	EGFR, HER2	Phase III Phase II	NCT00424255 NCT01044433 NCT01711658
	Afatinib	EGFR, HER2, ErbB4	Phase III	NCT01856478
				NCT01345669
				NCT01345682
	Sorafenib	VEGFR-2, VEGFR-3, Raf, PDGFR	Phase II	NCT00939627
	Sunitinib	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, RET, c-KIT	Phase II	NCT00387335
	Vandetanib	EGFR, VEGFR, RET	Phase II	NCT00459043
	Pazopanib	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, c-KIT	Phase II	NCT01377298
	Axitinib	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, c-KIT	Phase II	NCT01469546
	Nilotinib	BCR-ABL, c-KIT, PDGFR	Phase I	NCT01871311
MEK inhibitor	Trametinib	MEK	Phase I	NCT01725100
PI3K inhibitor	PX866	PI3K	Phase II	NCT01204099
	BKM120	PI3K	Phase II	NCT01527877
	BYL719	PI3K	Phase II	NCT01602315
	Rigosertib	PI3K, PLK	Phase II	NCT01807546
AKT inhibitor	MK2206	AKT	Phase II	NCT01349933
mTOR inhibitor	Rapamycin	mTOR	Phase II	NCT01195922
	Everolimus	mTOR	Phase II	NCT01133678
	Temsirolimus	mTOR	Phase II	NCT01172769
	CC-115	mTOR, DNA-PK	Phase I	NCT01353625
JAK inhibitor	Ruxolitinib	JAK	Phase I	NCT04822756
MET/VEGFR inhibitor	Foretinib	MET, VEGFR-2	Phase II	NCT00725764
	E7050/golvatinib	MET, VEGFR-2	Phase II	NCT01332266
MET inhibitor	LY2801653	MET	Phase I	NCT01285037
PDK inhibitor	Dichloroacetate	PDK	Phase I	NCT01386632
AMPK activator	Metformin	AMPK	Phase II	NCT01333852

Adapted from Suh Y, Amelio I, et al. Clinical update on cancer: molecular oncology of head and neck cancer. Cell Death Dis 2014;5:e1018. With permission from Nature Publishing Group

FDA approval of cetuximab followed demonstration of improved median survival in patients with refractory metastatic colorectal cancer whose tumors expressed EGFR [63, 64]. Concurrent with these studies, early-phase clinical trials were initiated to explore the combination of radiation and cetuximab in HNSCC patients [65]. High rates of complete response in these early trials together with strong preclinical data prompted the design of a phase III study to evaluate the efficacy of combining radiation and cetuximab [66]. Between 1999 and 2002, the Bonner phase III study enrolled 424 patients with locally advanced HNSCC who were randomized to curative-intent radiation or radiation plus weekly cetux-

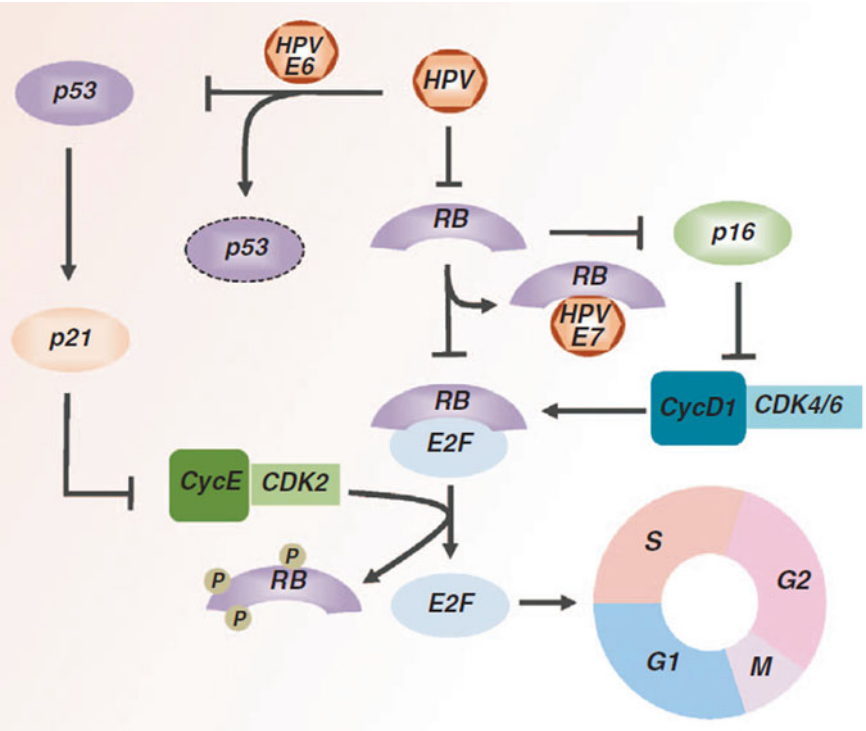

Fig. 20.2 Mechanism of action of the human papillomavirus (HPV) on cell cycle regulation. To progress from G1- to S-phase cell cycle, cells pass the G1 restriction point under the control of the retinoblastoma protein (pRb). pRb binds and represses E2F transcriptional factors. Mitogenic signaling through cyclin D1/CDK4 or cyclin D1/CDK6 phosphorylates pRb, promoting E2F release. Cyclin E/CDK2 completes pRb phosphorylation, allowing S-phase entry. HPV affects the cell cycle using viral oncoproteins, E6 and E7. The E6 protein binds p53 and promotes its degradation, whereas E7 protein binds and inactivates pRb. These viral oncoproteins determine cell cycle entry and inhibition of p53-mediated apoptosis. HPV-dependent inhibition of pRb promotes p16 accumulation. p16 represents a surrogate marker of HPV-positive HNSCC. Reprinted from Suh Y, Amelio I, et al. Clinical update on cancer: molecular oncology of head and neck cancer. Cell Death Dis 2014;5:e1018. With permission from Nature Publishing Group

imab. This trial demonstrated a near doubling of median survival and, most importantly, a durable ~9 % improvement in overall survival (Fig. 20.4) [67]. The absolute survival benefit of cetuximab in this study may reflect its interaction with radiation, a finding that critically underscores the potential value to investigate other molecular targeted agents combined with radiation for clinical benefit.

Several interesting preliminary findings emerge from subset analyses of the radiation +/− cetuximab HNSCC trial. Three radiation fractionation regimens were allowed in the trial (once daily, twice daily, and concomitant boost treatment schedules), and the benefit of cetuximab was most significant in patients receiving the concomitant boost fractionation schedule (56 % of study patients). Radiotherapy fractionation schedules were highly institution specific and may indicate a confounding variable. It remains unknown whether radiation fractionation reflects a true biologic interaction with EGFR signaling or simply a subset finding. There are several other interesting subsets that showed improved outcome favoring the cetuximab arm including patients with oropharynx cancer as opposed to larynx and hypopharynx, patients who developed grade 2–4 cetuximab rash, patients with higher Karnofsky performance status score [90–100], male gender, younger age, and US location for treatment. Although there was speculation that this favorable profile may reflect the demographic of likely HPV-associated patients, p16 staining data from archived specimens from the trial reveal that improved clinical outcome was observed in patients receiving cetuximab regardless of p16 status [68]. Such unplanned subset analyses are hypothesis generating; however, the primary finding from this trial is an absolute survival benefit for HNSCC patients receiving radiation plus cetuximab over that achieved with radiation alone. As a result of this study, cetuximab became the first FDA-approved molecular targeted therapeutic in HNSCC.

Following the demonstration of a durable overall survival benefit from the combination of cetuximab and radiation, a number of additional studies have been advanced to further define the role of cetuximab in the treatment of patients with locally advanced HNSCC. The phase II Eastern Cooperative Oncology Group (ECOG) 3303 trial explored the potential benefit of adding cetuximab to concurrent cisplatin chemoradiation in the treatment of locally advanced HNSCC and suggested an acceptable toxicity profile [69]; however, the phase III Radiation Therapy Oncology Group (RTOG) 0522 trial demonstrated no improvement in progression-free or overall survival with this combined regimen [70]. This result suggests that although the addition of cetuximab to radiation improves outcome in HNSCC, the addition of cetuximab to concurrent chemoradiation with cisplatin does not provide additional benefit. The ongoing phase III RTOG 1016 trial compares the use of radiation with either concurrent cetuximab or cisplatin in HPV-positive patients with locally advanced HNSCC. This important trial will provide new information about whether a molecular targeting agent can safely and effectively replace a cytotoxic agent in com-

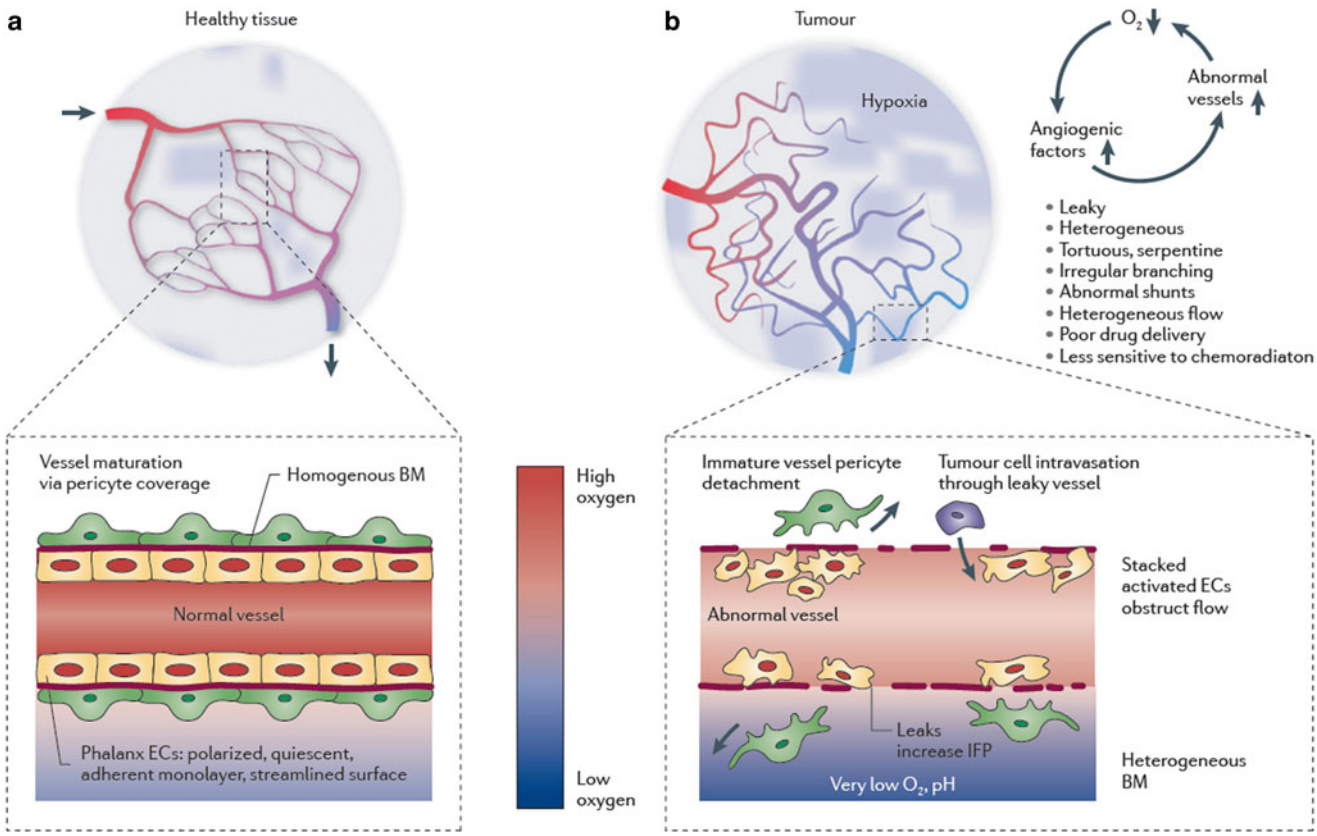

Fig. 20.3 Tumor vessels are structurally and functionally abnormal. (**a**) In healthy tissue, a regularly patterned and functioning vasculature is formed (*upper panel*), with a normal vessel wall and endothelium (*lower panel*). (**b**) In established tumors, the vasculature (*upper panel*) as well as the endothelium and vessel wall (*lower panel*) exhibit structural and functional abnormalities, leading to regions of severe hypoxia (represented by *blue shading*). *BM* basement membrane, *EC* endothelial cell, *IFP* interstitial fluid pressure. Reprinted from Carmeliet P, Jain RK. Principles and mechanisms of vessel normalization for cancer and other angiogenic diseases. Nat Rev Drug Disc 2011;10(6): 417–427. With permission from Nature Publishing Inc.

bination with radiation in the treatment of HPV-positive HNSCC. In the intermediate-risk postoperative setting, the phase III RTOG 0920 trial evaluates adjuvant radiotherapy with or without cetuximab in patients following resection of HNSCC. In the high-risk postoperative setting, the recently reported phase II RTOG 0234 study demonstrates safety and feasibility for combining cetuximab with either cisplatin or docetaxel in combination with radiation [71]. This study provides the rationale for the recently initiated phase III trial, RTOG 1216, which evaluates the efficacy of adjuvant chemoradiation with cisplatin, docetaxel, or docetaxel and cetuximab in the high-risk postoperative setting.

20.3.2 The Role of EGFR-Targeted Therapeutics in the Treatment of Recurrent or Metastatic HNSCC

The role of cetuximab in platinum-refractory metastatic/recurrent HNSCC has been investigated in three multicenter phase II trials. In one phase II trial, a total of 103 patients with platinum-refractory metastatic/recurrent HNSCC received cetuximab weekly until disease progression. The overall response rate was 13 %, with all responders manifesting partial responses [72]. This response rate was similar to that observed in other phase II trials of metastatic/recurrent HNSCC, in which cetuximab was added to the platinum-based chemotherapy regimen on which patients were failing [73, 74]. The similar response rates between cetuximab alone and cetuximab with chemotherapy in platinum-refractory HNSCC contrasted with prior observations in irinotecan-refractory metastatic colorectal cancer, in which cetuximab added to irinotecan showed improved activity compared to cetuximab alone [63].

In the first-line treatment of metastatic/recurrent HNSCC, an ECOG phase III study randomized 117 patients to cisplatin alone (100 mg/m^2 every 4 weeks) or with cetuximab (400 mg/m^2 cycle 1, followed by 250 mg/m^2 weekly) [75]. After a median follow-up of 31 months, the addition of cetuximab to cisplatin significantly improved response rate (26 vs. 10 %, $p=0.03$) but did not significantly alter progression-free survival (primary study endpoint) or overall

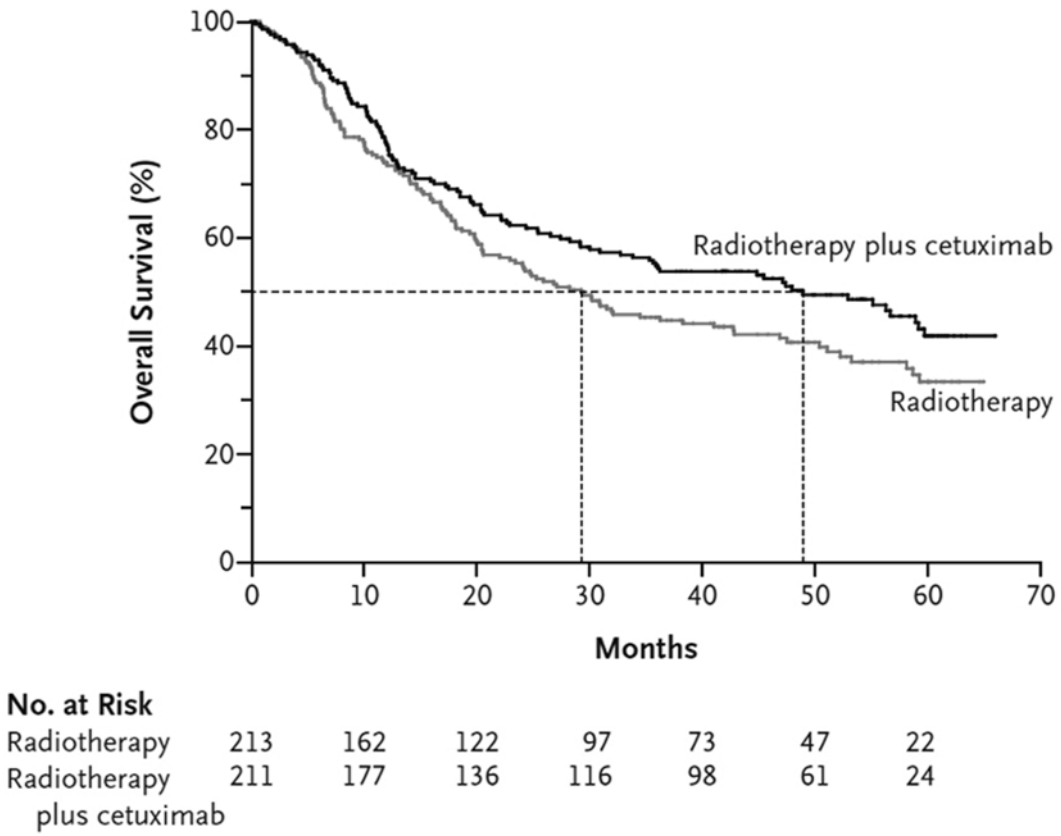

Fig. 20.4 Kaplan–Meier estimates of overall survival among all patients in the phase III international trial of radiotherapy with or without cetuximab in patients with stage III–IV HNSCC. The hazard ratio for death in the radiotherapy-plus-cetuximab group as compared with the radiotherapy-only group was 0.74 (95 % confidence interval, 0.57–0.97; $p=0.03$ by the log-rank test). The dotted lines indicate the median survival times (49.0 vs. 29.3 months). Reprinted from Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med. 2006; 354:567–578. Copyright © 2006 Massachusetts Medical Society. All rights reserved

survival. The better-than-anticipated survival of patients in the cisplatin arm rendered this study underpowered to uncover a statistically significant improvement in progression-free survival despite the strong improvement in tumor response with the addition of cetuximab. During the accrual of this trial, phase II studies involving cetuximab therapy in colon cancer [76] and other EGFR inhibitors in head and neck cancer [77] observed an intriguing correlation between the development of skin toxicity and biologic activity to EGFR inhibition. Such a correlation was also investigated in this ECOG study. Consistent with prior literature, the development of a cetuximab-related skin reaction was correlated with an improvement in overall survival (HR 0.42, $p=0.01$).

After phase II data demonstrated activity combining 5-fluorouracil with cetuximab and cisplatin [78], the EXTREME phase III trial was designed to investigate the efficacy of this regimen as first-line therapy for patients with metastatic/recurrent head and neck cancer [79]. Patients were included if their disease was considered unsuitable for local therapy and excluded if they received prior systemic chemotherapy less than 6 months or surgery or radiotherapy less than 4 weeks prior to study entry. A total of 442 patients underwent randomization at 81 centers in 17 European countries. Platinum-based chemotherapy involved a maximum of six cycles of either cisplatin (100 mg/m^2 on day 1) or carboplatin (area under the curve of 5 mg/ml on day 1) plus 5-fluorouracil (1000 mg/m^2/day for 4 days), delivered every 3 weeks. Cetuximab was administered at a dose of 400 mg/m^2 initially, followed by weekly infusions of 250 mg/m^2. In the cetuximab arm, patients with stable disease continued to receive cetuximab until disease progression or unacceptable toxicities, whichever occurred first. Patients in the chemotherapy alone group received no further active treatment. Of the 413 tumors tested by immunohistochemical analysis, 98 % had detectable EGFR, with 40 % or more EGFR-positive cells observed in 80 % of tested tumors. The addition of cetuximab to the platinum-based doublet regimen improved response rate (35.6 vs. 19.5 %, $p=0.0001$) and prolonged median progression-free survival (5.6 vs. 3.3 months, $p<0.001$) and median overall survival (10.1 vs. 7.4 months, $p=0.04$) (Fig. 20.5) without exacerbation of

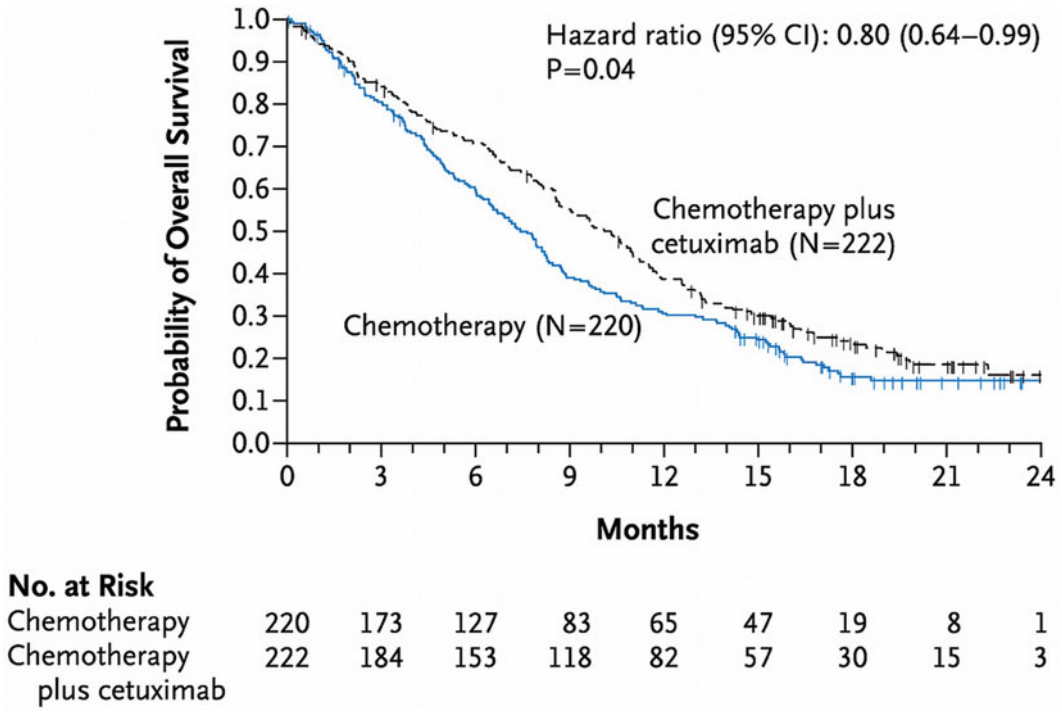

Fig. 20.5 Kaplan–Meier estimates of overall survival in the EXTREME phase III trial of platinum-based doublet chemotherapy with or without cetuximab in first-line treatment of recurrent metastatic HNSCC. The addition of cetuximab to the platinum-based doublet regimen prolonged median overall survival (10.1 vs. 7.4 months, $p=0.04$). Reprinted from Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008; 359:1116–1127. Copyright © 2008 Massachusetts Medical Society. All rights reserved

chemotherapy-related hematologic toxicities or quality of life. Preliminary analysis of EGFR gene copy number, assayed by fluorescent in situ hybridization (FISH), was not predictive of cetuximab efficacy [80]. As a result of these collective studies, cetuximab has also been FDA approved in combination with platinum/5-FU chemotherapy for first-line treatment and as a single agent after failure of platinum chemotherapies.

20.3.3 Inhibitors of Tyrosine Kinase Signaling in HNSCC

Small-molecule tyrosine kinase inhibitors (TKIs) bind to tyrosine kinase domains, such as that on the intracellular segment of EGFR, and inhibit phosphorylation, thereby blocking downstream signal transduction (Fig. 20.1). These agents have demonstrated antitumor activity across multiple preclinical models [81–89]. Of the anti-EGFR TKIs, gefitinib and erlotinib are the most advanced in their clinical development. Unlike monoclonal antibodies, these agents can be administered orally, mostly commonly on a once-daily basis. The phase III Iressa versus methotrexate or "IMEX" trial randomized 486 patients with recurrent/metastatic HNSCC to gefitinib 250 or 500 mg/day or methotrexate [90]. No benefit was observed in objective response rate (2.7 %, 7.6 %, 3.9 %, respectively), quality of life (13.4 %, 18.0 %, 6.0 %, respectively), or the primary endpoint of overall survival (median overall survival, 5.6, 6.0, 6.7 months, respectively). A phase III ECOG study was designed to randomize 330 patients with recurrent/metastatic HNSCC to docetaxel with or without gefitinib. The study was terminated early after an interim analysis demonstrated a low likelihood of reaching an overall survival benefit, the primary endpoint. Preliminary analysis of the 270 enrolled patients demonstrated prolongation of time to progression with the addition of gefitinib (median, 3.5 and 2.0 months with and without gefitinib, respectively) but no improvement in overall or progression-free survival [91].

Src kinase activation follows EGFR stimulation and can be inhibited with EGFR targeting in preclinical HNSCC models [82, 92]. Dasatinib, a small-molecule inhibitor of Src family kinases, BCR-ABL, c-KIT, and PDGFR, has been FDA approved for chronic myeloid leukemia due to its ability to inhibit BCR-ABL. Preclinical data has demonstrated the ability of dasatinib to overcome HNSCC tumor resistance to EGFR inhibition by cetuximab and to potentially resensitize resistant HNSCC cells to EGFR inhibition [93]. This has

prompted the clinical testing of dasatinib in ongoing phase II trials for recurrent/metastatic HNSCC. Preliminary results from a phase II study of dasatinib, dosed at 100 mg twice daily, in recurrent or metastatic HNSCC demonstrated notable rates of hospitalization (4 of 15 patients) and discontinuation (5 of 15 patients). Pharmacokinetic evaluation in this study is ongoing [94].

The PI3K/Akt/mTOR pathway has also been targeted in early-phase studies of patients with HNSCC. Multiple PI3K inhibitors have entered early-phase clinical testing in the setting of recurrent or metastatic HNSCC, either as single agents or together with cetuximab or conventional chemotherapeutics (NCT01204099, NCT01527877, NCT01602315, NCT01807546). The Akt inhibitor, MK2206, is under phase II investigation in recurrent or metastatic nasopharyngeal carcinoma (NCT01349933). In addition, the mTOR inhibitors, rapamycin, everolimus, temsirolimus, and CC-115, have also all been examined in phase II studies of HNSCC. Phase I results with everolimus and temsirolimus suggest safety [95–97], and a phase II study suggests activity for temsirolimus following progression on cisplatin and cetuximab [98]. Additional phase II data suggests that temsirolimus together with cetuximab may overcome cetuximab resistance in some patients with a limited 12.5 % response rate but a meaningful 7.2-month median duration of response among these responders [99]. A recent case report series suggests potential for guiding the clinical use of such agents based on the presence of PIK3A mutations or loss of PTEN expression as biomarkers for sensitivity to mTOR inhibitors [100].

The MEK inhibitor, trametinib, has shown clinical efficacy in the treatment of patients with BRAF mutant melanoma [101] and has entered phase I investigating in HNSCC (NCT01725100) following preclinical data suggesting a role for MEK in moderating the development of resistance to cetuximab in colorectal cancer [102, 103]. Similarly, IGFR may heterodimerize with EGFR and promote resistance to EGFR inhibition [104, 105]. To explore this further, randomized phase II trials are evaluating an anti-IGFR-1 monoclonal antibody, IMC-A12, alone or in combination with cetuximab in patients with recurrent/metastatic HNSCC (NCT00617734) or in the preoperative setting (NCT00957853). Amplification of the MET oncogene has also been associated with the development of resistance to EGFR-targeted therapeutics [106, 107] as well as worsened prognosis in HNSCC [29]. Early-phase studies of distinct MET inhibitors have been initiated (NCT00725764, NCT01332266, NCT01285037), and one of these, foratenib, demonstrated modest activity as a single agent in phase II study of recurrent or metastatic HNSCC with nearly half of patients showing minor tumor shrinkage but no responses greater than stable disease [108].

By blocking multiple biologic targets, multikinase inhibitors have the potential to inhibit several signaling pathways with a single oral agent. Among these, sorafenib, sunitinib, and vandetanib are furthest in their clinical testing in HNSCC. Sorafenib inhibits the activity of VEGFR, platelet-derived growth factor receptor (PDGFR), and the RAF/MEK/ERK signaling pathways, which are associated with tumor angiogenesis and tumor growth and proliferation. Sorafenib monotherapy in treatment-naïve recurrent/metastatic HNSCC was associated with median overall survival and time to progression of 8 and 4 months, respectively [109]. Sunitinib, FDA approved for renal cell carcinoma, also inhibits multiple kinases, including VEGFR, PDGFR, c-KIT, and FLT3, resulting in simultaneous inhibition of angiogenesis and tumor proliferation. Preliminary results from GORTEC 2006-01, a phase II study of sunitinib monotherapy in 37 evaluable patients with recurrent/metastatic HNSCC, demonstrated a partial response in one patient, stable disease in 18 patients, and progressive disease in 19 patients by RECIST criteria. Grade ≥3 bleeding occurred in six patients, with two of those experiencing fatal bleeding [110]. Collectively, these studies suggest modest activity for TKIs targeting various signaling pathways in HNSCC; however, with the exception of those targeting EGFR, these agents have not advanced beyond phase II clinical investigation.

20.3.4 Targeting Angiogenesis in HNSCC

Bevacizumab is a fully humanized monoclonal antibody specific to all isoforms of the VEGF-A ligand. Approved by the FDA for use in metastatic colorectal cancer, non-small cell lung cancer, and breast cancer, bevacizumab is the most mature agent in clinical testing of anti-angiogenic therapies for HNSCC. Several phase I trials have examined the feasibility of incorporating bevacizumab into concurrent chemoradiation regimens for curative HNSCC patients. Treatment of locally advanced head and neck cancer with bevacizumab and twice-daily radiation demonstrated poor efficacy in early-phase study [111], while use with conventional chemoradiation in nasopharyngeal cancer under the phase II RTOG 0615 study suggests promising safety and efficacy [112, 113]. In the ongoing phase III ECOG 1305 trial, 400 patients with recurrent or metastatic HNSCC are randomized to varied combinations of docetaxel/cisplatin or carboplatin/5-FU with or without bevacizumab with overall survival as the primary endpoint (NCT00588770).

Based on preclinical data demonstrating a favorable interaction between anti-VEGF and anti-EGFR therapies [114] and the potential for anti-VEGF therapies to impact EGFR resistance [115, 116], a phase I/II trial of combining bevacizumab with erlotinib in recurrent/metastatic HNSCC was conducted [51]. In the phase I component, ten patients were enrolled in three successive cohorts with no dose-limiting

toxicities. In the phase II component, 46 patients were enrolled on the highest dose of bevacizumab (15 mg/kg every 3 weeks). Median overall survival and progression-free survival were 7.1 and 4.1 months, respectively. The overall response rate was 14.6 %, with four patients demonstrating a complete response. In the locally advanced setting, a phase II trial of induction chemotherapy of paclitaxel, carboplatin, 5-FU, and bevacizumab for two cycles, followed by concurrent chemoradiation with paclitaxel, bevacizumab, and erlotinib, enrolled 60 patients. Preliminary analysis demonstrated an 18-month progression-free survival and overall survival of 85 % and 87 %, respectively, after a median follow-up of 16 months [117]. In the recurrent/metastatic setting, the addition of bevacizumab to pemetrexed showed a 30 % response rate and 5 % complete response and was associated with a 15 % rate of severe bleeding events [118]. In patients with locally advanced disease, the addition of bevacizumab to chemoradiation with concurrent cetuximab and pemetrexed is being investigated in a phase II trial, and preliminary data analysis suggests safety but no of improvement in outcomes with bevacizumab [119]. On the whole, these studies suggest that targeting angiogenesis may be a viable therapeutic strategy in HNSCC, though this remains to be proven in ongoing clinical investigations.

20.4 Novel Toxicities Associated with Molecular Targeted Therapeutics in HNSCC

The toxicities of cytotoxic chemotherapies have historically provided a strong impetus for the development of molecular targeted agents under the rationale that the enhanced specificity of their therapeutic mechanism may reduce or eliminate off-target toxicities. The prospect of reduced toxicity has raised particular interest in the integration of molecular targeted therapeutics for locally advanced disease where the potential for cure with multimodality approaches can be limited by treatment-related toxicities. In the RTOG 9111 study, for example, concurrent chemoradiation resulted in a 21 % absolute increase in high-grade toxicity and a near doubling of acute mucosal toxicity compared to radiation alone [120, 121]. More recently, improved conformal targeting of radiation has been demonstrated to reduce toxicity in the treatment of patients with SCCHN, yet the potential benefit of further improving the physical targeting of radiation may be approaching a plateau, in many instances limited by unavoidable anatomic constraints.

The interaction of radiation and chemotherapy was prominently described in the 1970s by George Steel, who postulated four mechanisms by which combined modality treatment could improve clinical outcomes [122]. The theme of independent toxicities was particularly critical to Steel's conceptualization since combined treatments with incompletely overlapping adverse effects allowed for improved disease control without prohibitive toxicity and thereby a greater therapeutic window than single modality dose escalation. Despite clear successes, the reality of chemoradiation in many clinical contexts is a modest improvement in clinical outcome accompanied by an increased toxicity profile. The limited specificity of most conventional chemotherapy agents commonly results in not only enhanced tumor response but also increased normal tissue toxicity when combined with radiation. The development of molecular targeted therapeutics presents a renewed opportunity to exploit the beneficial cooperative effects of combined modality treatment. The diversity of contemporary molecular targeted drugs was not fully imagined in the 1970s, and a modernization of the Steel hypothesis has been proposed to describe the exploitable interactions of radiation and molecular anticancer agents (Fig. 20.6) [123]. Previously discussed results from clinical investigation of the concurrent use of radiation and cetuximab demonstrate cooperative interaction between these agents with reduced toxicities compared to conventional cisplatin-based chemotherapy. While molecular targeted therapeutics do not typically induce bone marrow suppression, mucositis, neuropathy, or hair loss that commonly accompanies cytotoxic chemotherapy, these agents nevertheless do have their own toxicity profiles.

Cetuximab-related toxicities generally involve skin and allergic reactions (Tables 20.2 and 20.3). Encompassing multiple different manifestations, the skin rash associated with cetuximab is most frequently acneiform in appearance and generally distributed in skin areas rich in sebaceous glands, such as the face, neck, shoulders, upper trunk, and scalp (Fig. 20.7). Development of this rash is largely attributed to high levels of EGFR expression in the epidermis and hair follicles. Approximately 70 % of cetuximab-related skin reactions are grade 1 or 2 and resolve without the need for pharmacologic intervention [66]. Importantly, in head and neck cancer [67, 75] and other tumor sites [124], the development of a cetuximab-related rash appears to correlate with improved therapeutic activity. On the other hand, small-molecule inhibitors of EGFR are most commonly associated with skin rash and diarrhea. In the setting of non-small cell lung cancer, this rash is also predictive of therapeutic response, and efforts have been made in this setting to utilize skin reaction as a metric for dose escalation with favorable effect in a recent phase II study [125].

As a chimeric mouse–human IgG1 monoclonal antibody, cetuximab is also associated with allergic and occasional anaphylactic reactions. Though the product label indicates that severe hypersensitivity reactions occur in approximately 3 % of patients, higher rates have been reported in a few distinct geographic regions including the southeast USA and in Sydney, Australia, as compared to other areas [63, 126–128].

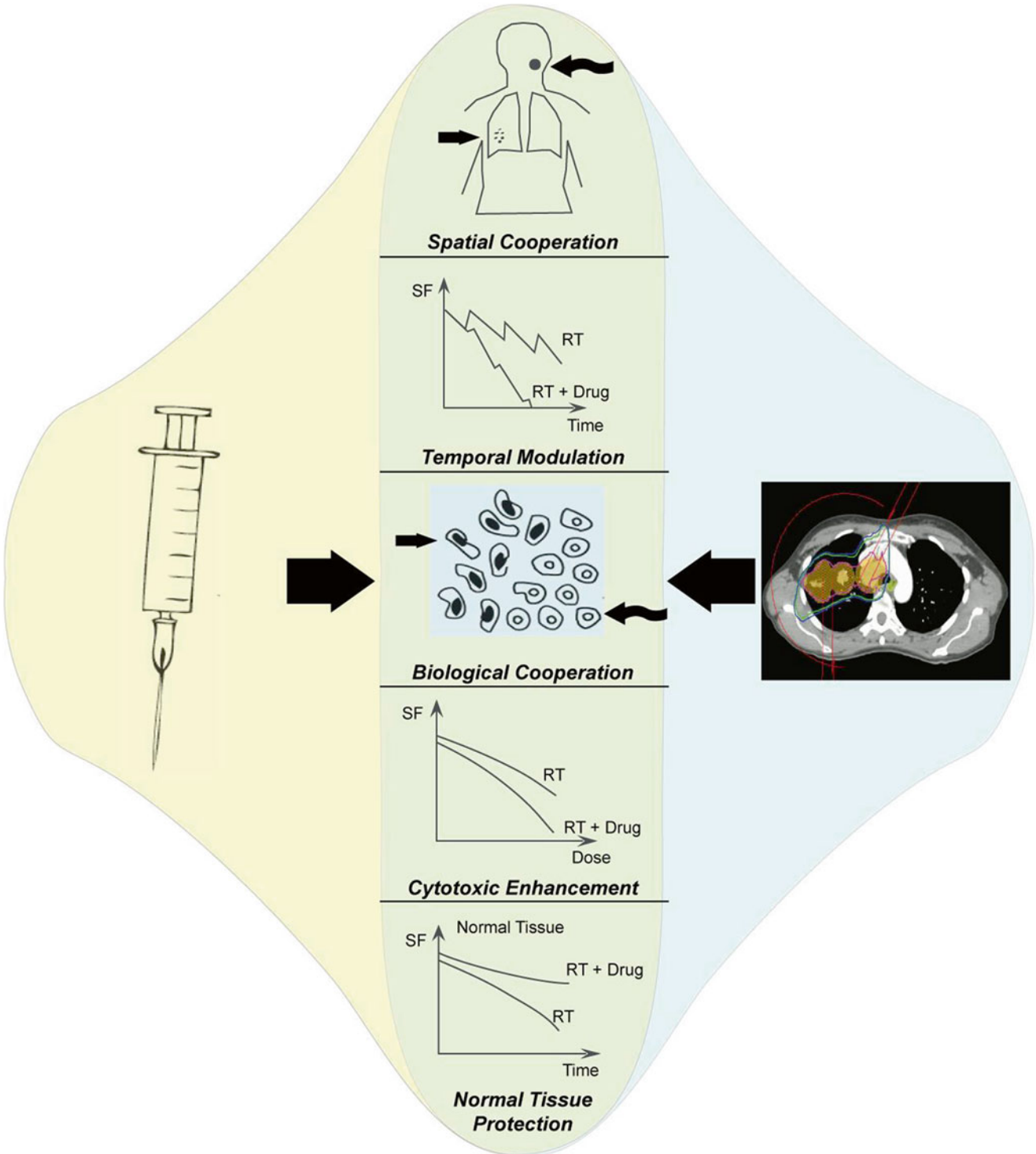

Fig. 20.6 Schematic illustration of modernized Steel hypothesis. The interaction of radiation and molecular targeted therapeutics can take several forms and be exploited to improve clinical outcomes in the treatment of malignancy. Originally described by Steel in the 1970s, the growing complexity of such interactions prompts revision of this original framework. The potentially exploitable interactions of radiation and molecularly targeted therapeutics include spatial cooperation, temporal modulation, biological cooperation, cytotoxic enhancement, and normal tissue protection. Abbreviations: *SF* surviving fraction of cells, *RT* radiation therapy. From Morris ZS and Harari PM: J Clin Oncol 32(26), 2014:2886–93. Reprinted with permission. Copyright © (2014) American Society of Clinical Oncology. All rights reserved

Table 20.2 Toxicities of cetuximab in combination with radiation

Adverse event	Radiation alone (% of patients)	Radiation + cetuximab (% of patients)	*p* value
Mucositis	52	56	0.44
Xerostomia	3	5	0.32
Dysphagia	30	26	0.45
Dermatitis	18	23	0.27
Weight loss	7	11	0.12
Asthenia	5	4	0.64
Acneiform rash	1	17	<0.001
Infusion reaction	0	3	0.01

Comparison of grade ≥ 3 toxicities in phase III international trial of radiation with or without cetuximab for patients with stage III–IV HNSCC
Based on data from Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med. 2006; 354:567–578

Table 20.3 Toxicities of cetuximab in combination with chemotherapy

Adverse event	Chemotherapy (% of patients)	Chemotherapy + cetuximab (% of patients)	*p* value
Neutropenia	23	22	0.91
Anemia	19	13	0.12
Thrombocytopenia	11	11	1.00
Leukopenia	9	9	1.00
Skin reaction	<1	9	<0.001
Sepsis	<1	4	0.02

Comparison of grade ≥ 3 toxicities in the EXTREME phase III trial of platinum-based doublet chemotherapy with or without cetuximab as first-line treatment of recurrent or metastatic HNSCC
Based on data from Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008; 359:1116–1127

Many of these reactions occur within minutes after a patient's first exposure to the drug, compatible with IgE-mediated reaction. Prior studies suggest an association between cetuximab-related reactions and the presence of IgE antibodies directed against galactose-α-1,3-galactose prior to the first infusion with cetuximab. Prior exposure to galactose-α-1,3-galactose may induce the generation of galactose-α-1,3-galactose-specific IgE antibodies in some patients, placing them at increased risk for cetuximab-related anaphylactic reactions [129].

Under normal physiological circumstances, more than 99 % of endothelial cells are quiescent [130, 131]. During early development, anti-angiogenic therapies were anticipated to carry minimal toxicity, given the selectiveness of these agents for proliferating endothelial and perivascular cells [132, 133]. Clinical experience to date, however, has changed these expectations, with a characteristic toxicity profile now better understood. Underlying these toxicities are targeted signaling pathways that are critical not just for angiogenesis but also for other physiological processes. The possibility for "off-target" effects exerted by angiogenesis inhibitors on other signaling pathways complicates this picture. The most typical side effects of anti-angiogenic agents involve hypertension, hemorrhagic complications, thromboembolic events, wound healing, viscera perforation, hypothyroidism, immunosuppression, proteinuria, edema, and hand-foot syndrome [134, 135].

It is important to also consider that molecular targeted therapeutics, while associated with distinct toxicities, may also play a role in minimizing toxicities associated with conventional chemotherapy and radiation. Notable in this regard in HNSCC is palifermin, a truncated recombinant form of human keratinocyte growth factor. This agent, which stimulates proliferation and differentiation of mucosal epithelial cells, has been investigated and found to be effective in a phase III study of patients undergoing chemotherapy prior to autologous hematopoietic stem cell transplant [136]. A subsequent phase III investigation was initiated in patients receiving concurrent chemoradiation for locally advanced HNSCC but was closed due to poor accrual.

20.5 Next-Generation Molecular Targeted Agents in HNSCC

20.5.1 Second- and Third-Generation Anti-EGFR Therapeutics

While cetuximab is a chimeric mouse–human antibody, a fully humanized EGFR antibody, panitumumab, has been developed and approved for treatment of colorectal cancer.

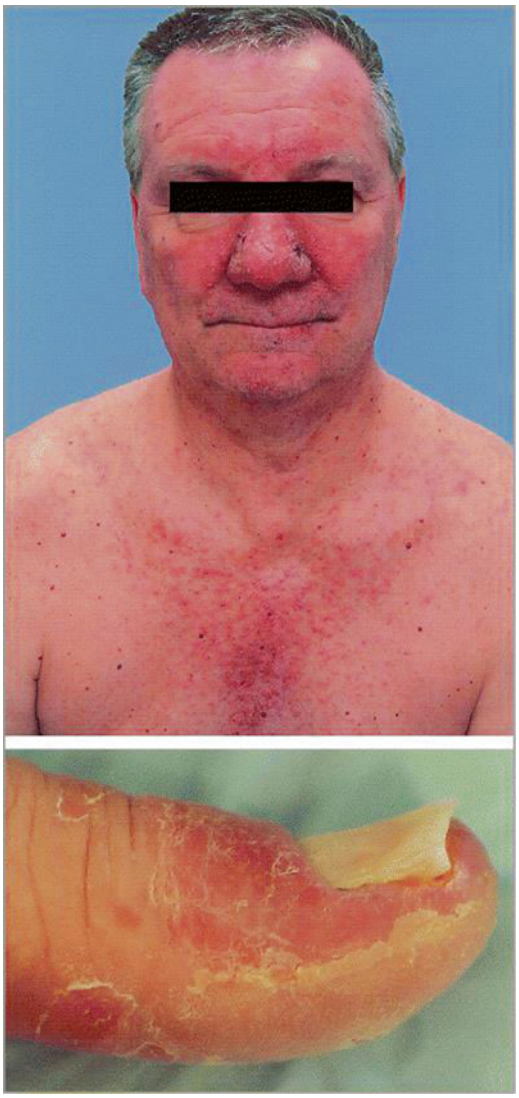

Fig. 20.7 Characteristic dermatologic side effects of EGFR inhibition. Acneiform rash occurring on the scalp, face, and neck of an individual receiving the small-molecule epidermal growth factor receptor (EGFR) inhibitor erlotinib (*upper panel*). Tender paronychia with onycholysis in a patient receiving the monoclonal anti-EGFR antibody cetuximab (*lower panel*). Reprinted from Lacouture ME and Lai SE. The PRIDE (papulopustules and/or paronychia, regulatory abnormalities of hair growth, itching, and dryness due to epidermal growth factor receptor inhibitors) syndrome. British Journal of Dermatology. 2006; 155(4): 852–854. With permission from John Wiley and Sons

The phase III SPECTRUM study of panitumumab in combination with chemotherapy in recurrent or metastatic HNSCC did not show improvement in survival, although unplanned subgroup analysis suggested improved survival in p16-negative patients treated with panitumumab compared to controls [137]. One possible reason for reduced efficacy of panitumumab compared to cetuximab may be the reduced capacity of this IgG2 antibody to either fix complement or elicit antibody-dependent cell-mediated cytotoxicity (ADCC) relative to the IgG1 isotype of cetuximab [138]. The clinical relevance of ADCC in antitumor antibody treatments is supported by studies correlating Fcγ receptor (FcγR) polymorphisms with clinical outcomes following treatment with antitumor antibodies such as rituximab, trastuzumab, and cetuximab [139–147]. In vitro studies on HNSCC cell lines have demonstrated that FcγR polymorphisms correlate with sensitivity to cetuximab [148, 149] and also demonstrate that response to cetuximab can be modulated by concurrent treatment with ADCC stimulatory cytokines [150, 151]. To date, however, no clinical study has determined whether a correlation exists between FcγR polymorphisms and clinical outcomes in HNSCC patients treated with an anti-EGFR antibody.

In an effort to optimize ADCC and elicit EGFR inhibition with minimized toxicity, second-generation anti-EGFR antibodies have been developed including the humanized IgG1 antibody, nimotuzumab, and the fully human IgG1 antibody, zalutumumab. Early-phase studies of nimotuzumab conducted in Cuba suggest safety for the use of this agent together with radiation in locally advanced HNSCC [152]. A subsequent randomized phase II study in India suggests improved response rate and progression-free survival with the addition of nimotuzumab to radiation therapy in patients with locally advanced HNSCC [153]. In contrast to the results of RTOG 0522, this phase II study also suggested improved progression-free and overall survival with the addition of an EGFR antibody (nimotuzumab) to cisplatin chemoradiation; however, phase III data is not available to support this possibility. Zalutumumab, on the other hand, has been investigated in a phase III study of HNSCC patients with platinum-refractory recurrent or metastatic disease, and results indicate efficacy for this agent with improved progression-free but not overall survival [154]. A phase III Danish investigation of cisplatin-based chemoradiation with or without zalutumumab in locally advanced HNSCC showed no benefit with respect to survival or local control [155], consistent with the findings of RTOG 0522.

If efficacy is proven for these second-generation antibodies, they may offer the potential for reduced toxicity compared to cetuximab. In contrast to cetuximab, panitumumab and zalutumumab are fully human and therefore carry less theoretical risk for allergic reaction. On the other hand, nimotuzumab has a reduced binding affinity for EGFR that has been suggested by preclinical data to result in persistent binding to tumor cells with high levels of EGFR expression and reduced binding to follicular and cutaneous cells with more moderate EGFR expression [156]. Clinical data support this possibility and suggest a reduction in cutaneous toxicities without a reduction in therapeutic efficacy for nimotuzumab in comparison to cetuximab [157].

Third-generation approaches to antibody-based targeting of EGFR have now begun to enter clinical trials. Among these is the bi-specific MEHD7945A antibody, which targets both EGFR and HER3 and has been demonstrated to give rise to ADCC in vivo using a murine animal model [158]. Interestingly, in preclinical studies, both MEHD7945A and a mutant version not recognized by FcγR similarly inhibit tumor growth initially, but wild-type MEHD7945A results in a more prolonged tumor suppression following a single treatment. A similar pattern (comparable initial response but more sustained tumor suppression) is observed when the effect of MEHD7945A is compared to that of monospecific EGFR and HER3 antibodies in treatment of HNSCC xenograft tumors [158]—perhaps suggesting a more efficient induction of ADCC with the bi-specific MEHD7945A. A recently reported phase II investigation of MEHD7945A in patients with metastatic HNSCC indicates activity comparable to cetuximab with no evidence of improvement in response or disease-free survival but with increased rates of grade 1–2 gastrointestinal toxicity including diarrhea and mucosal inflammation [159]. Various other approaches to the modification of antibody-based targeted therapeutics have begun to emerge in preclinical and early-phase clinical investigation including the use of antibody cocktails that simultaneously target multiple epitopes, single Fab-armed antibodies that modulate the potential effect of antibodies in facilitating receptor cross-linking, and the development of immunocytokines—antibodies that are modified, often by genetic fusion with a cytokine, for the purpose of augmenting antitumor immune response [138].

Second-generation small-molecule therapeutics targeting EGFR have also been developed including lapatinib, which has dual specificity for EGFR and HER2 and is approved for use in breast cancer. Although, small-molecule inhibitors of EGFR have generally shown limited efficacy in the treatment of HNSCC, lapatinib has shown activity in p16-negative tumors in combination with chemoradiation [160]. Lapatinib is currently being evaluated by phase III investigation in the recurrent/metastatic setting in combination with capecitabine chemotherapy (NCT01044433) and in the high-risk adjuvant setting by concurrent addition of lapatinib to cisplatin chemoradiation followed by 1 year of adjuvant lapatinib (NCT00424255). In addition, a phase II study in patients with locally advanced HPV-negative HNSCC is examining concurrent use of lapatinib with cisplatin chemoradiation followed by 3 months of lapatinib (NCT01711658). Afatinib, a small-molecule inhibitor of EGFR, HER2, and HER4, exhibits a distinctive pattern of irreversible binding and inhibition. This agent has entered clinical investigation in the recurrent/metastatic, neoadjuvant, and adjuvant settings including a phase II study, ECOG 1311, which explores the use of afatinib after concurrent chemoradiation in individuals with high risk of recurrence (NCT01856478, NCT01538381, and NCT01345669).

20.6 Next-Generation Molecular Targets in HNSCC

20.6.1 Targeting Regulators of Transcription and Translation in HNSCC

The NOTCH signaling pathway is a complex network involved in cellular differentiation, survival, and proliferation. Four transmembrane receptors, NOTCH 1–4, engage and bind two ligand families (Delta-like 1, 3, and 4 and Jagged 1 and 2). Upon ligand binding, NOTCH is cleaved by ADAM metalloprotease and γ-secretase. The cleaved intracellular fragment of NOTCH translocates into the nucleus where it interacts with the nuclear DNA-binding factors and recruits coactivators to turn on transcription factors of target genes including a set of basic helix-loop-helix factors of the Hes and Hey families. Tumor genome studies indicate that NOTCH family receptors may be mutated in 15 % of HNSCC tumor samples [9, 10], while integrated sequencing methods suggest the NOTCH pathway may be disrupted in 66 % of HNSCC [161, 162]. These studies suggest that, in contrast to T-cell acute lymphoblastic leukemia where NOTCH signaling may be oncogenic [163], in the context of HNSCC, this pathway may be tumor suppressive. Consistent with this observation, NOTCH1 signaling may suppress the expression of HPV E6 and E7 in HPV-positive malignancies [164]. The role of NOTCH1 in HNSCC continues to be actively investigated. Existing molecular agents targeting γ-secretase offer an opportunity to negatively regulate this pathway, while recovering a loss of NOTCH signaling activity may be more difficult to redress.

A number of molecularly targeted agents have been developed that may globally modulate gene expression in tumor cells. Histone deacetylase (HDAC) family proteins regulate DNA transcription through specific histone modifications, and HDAC mutations have been observed in HNSCC that correlate with both advanced tumor stage and poor survival [165, 166]. HDAC inhibitors have entered clinical development and these agents may alter gene transcription mediated by NOTCH and other transcription activators. However, phase II study of the HDAC inhibitor romidepsin in metastatic HNSCC did not demonstrate any objective responses among a cohort of heavily pretreated patients [167].

The process of RNA translation also offers unique opportunities for molecular targeting. Micro-RNAs (miRNAs) are endogenous, small, noncoding RNA sequences of 18–25 nucleotides that modulate gene expression at both the transcription and translation levels with each miRNA influencing expression of multiple genes and single mRNAs being targeted by multiple miRNAs. In HNSCC expression, certain miRNAs (miR-21, miR-106b, miR-181, and miR-211) are associated with tumor invasion, lymph node involvement, and/or metastasis [168–174], while others (let-7, miR-

133a/b, and miR-200a) suppress tumor cell migration, proliferation, and metabolism [170, 175–178]. Such roles suggest potential for miRNAs to serve as a novel class of molecular targets in HNSCC.

Molecular agents targeting the proteasome of tumor cells may modulate ubiquitin-mediated protein turnover and cellular stress response mechanisms. Bortezomib, a small-molecule inhibitor of the 26S proteasome subunit, has been approved for use in refractory multiple myeloma. Early-phase studies have examined the use of bortezomib with radiation alone (NCT00011778) or with radiation, cetuximab, and cisplatin in locally advanced HNSCC (NCT01445405, NCT00629226). In addition, bortezomib has been evaluated together with irinotecan (NCT00103259) and also with docetaxel (NCT00425750) in metastatic HNSCC. Results reported from these studies thus far suggest safety without clear indication of improved efficacy [179].

20.6.2 Targeting p53 and Cell Cycle Regulation in HNSCC

Redressing p53 mutation has been a subject of intense research for decades but so far has yielded modest clinical success. A novel targeted oncolytic adenovirus, ONYX-015, has been engineered to selectively replicate in and lyse p53 mutant cells. Phase II clinical investigation of intra-tumor injection of this agent along with systemic cisplatin/5-FU in recurrent or metastatic HNSCC has suggested efficacy [180]. A closely related oncolytic adenovirus, H101, was developed and subsequently approved for HNSCC in China following phase III demonstration of enhanced tumor response rate versus a conventional chemotherapeutic regimen [181]. Subsequent studies have challenged the selectivity of these viruses for p53 mutant cells and stalled their development in the USA and Europe [182]. A distinct virus, INGN 201, utilizing a replication-defective adenovirus serotype 5 vector with a *p53* combinatorial DNA insertion has been developed for administration directly into a tumor with the aim of delivering wild-type *p53* genes to cancer cells. A phase III trial of INGN 201 compared to methotrexate in HNSCC refractory to surgery, radiotherapy, and platinum- or taxane-based chemotherapy showed a better response to adenoviral p53 gene therapy in patients with wild-type p53 or low levels of mutant p53, whereas those with higher levels of mutant p53 responded better to methotrexate [183]. A phase II feasibility study of surgery with perioperative INGN201 gene therapy followed by chemoradiation for locally advanced resectable HNSCC has also completed accrual [184]. Additional small-molecule therapeutics aimed at reactivating p53 and others that antagonize the ubiquitin ligase, MDM-2, to prevent p53 degradation have entered preclinical and early-phase clinical studies [185]. In further targeting the dysregulation of cell cycle that arises from mutation of p53 and Rb, a recent phase II trial in India has examined the use of a cyclin-dependent kinase inhibitor, P276-00, in HNSCC with results not yet reported (NCT0089954).

20.6.3 Targeting Cellular Metabolism in HNSCC

Cellular metabolism may present a novel opportunity for molecular targeting in HNSCC. The Warburg effect was first described in the 1920s and documents the enhanced role for glycolytic metabolism in tumor cells even in the presence of adequate oxygen. Preclinical research suggests that such aberrant metabolism may promote biosynthetic pathways and provide for the metabolic requirements of a prolonged proliferative state. Critical to the regulation of this metabolic state are the PI3K/Akt/mTOR and AMP-activated protein kinase (AMPK) signaling pathways. Molecular approaches to targeting the PI3K/Akt/mTOR pathway have been previously discussed in this chapter. Interestingly, the diabetes medication, metformin, may offer selective targeting of AMPK, and this agent has now entered phase I/II clinical investigation in combination with paclitaxel in metastatic/recurrent HNSCC (NCT01333852). Pyruvate dehydrogenase kinase (PDK) has also been targeted for inhibition with dichloroacetate in a phase I study of recurrent HNSCC (NCT01163487). This enzyme phosphorylates and inhibits pyruvate dehydrogenate and may thereby modulate the balance between oxidative phosphorylation and glycolysis in tumor cell metabolism.

20.6.4 Molecular Targeted Immunotherapies in HNSCC

Preclinical studies demonstrate a critical role for the immune system in regulating tumor development following carcinogen exposure [186, 187] and highlight the selective effects of immunoediting, which result in propagation of poorly immunogenic tumor phenotypes in immune-competent hosts [188]. Even poorly immunogenic tumors are frequently associated with tumor-infiltrating lymphocytes capable of eliciting antitumor cell responses in vitro [189]. This suggests a therapeutic opportunity for treatments that modulate mechanisms of tumor tolerance among immune cells, and T-cell checkpoint receptors are particularly promising molecular targets in this regard. These receptors function as co-regulatory molecules and can inhibit T-cell activation following antigen recognition by the T-cell receptor (TCR). These mechanisms, normally involved in maintenance of self-tolerance, can be co-opted by tumor cells to avoid immune detection.

CTLA-4 is a T-cell checkpoint receptor that is constitutively expressed at low levels on the surface of naïve effector and regulatory T cells. Full T-cell activation requires not only TCR binding but also engagement of co-stimulatory molecules such as CD28 with their ligands B7-1/2. In the context of strong or prolonged TCR signaling, CTLA-4 expression is upregulated, and CTLA-4 competes with CD28 for binding of B7-1/2 resulting in inhibition of further T-cell activation [190]. Programmed cell death-1 (PD-1) is another example of a checkpoint receptor that is expressed on activated T cells as well as B cells and monocytes. Its ligands, PD-L1 and PD-L2, are expressed on antigen-presenting cells, tumor cells, placenta, and cells in an inflammatory microenvironment. Binding of PD-1 by its ligands results in inhibition of T-cell activation. Importantly, tumor cell expression of PD-L1 is correlated with diminished tumor-infiltrating lymphocytes and poor clinical outcome for multiple cancer types [191]. In the context of recurrent or metastatic HNSCC, multiple phase III studies are now exploring the utility of T cell checkpoint blockade using the anti-PD-1 antibodies pembrolizumab (NCT02358031, NCT02252042) or nivolumab (NCT02105636), or a combination of the anti-PD-L1 antibody durvalumab and the anti-CTLA-4 antibody tremelimumab (NCT02551159, NCT02369874). Importantly, the phase III CheckMate141 study of nivolumab versus investigator's choice of therapy (NCT02105636) was recently stopped early after it was determined that the primary endpoint of improvement in overall survival had been met. The study enrolled 361 patients with recurrent or metastatic HNSCC of the oral cavity, pharynx, or larynx following progression on platinum-based therapies. Intriguingly, multiple preclinical and clinical studies suggest that radiation may serve as an immunologic adjuvant, further enhancing the susceptibility of a tumor to immunologic response and offering an opportunity for synergy with immunotherapeutics in HNSCC and other cancers [192].

20.7 Conclusion

Molecular targeted therapies for head and neck cancer offer promising opportunities to improve upon clinical outcomes achieved with conventional treatments. Most notable in this regard have been the phase III clinical data demonstrating measurable survival benefits with the use of cetuximab in locally advanced and recurrent/metastatic HNSCC. Multiple other molecular targeting agents have shown activity against HNSCC in clinical testing, yet only cetuximab has gained an established role in standard clinical practice. The toxicities of molecular targeted agents are unique to their signaling cascades and do not appear to substantially overlap the toxicities of conventional treatments.

Although radiation is a critical treatment modality for a substantial proportion of cancer patients worldwide, there is a relative dearth of clinical trials that formally explore combinations of radiation and molecular targeted therapeutics (Fig. 20.8). This may reflect the predominant approach to

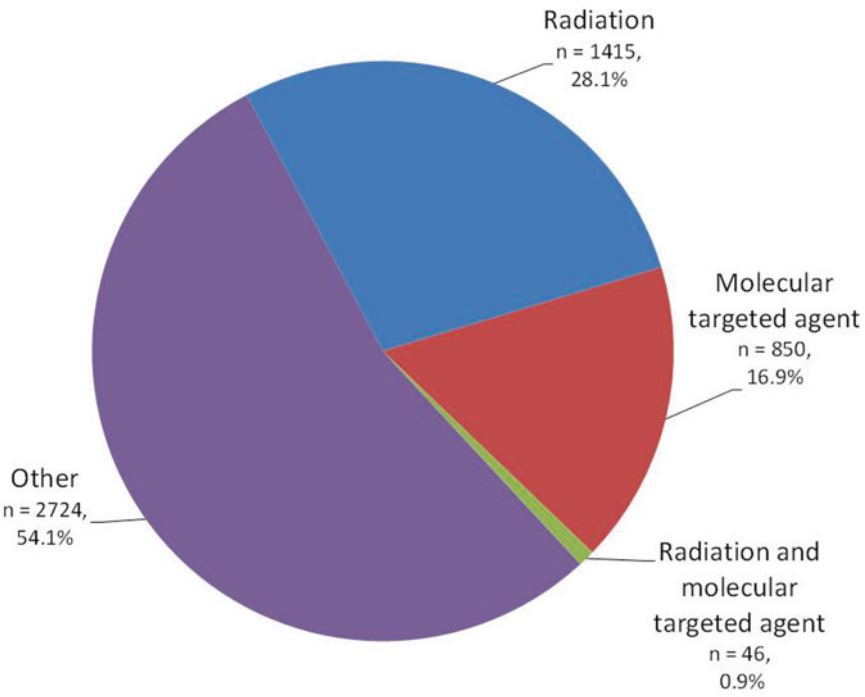

Fig. 20.8 Distribution of current phase III clinical trials in oncology. A search of www.clinicaltrials.gov for phase III clinical trials returned 5035 trials for condition = "cancer." When intervention = "radiation" was added to this search, 1461 studies were identified. When the 5035 phase III cancer trials were sorted by intervention, 896 studies involved a molecular targeted agent as defined in this review. Of these, only 46 studies examined a combination of a molecular targeted agent and radiation. Nine studies involving total body irradiation were excluded from the latter category. From Morris ZS and Harari PM: J Clin Oncol 32(26), 2014:2886–93. Reprinted with permission. Copyright © (2014) American Society of Clinical Oncology. All rights reserved

contemporary cancer drug development that emphasizes demonstration of efficacy in the metastatic setting prior to evaluation with standard treatments in the curative setting. Such a paradigm unintentionally deflects the investigation of molecular agents that may hold potential for clinical benefit in established treatment regimens with radiation. Consequently, this approach may fail to identify agents that ultimately provide their strongest clinical impact by exploiting basic principles of radiobiology (repair, repopulation, redistribution, and reoxygenation) and may overlook agents that work most effectively in combination with radiation. Earlier stage evaluation of new molecular agents in combination with radiation may therefore prove invaluable.

The future impact of targeted therapies in HNSCC will rely on systematic preclinical and clinical evaluation of promising new agents and advances in our ability to predict those patients most likely to benefit. It will be critical to stratify HNSCC patients based on HPV status, provide clear definition of clinical endpoints, and incorporate evaluation of toxicity profiles and cost-effectiveness. Strong partnership between academic and industry investigators will be valuable, as will the engagement of federal funding that has historically lagged in radiation oncology [193]. Ultimately, the successful advancement of molecular targeting agents in HNSCC will require demonstration of improvement in cancer cure and palliation. With our increased understanding of molecular and genetic footprints for HPV-positive and HPV-negative HNSCC, there are promising opportunities for significant advances using a combination of radiation with selected molecular targeted therapeutics.

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Laser Endoscopic Treatment

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Abstract

After a review of CO_2 laser technique in the treatment of head and neck cancers, the results of the literature are presented for each localization. For early glottic cancers T1–T2, the specific survival rate at 5 years is around 100 %, with a local recurrence rate of 10 % and an incidence of total laryngectomy limited to 2–3 %, lower than after radiotherapy. For supraglottic cancers, the expertise is important; techniques, indications, and results differ depending on the authors. One observes 10 % of local recurrence for T1–T2 and 20 % for T3–T4, with a specific survival rate of 80 % at 5 years. This disparity is stronger for pharyngeal cancers, with a local recurrence rate from 5 to 25 % for the oropharynx and from 10 to 30 % for the hypopharynx. For precancerous lesions, laser gives a local recurrence rate around 10 %, which can be salvaged without total laryngectomy—contrary to postradiation salvage—with a specific survival rate near 100 %. Laser debulking of obstructing tumors can be performed in order to avoid tracheotomy. Postradiation recurrence can be salvaged by laser only for a few parts, with an important rate of new recurrences and total laryngectomies.

Keywords

CO_2 laser • Endoscopic surgery • Transoral laser microsurgery (TLM) • Glottic carcinoma • Supraglottic carcinoma • Hypopharyngeal carcinoma • Oropharyngeal carcinoma • Cancer • Laryngeal carcinoma in situ • Glottic dysplasia • Airway obstruction • Recurrent laryngeal cancer

21.1 Introduction

Endoscopic removal of early laryngeal cancers was reported as early as 1915 [1]. The development of direct suspension laryngoscopy and subsequent use of microscopic examination was pioneered by Chevalier Jackson in the 1930s and Oskar Kleinsasser in the 1960s. The electric bistoury was introduced to surgery by Cushing in 1926, following the work of Bovie [2]. Einstein developed the theoretical design of the laser in 1917. The first pulsed ruby laser was described by Maiman in 1960 and then used a few months later to treat a retinal tumor [3]. The carbon dioxide laser (CO_2 laser), coupled with use of the microscope in direct suspension laryngoscopy, was first used by Jako and Strong in the early 1970s, and subsequently by other members of the Boston University group [4]. Used principally for benign lesions, in 1975 Strong reported three cases of laryngeal cancer excision using the CO_2 laser [5]. In the early 1980s, Wolfgang Steiner was responsible for the development and growth of CO_2 laser in the treatment of head and neck cancers. Table 21.1 presents an historical synopsis.

The term "laser" is an acronym for "light amplification by stimulated emission of radiation." It consists of a spatially and temporally coherent beam of light produced by amplifying

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Table 21.1 Historical synopsis

1915	Lynch [1]	Endoscopic resection of 9 early glottic cancers
1917	Einstein	Theoretical design of laser
1960	Maiman [3]	Ruby laser for retinal tumor
1970	Jako–Strong [4]	CO_2 laser for benign laryngeal lesions
1975	Jako–Strong [5]	CO_2 laser for 3 laryngeal cancers
1980	Steiner [6]	CO_2 laser for head and neck cancers
1992	Eckel [7]	67 T1–T2 glottic cancers
1993	Steiner [8]	130 T1–T2a glottic cancers
1998	Iro [9]	141 supraglottic cancers
2001	Steiner [10]	129 pyriform sinus cancers
2003	Steiner [11]	48 tongue base cancers
2005	Motta [12]	719 T1–T3 glottic cancers
2008	Martin [13]	172 hypopharyngeal cancers
2011	Haughey [14]	204 oropharyngeal cancers
2013	Canis,…, Steiner [15]	277 supraglottic cancers
2014	Canis,…, Steiner [16]	122 T3 glottic cancers

a stimulated emission beam, enabling a large amount of energy to be concentrated upon a small surface. Following production of the first ruby laser in 1960, various types of medical lasers were developed, differing in terms of their physical characteristics. The argon laser has coagulative properties, the Nd:YAG laser has absorptive properties, and the CO_2 laser has cutting properties. Because the CO_2 laser beam is invisible, a red-colored coaxial helium-neon beam is used to enable localization. A micromanipulator mounted on a mirror allows maneuvering of the beam. The length of a CO_2 laser wave results in it having a high capacity to absorb water, and thus tissue, resulting in heating and destruction of tissue. The first CO_2 lasers had a spot of approximately one millimeter in size. As a result of subsequent progress, the size of the spot has been reduced to around 200 µm, for example, with the Acuspot. In contrast to the electric bistoury, which is active when in contact with tissue, the laser is used at a distance, allowing it to be used on the larynx and hypopharynx. The CO_2 laser is the principal laser used in the treatment of head and neck cancers, and this chapter will be devoted to discussions of this tool.

21.2 Laser Techniques

Precautions are required when using a CO_2 laser, as it is capable of being reflected and the resulting heat is liable to ignite. All operating theater staff must wear eye protection. The patient's eyes are closed and a cloth covers the patient's face around the laryngoscope. The endotracheal ventilation tube should be a Mallinckrodt, Xomed, or other specific laser tube designed such that it will not catch fire when touched by the laser beam. A moist cotton pad must protect the inflated cuff. Another ventilation solution consists of using a supra- or subglottic ventilation jet, which has the inconvenience of moving the laryngeal structures with each insufflation. Whether a ventilation tube or ventilation jet is used, it is recommended that the oxygen level be limited to 30 % of the ventilation gas.

Various methods and techniques facilitate the use of the laser. As with diagnosis using a direct microlaryngoscopy, the use of a head clamp, a remote-controlled operating table, a height-adjustable chair, direct and lateral viewing optics via the laryngoscope, and palpation by microforceps are required. A direct view of the anterior part of the larynx is always more difficult to attain. A tooth guard, possibly made of a thermoplastic material for making Kerr type dental molds, is useful. Manual pressure by a nurse on the patient's neck is guided by a screen, allowing direction of the pressure to improve visibility. The loose movement of the epiglottis within the larynx can distort the anterior view. This can be remedied by passing a stitch through the epiglottis, holding it to the side of the laryngoscope while it is reinserted. A large suction tube is fixed to the laryngoscope to extract smoke produced by tissue vaporization. The laser beam is always used at the highest magnification possible while cutting, in order to destroy the least amount of tissue possible and allow for greater reliability of histological margins. The Acuspot allows the width of the section line to be reduced to, at best, 200 µm. The laser beam coagulates small vessels, while bleeding from larger vessels is stemmed using a monopolar suction coagulator.

The resected specimen is always spread out and oriented upon a support such as a corkboard, in such a way as to enable precise histological analysis of the margins. So, adequate laser reresections are feasible in case of involvement. After removal of the specimen, tissue remaining at the level of the vocal cord is adjusted to improve voice result. In the event that a large amount of cartilage is exposed, it is standard procedure to prescribe antibiotic therapy to prevent chondritis. Postintervention scarring often lasts 2 to 3 months or more; granulomas may form and can be mistaken for an

early recurrence. Some surgeons recommend a second look under general anaesthesia at 2 or 3 months postoperatively, and some even perform a third look [17].

21.3 Glottic Cancers

Before the creation of CO_2 lasers, early laryngeal cancers were treated endoscopically. In 1915, Lynch reported nine cases of endoscopic resection [1]. In 1973, Lillie and De Santo obtained excellent results in a series of 57 patients [18]. Nevertheless, it wasn't until the 1972 description by Strong and Jako of the use of the CO_2 laser, coupled with direct suspension microlaryngoscopy, that endoscopic resection really gained popularity [4]. The first publications reported between 1985 and 1990 included a limited number of patients and had only a short oncologic follow-up. Following Steiner, German teams were the first to publish a series of one hundred patients with survival rate calculation, between 1990 and 1995 (Eckel and Thumfart [7], Steiner [8], Rudert and Werner [19]). Subsequently, other teams published their oncologic and functional results, although points of controversy still remained (Table 21.1).

In the English-speaking world, radiation coupled with salvage surgery is a common approach in the treatment of early glottic cancers. Radiation is accompanied by a high rate of recurrence, approximately 10 % for T1 and 30 % for T2 tumors, according to various authors and publications [20]. Partial open surgery results in a recurrence rate of around 5 % [21, 22].

The use of laser technique and its indications are controversial. Minimalists limit its use to small cancers of the medial third of the vocal cord, while maximalists treat even advanced T4 laryngeal cancers, involving endoscopic resection of cartilaginous segments. Depending upon the indications, the technique and the results are highly variable. For small tumors, the majority of surgeons advise *en bloc* resection. For larger tumors, some surgeons apply the same principle while others, following Steiner, recommend piecemeal resectioning, using Moh's technique [6]. The European Laryngological Society's classification system is widely used in Europe [23]. Cordectomy is classified as superficial, transmuscular, or radical, possibly extending to the anterior commissure, the arytenoid, the ventricular fold, or subglottis [24]. Anterior commissure extension is the subject of much debate, due to the possible risk of tumoral extension along the Broyle ligament. For some surgeons, even a superficial extension of the anterior commissure is a contraindication against endoscopy. For many others, it is not a contraindication as long as the extension is superficial. And for yet other surgeons, even significant extension does not constitute a contraindication [25, 26]. A superficial supraglottic or subglottic extension does not constitute a real contraindication for many authors. Decreased mobility (T2b) requires care and necessitates a radical cordectomy with removal of the entire muscular thickness [27]. Extension of the contralateral vocal cord leads to a synechia and strongly alters the vocal result, rendering this procedure controversial. Finally, only a few authors advise piecemeal cartilaginous excision for T3 or T4 lesions [8, 28]. Most authors attach crucial significance to the histological examination of superficial and deep margins, but this is not always the case. Some recommend a second examination a month or two after initial surgery to confirm that there has been no recurrence [17]. We do not see the need for this if the histological specimen removed *en bloc* has been analyzed with care and shows no tumor at the surgical margins. Our only indication for revision under general anaesthesia is that of a granuloma that lasts more than 4 or 5 months or which alters vocal quality.

Large series with sufficient oncologic follow-up are now available. Table 21.2 summarizes the most significant publications. Several series include 200–300 patients, with Motta publishing results for 400 cases. For T1–T2 and excluding T3 lesions, the adjusted survival rate at 5 years is close to 100 %. Patients do not die as a result of their glottic tumor. Motta alone reported less favorable results. The local recurrence rate is around 10 %, varying from 0 to 20 %. Treatment of these recurrences is effective. A total laryngectomy rate of approximately 2 to 3 % is reported, ranging from 0 to 10 %, and higher in the case of T2 and T3 tumors. The overall survival rate at 5 years is around 80 %. Numerous studies demonstrate that failures are more frequent in the event of involvement of the anterior commissure, in the presence of decreased mobility, and even more so in the event of glottic fixation or when cartilage is affected [12, 26, 27]. Usually, laser treatment is not followed by radiation. Some surgeons recommend postoperative radiotherapy when compounding factors exist, such as involvement of the anterior commissure or decreased mobility [27].

In light of this literature, it has become clear that laser resection gives better results than radiation or partial open surgery for the majority of T1 and T2 glottic tumors. This superiority should be qualified in light of the significant expertise required to carry out laser resection. Less favorable results are reported in certain limited series [40]. Moreover, series with the worst outcomes are not even published. The problem of anterior commissure involvement and decreased mobility remains, with both laser resection and radiation therapy producing less favorable results. As far as we are concerned, laser resection does not rule out the possibility of partial open surgery in T1 and T2 glottic cancers found to have significant anterior commissure involvement or found to be immovable with microinstruments.

Only few authors advise endoscopic treatment of T3 glottic cancers (see Table 21.2). The local recurrence rate is around 30 %, with total laryngectomy rate of 20 %.

Table 21.2 Literature concerning laser of early and advanced glottic carcinomas

Authors	Year	Number of patients	Classification	Local recurrence (%)	Salvage total laryngectomy (%)	5-year specific survival (%)	5-year overall survival (%)
Early cancers							
Eckel [7]	1992	67	T1–T2	9	9	100	–
Steiner [8]	1993	130	T1–T2a	8	1	100	86
Rudert [19]	1995	108	T1–T2	9	3	100	–
Eckel [29]	2000	285	Tis–T2	14	6	99	71
Moreau [24]	2000	97	T1–T2	0	0	97	78
Gallo [30]	2002	139	T1	6	0	100	–
Brondbo [31]	2004	118	T1a	10	2	99	–
Mortuaire [32]	2004	110	Tis–T1–T2	20	8	97	87
Peretti [33]	2004	322	Tis–T1–T2	9	3	99	88
Steiner [25]	2004	263	T1–T2a	13	3	–	–
Motta [12]	2005	432	T1	15	3	97	85
		236	T2	34	18	87	77
Peretti [27]	2005	55	T2	23	15	100	76
Ledda [34]	2006	103	Tis–T1–T2	3	0	–	92
Mahler [35]	2010	188	T1a	8	1	98	78
Mantsopoulos [36]	2012	143	T2	11	–	91	64
Canis [37]	2014	404	T1a	14	1	98	88
Breda [38]	2014	165	T1–T2	–	6	96	–
Advanced cancers							
Motta [12]	2012	51	T3	37	20	72	64
Peretti [39]	2013	89	T2–T3	32	18	99	92
Canis [16]	2014	122	T3	32	17	84	59
Breda [38]	2014	40	T3–IV	–	28	90	–

When we consider the treatment of glottic cancers, we should also consider the resulting vocal quality. Studies attempt to compare three treatment methods: radiotherapy, laser surgery, and open surgery [31]. The occurrence of salvage total laryngectomies is higher after radiation than after laser resection (Table 21.2), reducing the quality of vocal results obtained by radiotherapy. When laser resection is extended to the contralateral cord, synechia alters vocal quality. Radical cordectomy up to the cricoid only results in a compensatory voice being produced via the supraglottis.

21.4 Supraglottic Cancers

Endoscopic resection of limited supraglottic cancers was reported by Jackson and Jackson in 1939 [41]. After Jako and Strong, in 1978 Vaughan was the first to describe the use of resection using a CO_2 laser for neoplasms of the suprahyoid epiglottis [4, 42]. Following his example, Zeitels and Davis used the CO_2 laser for small cancers and to remove obstruction of tumors causing dyspnea, routinely following the endoscopic operation with radiation treatment [43]. It was in Europe, with Steiner in 1979 followed by Rudert, Motta, and Eckel, that CO_2 laser endoscopic resection of supraglottic cancers really developed, without the use of systematic postoperative radiation treatment [19, 44–46].

A rise in the number of glottic cancers in the 1990s allowed the oncologic efficacy of endoscopic resection using the CO_2 laser to be demonstrated on several series of hundreds of patients. In contrast, supraglottic cancers are more rare and treatment indications are more controversial; hence, the current literature includes primarily reports of only 30–40 patients with short oncologic follow-up. Currently, only a few authors have published series of a hundred or more patients. The surgeon-dependent nature of this type of exercise calls for care in interpreting results and does not enable generalizations to be made.

Steiner was the real pioneer in developing the technique of piecemeal resection for the removal of large supraglottic cancers, extending its indication even to T4. Others remain loyal to *en bloc* resection, with more limited indications for laser use. The use of the bivalve laryngoscope as well as thicker forceps and suction tubes is indispensable for this type of resection. For small, limited tumors classed as T1, which are rare, all authors recommend *en bloc* resection. As soon as tumors become larger, Steiner recommends his piecemeal approach. Resection is carried out craniocaudally and layer by layer, using Moh's technique (Fig. 21.1a, b). The first lateral incision cuts across the tumor on the median sagittal plane, allowing the surgeon to evaluate tumoral depth and thus the amount of tissue requiring removal. If the tumor is bulky, additional sections are carried out across the tumor. Where

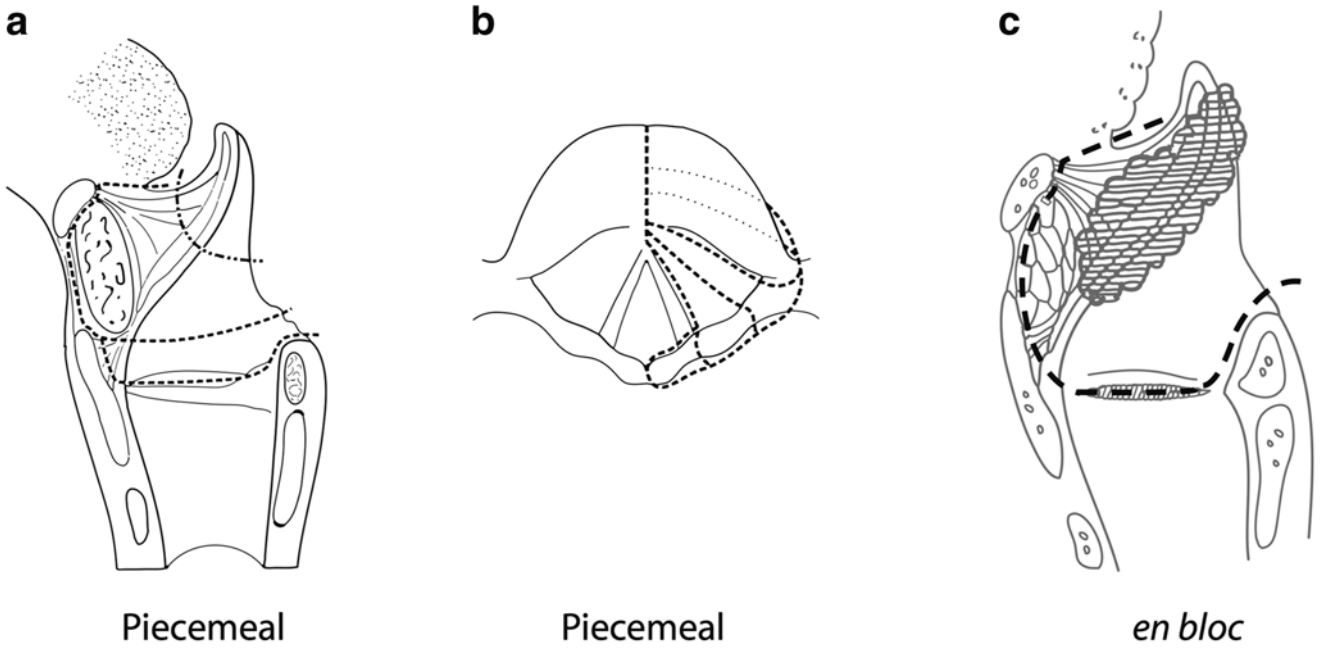

Fig 21.1 Piecemeal (**a**, **b**) or *en bloc* (**c**) supraglottic resection. (**a**, **b**)—Reprinted from Rudert HH, Werner JA, Höft S. Transoral carbon dioxide laser resection of supraglottic carcinoma. Ann Otol Rhinol Laryngol 1999;108:819–827. With permission from Sage Publications. (**c**)—Reprinted from Moreau P. Treatment of laryngeal carcinomas by laser endoscopic microsurgery. Laryngoscope 2000;110:1000–1006. With permission from John Wiley & Sons Ltd

required, the thyroid cartilage or anterior glottal commissure is resectioned; thus, an endolaryngeal evisceration is carried out. As far as we are concerned, we remain convinced that *en bloc* resection enables greater certainty in the analysis of histological margins than piecemeal resection (Fig. 21.1c). Where the preepiglottic space is involved this is not a contraindication if the involvement is minor, that is to say, if it remains far from the hyoid bone. It may reach close to the thyroid cartilage without affecting it. Extension of the anterior commissure is, for us, a contraindication to CO_2 laser resection.

The classically quoted risk of lymph node involvement is around 30 % for supraglottic tumors and higher for tumors of the aditus. The majority of authors recommend carrying out a bilateral neck dissection; unilateral dissection is appropriate when the tumor is highly lateralized. In the event of a very superficial microinvasive tumor, the indication for neck dissection remains controversial. Postoperative radiation is indicated in the event of lymph node involvement, particularly significant involvement, and in cases where tumor margins are not resectable endoscopically. For some surgeons, such as Davis, postoperative radiation is routine [47].

Table 21.3 presents the most significant published series. For T1 and T2 tumors, the local recurrence rate varies between 0 and 15 %. When T3 and T4 are included in the series, the local recurrence rate rises to 20–30 %. The compilation found 138 recurrences in 944 patients, for a rate of 15 %. A large part of these recurrences improved with effective salvage treatment. The adjusted survival rate at 5 years varies between 70 and 100 %, dependent primarily upon lymph node involvement and distal metastases. The overall survival rate at 5 years is on the order of 60–80 %.

The unanimously recognized advantages of this approach include the avoidance of tracheotomy, simpler postoperative course than with open supraglottic laryngectomy, and more rapid removal of nasogastric tubes [52]. Salvage treatment after recurrence with an endoscopic resection is clearly more effective than after radiation or open surgery.

21.5 Pharyngeal Cancers

While the CO_2 laser is commonly used for the treatment of glottic laryngeal cancers, its use to treat the pharynx remained marginal in 2000, but is now increasing.

The overall survival rates of cancers of the pharynx are not favorable, with a survival rate at five years of 50 % for oropharyngeal cancers and of 30 % for hypopharyngeal cancers. Wolfgang Steiner pioneered the use of CO_2 laser to treat cancers in different regions of the head and neck, notably of the pharynx, at the beginning of the 1980s. He replaced the use of the electric bistoury with the CO_2 laser for all transoral resections, whether in the oral cavity itself, the oropharynx, or the hypopharynx. Others, including us, have reserved the use of the CO_2 laser to regions that are inaccessible for transoral resection using an electric bistoury.

Table 21.3 Literature concerning laser of supraglottic carcinomas

Authors	Year	Number of patients	Classification	Local recurrence (%)	5-year specific survival (%)	5-year overall survival (%)
Eckel [7]	1992	15	T1–T2	0	–	–
Zeitels [43]	1994	19	T1–T2	0	–	–
Eckel [46]	1997	46	T1–T2	9	72	59
Ambrosch [44]	1998	48	T1–T2	8	83[a]	76
Iro [9]	1998	141	T1–T4	16	66[a]	–
Rudert [48]	1999	34	T1–T4	29	80[b]	62[b]
Moreau [24]	2000	18	Tis–T3	0	100	63
Motta [45]	2004	124	T1–T2–T3	18–33–23	97–94–81	82–59–51
Davis [47]	2004	46	T2	3	–	63[c]
Cabanillas [49]	2008	26	T1–T3	8	80	–
Bussu [50]	2009	70	T1–T2–T3	12	89	75
Peretti [51]	2010	80	Tis–T3	4	97	84
Canis [15]	2013	99	I–II	15	92	77
Canis [15]	2013	178	III–IV	18–24	81	59

[a]Recurrence-free survival
[b]3-year survival
[c]Non-actuarial survival

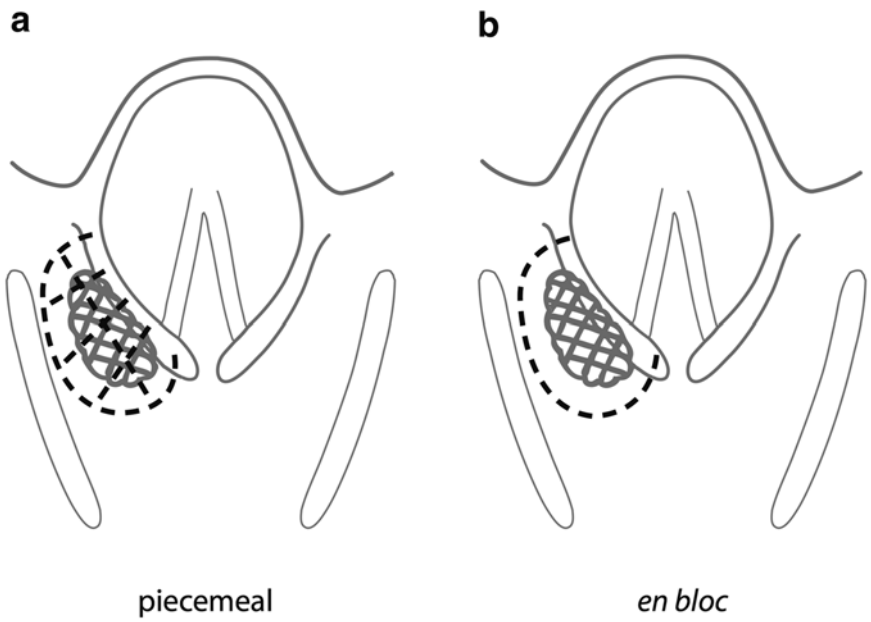

Fig 21.2 Piecemeal (**a**) or *en bloc* (**b**) pharyngeal resection

The material used for laser resection of pharyngeal lesions is comparable to that used for supraglottic cancers, requiring the use of a bivalve Weerda-type laryngoscope and thicker and more rigid forceps and suction tubes.

The indications for laser resection vary widely depending upon the author. Some surgeons use this technique only in a minority of the pharyngeal cancers they treat, limiting its indication to small early tumors, which are resectionable *en bloc* with healthy superficial and deep histological limits [53, 54]. Scanner data and mobilization of the tumor with the help of microforceps allow the depth of the extension to be evaluated and more precise evaluation to determine the appropriateness of laser resection. In contrast, Steiner and others use it to treat T3 and T4 tumors. He collated 31 pT3–T4 cancers from 129 laser resections [10]. As soon as the tumor reaches more than 1 cm in diameter, he recommends sectioning through the tumor and removing it piecemeal craniocaudally and layer by layer, according to Moh's technique (Fig. 21.2) [6]. All the authors agree that histological analysis of the tumor margins is crucial and requires the correct orientation of the specimen and a meticulous analysis of the superficial and deep margins, whether the resection is carried out *en bloc* or piecemeal [55, 56]. Steiner claims that transsectioning the tumor in this way enables

him to better evaluate the depth of the infiltration and prevents hindrance by the tumoral volume. Others claim that histological analysis of all limits is more accurate with *en bloc* resection.

Unilateral or bilateral neck dissection is carried out depending upon the location of the tumor, either during the same operation or a few weeks later. This delay is required when there is a risk of communication between the two fields. For Rudert, postoperative radiation is routine [53]. For others, it is routine only in the event of lymph node involvement [54]. For Steiner, it is systematic in the event of advanced lymph node involvement, extracapsular spread, or carcinomatous lymphangitis [10].

Table 21.4 presents the results of the largest published series. In terms of the oropharynx, the authors find a 5-year specific survival rate of 70–80 %, with a local recurrence rate between 5 and 25 %. For the hypopharynx, the 5-year specific survival rate decreases around 60–70 %, with local recurrence from 10 to 30 %. The overall survival rate remains low for this hypopharyngeal localization, around 50 %. The difference between specific and overall survival is partially linked to second primaries, which are particularly common in these localizations [54].

One big advantage of the laser is that effective treatment of recurrences is possible, whether by repeat laser resectioning, radiation therapy, or open surgery. Another results from the simplicity of postoperative courses, with a reduction in the length of hospitalization, the avoidance of tracheotomy, and recovery of swallowing function and phonation. Bleeding is an immediate postoperative complication in around 5 % of cases and can be fatal [13, 54, 59].

21.6 Precancerous Lesions

In 1923, Jackson introduced the concept of precancerous lesions of the larynx [62]. In 1952, Altman reported the first studies of in situ laryngeal carcinomas, analogous to those of the cervix [63]. In 1974, Strong described the use of the CO_2 laser for the treatment of premalignant lesions [64].

These precancerous stages have been classified by the World Health Organization [65]. Severe dysplasias are usually grouped with in situ carcinomas in a group called "high-level precancerous" lesions, reflecting their significant tendency to become invasive. Classic treatments used for severe dysplasias and in situ carcinomas are stripping, external radiation, and laser resection.

When work with the CO_2 laser first began, some surgeons would use it to vaporize the mucous membrane, while others would perform a resection with histological margin examination. The first lasers had a spot that was around a millimeter in diameter, which did not allow for dissection of Reinke's space. Resection inevitably took place in the superficial part of the vocal ligament, or even the musculature. Technological progress has enabled the spot to be reduced to 100 or 200 µm, allowing us to pass into Reinke's space while retaining the vocal ligament. Supra- or subglottic extension requires correct visualization, with resection of the false cord in the event of extension towards the ventricle or a transversal section of the glottic musculature in the event of inferior extension. Contralateral or bilateral extension causes problems of anterior glottic synechia, altering the vocal quality. As with stripping, a resection carried out in stages can resolve this difficulty. Initially, we tend to treat the side which has been most affected, going up to the median line on the anterior

Table 21.4 Literature review concerning laser of pharyngeal carcinomas

Authors	Year	Number of patients	Localization	Local recurrence (%)	5-year specific survival (%)	5-year overall survival (%)
Oropharynx						
Steiner [11]	2003	48	Base of tongue	15	73[a]	52
Grant [57]	2009	69	Oropharynx	6	87–72	86
Haughey [14]	2011	204	Oropharynx	4	84	78
Canis [58]	2013	102	Tonsil	~25	~70	~57
Hypopharynx						
Steiner [10]	2001	129	Pyriform sinus	13	76[a]	53
Rudert and Höft [53]	2003	29	Hypopharynx	28	58	48
Vilaseca [59]	2004	28	Hypopharynx	18	59	43
Martin [13]	2008	172	Hypopharynx	26	72	52
Karatzanis [60]	2010	119	Hypopharynx	15	73	-
Moreau [61]	2014	36	Hypopharynx	8	86	45

N.B. The study of Steiner 2001 is included in Martin 2008
The survival of Vilaseca is 4, and not 5-year
[a]5-year recurrence-free survival

Table 21.5 Literature concerning laser of "in situ"

Technique	Authors	Year	Number of patients	Local recurrence (%)	Total laryngectomy (%)	5-year specific survival (%)	5-year overall survival (%)
1. Stripping	Miller [66]	1971	100	25	–	–	–
	Hintz [67]	1981	27	63	19	93[a]	–
	Stenersen [68]	1988	41	46	–	–	–
2. Radiotherapy	Pene [69]	1976	79	15	10	–	–
	Elman [70]	1979	69	17	14	–	–
	Le [71]	2000	54	18	13	98	–
	Spayne [72]	2001	67	1	1	100	84
	Garcia-Serra [73]	2002	30	10	10	100	80
	Charbonneau [74]	2008	61	6	5	~97	90
	Sengupta [75]	2010	37	11	5	100	83
3. Laser	Steiner [8]	1993	29	9	0	100	–
	Moreau [24]	2000	26	4	0	100	83
	Eckel [29]	2000	31	6	0	100	86
	Damm [76]	2000	29	14	0	100	–
	Roedel [77]	2009	34	12	0	100	82

[a]Salvage—augmented local control rate

commissure, and 2 or 3 months later carry out resection of the contralateral side, slightly overlapping the median line.

Table 21.5 presents the results of the three main treatment techniques: stripping, radiotherapy, and laser resection. The rate of recurrence after stripping is very variable, ranging from 10 to 60 % according to different authors. It is higher than that seen with the two other techniques. After radiation, the local recurrence rate varies between 0 and 20 %. Sadri compiled 605 patients who had undergone radiotherapy and reported a 12 % recurrence rate [78]. Radiotherapy, however, gives a specific survival rate of close to 100 %, but a total laryngectomy rate of 10 %. With the CO_2 laser, the local recurrence rate is between 5 and 15 %, averaging approximately 10 %. The major advantage of the CO_2 laser is that these recurrences can be treated in a non-mutilating way, either by repeating the laser resection or by radiation, with a rate of conservation of the larynx close to 100 % and a specific survival rate also close to 100 %. The surgeon-dependent nature of laser treatment is similar to that seen with invasive cancers. Small published series often show higher rates of recurrence, testimony to the importance of the surgeon's skill [71, 79].

One of the major advantages of the laser is the ability to precisely classify the tumor. Patients receive radiotherapy on the basis of a biopsy which has shown a precancerous stage while the lesion may in fact be microinvasive elsewhere. Laser resection enables classification of certain precancerous stages to be modified, based on analysis of the specimen, thus allowing for appropriate treatment following determination of the true extension of the tumor.

An argument often advanced in favor of radiotherapy is that of vocal quality. The rate of salvage total laryngectomy after radiation renders this argument null and void. While laser resection is limited to the superficial part of Reinke's space, the mucosal wave in stroboscopy is salvaged, with no consequences for the voice. However, minor vocal consequences often occur for various reasons: Reinke's space cannot be detached, for example, in case of hypertrophic laryngitis, deep biopsy resulting scarring, or in the event of subglottic, supraglottic, or contralateral extension.

21.7 Debulking of Airway Obstruction

Pharyngeal or laryngeal cancers causing dyspnea require immediate restoration of a sufficient respiratory channel. The classic solution is a tracheotomy, carried out where required under local anaesthesia, prior to a total laryngectomy. The risk of recurrence around the orifice of the tracheotomy is estimated at between 3 and 40 %, particularly where the tracheotomy cuts across the tumoral tissue, but also as a result of neoplastic seeding [80]. Peristomal recurrences constitute an extremely unfavorable factor with a mortality rate of 80–90 % [80, 81]. To avoid the need for tracheotomy, radical treatment can be proposed in the form of an emergency total laryngectomy [82]. The absence of an earlier assessment and practical contingencies, however, do not always permit this. A third possibility is the restoration of a sufficient airway passage by tumoral debulking using laser endoscopy [83]. The concept is simple; performing it is less so. Tumoral transsectioning often results in hemorrhage, which is difficult to control. The remaining tumor has a crumbly texture which can obstruct the airways again immediately. Subglottic extension, which is often dyspneal, makes this difficult to carry out and is further

hindered by the presence of the ventilation tube. The ventilation jet is no simpler as an airway return has to be restored to avoid pulmonary complications. In the event of localization at the level of the laryngeal aditus, laser resection can result in aspiration. It is not rare to have to repeat endoscopic disobstruction. An endoscopic resection on the side which is not affected by the tumor occasionally helps.

Debulking, however, most often enables a sufficient airway channel to be restored for a few weeks, allowing for the usual extended assessment to be carried out and for the curative procedure to be scheduled under the best conditions [6, 83]. Other types of laser techniques and different methodologies have been used with success, including the microdebrider [84].

21.8 Salvage after Glottic Radiation Failure

Postradiation salvage surgery is difficult. The majority of T1–T2 glottic cancers are salvaged by total laryngectomy, with a failure rate of 20–50 % [85, 86]. In a minority of cases, open partial surgery is used, with a local recurrence rate of between 5 and 25 % [87, 88]. Series published on salvage with laser resection are presented in Table 21.6. They are limited to a few dozen patients, demonstrating the small proportion of cases in which this laser surgery is possible. New recurrences can be seen in 15–60 % of cases. Compilation of these series found 106 new recurrences in 241 patients, for a rate of 44 %. Laser resection can be repeated in the event of recurrence. The rate of total laryngectomy is between 15 and 50 %. Some of these patients die from their cancer in the event of recurrence, but it is difficult to determine the exact proportion. All authors underline the technical difficulties of this laser resection in radiated areas as a result of imprecise margins.

21.9 Discussion

Steiner uses the CO_2 laser to carry out transoral resection of oral cavity cancers and those of the upper oropharynx, soft palate, or tonsillar area [6]. Other authors remain attached to conventional transoral instruments, such as the electric bistoury and "cold" instruments. They avoid the inconveniences of laser: coagulation necrosis at the margins, which renders scarring more difficult and increases the risk of stitches failing, and axial radiation complicating resection of the deepest part of the specimen.

Histologic analysis of margins is more difficult with CO_2 laser resection than with traditional means. A tissue thickness of 0.5 mm is destroyed by the laser section, reduced at best to 200 µm with Acuspot. The margins are subject to coagulation necrosis, which further complicates the analysis. When the laser was initially used, some authors advised the destruction of the tumor by vaporization without histological control of the margins. No significant series supports this concept. Formal or possible involvement of the resection margins of the specimen often occurs, in about 25–30 % of cases [55, 56]. Reresection for an inadequate margin uncovers residual tumor in only 20 % of cases [56]. True histological involvement of the margins is associated with a higher rate of locoregional recurrence, an increased rate of distal metastases, and a reduced specific survival rate [55, 56, 94]. Here we begin to appreciate all the difficulties of interpreting the histological involvement of the margins and the need to meticulously analyze them. Could a focal spread upon a margin be considered as insignificant following tissue destruction? Is an infra-millimetric deep limit sufficient? Does the piecemeal resectioning technique enable as relevant an analysis of the margins as *en bloc* resection?

Lymph node involvement in supraglottic and pharyngeal tumors often occurs. Bilateral neck dissection is indicated in the event of median or near-median tumor, and unilateral dissection in the event of a lateralized tumor. In the event of a microinvasive tumor, with less than 2 mm infiltration, the indication is more subtle. For the supraglottis, where lymph node involvement is more rare, a microinvasive tumor prompts simple monitoring. For the pharynx, the discussion remains open. If the tumor is clearly invasive, neck surgery can be carried out during the same operation, but can also be deferred. In the event of laser resection adjoining the cervical region, it is preferable to delay neck surgery in order to avoid communication between the two operating areas and the risk of fistula formation.

Table 21.6 Literature concerning laser of recurrent glottic carcinomas after radiotherapy

Authors	Year	Number of patients	Local recurrence (%)	Total laryngectomy (%)
Quer [89]	2000	24	25	25
de Gier [87]	2001	40	58	50
Steiner [90]	2004	34	59	21
Ansarin [88]	2007	37	35	30
Roedel [91]	2010	53	58	26
Del Bon [92]	2012	35	16	13
Han [93]	2012	18	44	33

Mastering resection with the help of the CO_2 laser is not easy. Most of the large series published have been carried out by a single surgeon, who has progressively enlarged the indications and who has acquired an optimal technique. Large published series give better results than the smaller ones. Teaching appears more difficult than with open surgery. This surgeon-dependent nature of the endoscopic approach limits its growth and results in a disparity of results.

The term "laser" evokes new technology, which gives rise to great enthusiasm. In oncology, prudence imposes itself. In the past, various technologies such as color lasers and photosensitizers were tested with lukewarm results [95, 96]. The CO_2 laser is only one methodology used in surgical section, next to diode lasers, the KTP laser and pulsed dye laser [97, 98]. Recent literature proposes the use of transoral robotic surgery. One big advantage of this technique is that there is no exposition limitation, no necessity of direct visualization. So, specially at the level of the supraglottis and the base of the tongue, robotic surgery seems to facilitate the action of resection and pick up a part of indications.

Some inconvenience of the robot consists in more important destruction of tissues with necrosis and lack of instrumental palpation. Coupling the CO_2 laser with a robot appears to be a promising concept [99].

21.10 Conclusions

Over the course of 30 years, driven by Wolfgang Steiner, the CO_2 laser has become one of the means of treating early cancers of the upper aerodigestive tract. For dysplasias and in situ carcinomas, its results are better than those of radiation treatment, by decreasing the need for salvage total laryngectomy. For early glottic T1 and T2 cancers, removable endoscopically, it gives a specific survival rate of close to 100 % with a total laryngectomy rate of around 2–3 %, a rate less than that seen following radiotherapy. In the event of decreased mobility and fixation, the results are less favorable. Many authors prefer to perform open partial laryngectomy in these cases. For supraglottic cancers, the use of CO_2 lasers requires significant expertise. No consensus exists on the indications. A local recurrence rate of approximately 10 % is seen in T1 and T2 tumors and 25 % for T3 and T4 tumors. These can most often be salvaged. The specific survival rate at 5 years is 85 %, depending mainly upon the extent of distal and lymph node metastases. For pharyngeal cancers, indications also vary depending upon the authors. The role of metastasis and of second primaries is of clear dominance in determining outcome. The rate of local recurrence is 20 % with a specific survival rate of 70 % and an overall survival rate of 50 %.

Beyond simple morbidity, the fact that a tracheotomy can be avoided and that the postoperative course is simpler, the major advantage of laser resection remains the absence of locoregional dissemination. This allows for effective salvage treatment to be carried out, whether by repeat laser resection, open surgery, or radiation. One inconvenience is the difficulty of learning this technique and hence its surgeon-dependent nature. Table 21.7 summarizes the advantages and the limitations of CO_2 laser use.

Table 21.7 Advantages and limitations of laser

	Advantages	limitations
Global	More precise classification of T	Required expertise
	Avoid local dissemination	Surgeon-dependent nature
	Excellent salvage in case of local recurrence	Inadequate endoscopic exposition
	Postoperative course very simple	
	low cost	
Glottic	For T1–T2a,	Involvement of anterior commissure
	–Local recurrence 10 %,	Glottic fixation
	–Salvage total laryngectomy 2–3 %	Low vocal quality in case of radical or bilateral cordectomy
Supraglottic	Avoid tracheotomy	Disparity of contraindications:
	Local recurrence 15 %	–T4, a part of T3
		–Extension near hyoid bone and to glottic area
Pharyngeal	Local recurrence 20 %	Controversy of indications and techniques
	Very useful in case of multiple tumors	Overall survival ~ 50 %
Precancerous	Local recurrence 10 %	2 stages in case of bilateral glottic extension
	Specific survival ~ 100 %	
	Avoid salvage total laryngectomy	

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Transoral Robotic Surgery in Head and Neck Cancer

22

Sylvain Morinière

Abstract

As partial laryngeal surgery in the 1970s and endoscopic laser surgery in the 1990s, the transoral robotic surgery (TORS), which emerged in 2006, was initiated in an attempt to reduce functional and aesthetic sequela while maintaining oncological efficacy. However, this type of endoscopic surgery involves difficulties associated with the robot-related materials (robot, retractor, laryngoscope, and instrumentation), apprehension of the patients, the exposure of the tumor, and each surgeon's learning curve. The aim of this chapter is to make an update on robotic surgery for the treatment of cancers of the upper aerodigestive tract, to consider the functional and oncological results, and to see the prospects for development in the coming years.

Keywords

Robotic surgery • Head and neck cancer • Endoscopy • Transoral surgery • Pharynx • Larynx

Key Points

Advantages of TORS

- The use of 3D endoscope at 0 or 30° offers a large access to the pharyngeal cavity.
- TORS allows gestures with high precision and removes the tremors.
- TORS allows early oral feeding and decreases the number of tracheotomies required.
- TORS for the tumors T1 T2 of the pharynx has the same oncological results as conventional open surgery.

Limitations of TORS

- The start of robotic surgery must be planned so that the whole team is properly informed before initiating the first case.
- The TORS surgeon, using the specific mouth gag, must do the preoperative endoscopy to select patients eligible for robotic surgery.
- The lack of force feedback makes the highly invasive tumors ineligible for TORS.

22.1 Introduction

The development of partial laryngeal surgery in the 1970s [1] and endoscopic laser surgery in the 1990s [2] aimed to reduce functional and aesthetic sequela while maintaining oncological efficacy. The development of transoral robotic surgery (TORS), which emerged [3] in 2006, was also initiated in an attempt to achieve this goal. Robots were first used in surgery in 1988 during CT-guided stereotactic neurosurgery [4]. After locating the lesion by CT scan, the robot aimed for the area of interest with more precision than a human surgeon. At the end of the 1990s, Intuitive Surgical® developed the Da Vinci robot for urologic, gynecologic, and thoracic laparoscopy. In 2005, B. O'Malley and G. Weinstein's team in Philadelphia, Pennsylvania, USA,

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used the Da Vinci robot to treat a benign oropharyngeal tumor after a feasibility study was conducted on a porcine model [5]. Studies evaluating TORS for the treatment of upper aerodigestive tract cancer were published as early as 2008 [6]. Current indications for robot surgical procedures include T1–T2 tumors of the oropharynx and the supraglottic larynx.

However, this type of endoscopic surgery involves difficulties associated with the robot-related materials (robot arms, retractor, laryngoscope, and instrumentation), apprehension of the patients, the exposure of the tumor, and each surgeon's learning curve. The aim of this chapter is to update the current status of robotic surgery for the treatment of cancers of the upper aerodigestive tract and to consider the prospects for robotic surgery development in the coming years.

22.2 The Principles of TORS

All TORS procedures are performed under general anesthesia with an oral or nasotracheal intubation. The Da Vinci robot has several components, including the robot, a surgeon's console, light sources, 3D camera, and mono- and bipolar generators. The use of one of the three specific mouth gags available (FK Olympus®, LARS retractor Fentex®, and M Micro France®) is recommended. These permit a large access to the pharynx in order to place the 8 mm optical at an angle of 0 or 30° within the pharynx using the two robotic arms equipped with instruments (Maryland forceps and monopolar electrocautery) (see Fig. 22.1). These arms are controlled by the surgeon who works near the patient from a console with 3D vision and up to 10 times magnification. Installation time (approximately 20–30 min) of the retractor and arms is essential. Good exposure of the tumor is key to a successful TORS procedure. An assistant is always positioned at the patient's head to aspirate fluids and fumes as well as monitoring the position of the arms in the mouth to prevent potential conflicts. An operating room nurse loads and cleans the instruments on the robot arm. At the console, the surgeon manipulates two joysticks that transmit motion to instruments with a ratio of 5:1. This allows for gestures with high precision and removes the possibility of tremors. The use of these joysticks is very natural, which allows for the operator to work in a comfortable sitting position. It is necessary to replace the retractor and the robot arms during tumor resection. The tumor resection is performed using the unipolar forceps, and hemostasis is performed with the Maryland forceps. The wound is left to control healing or sutured with local flap, depending on its location.

22.3 Indications

As stated by Weinstein et al. [5], a preoperative endoscopy can be used to select patients eligible for robotic surgery. The surgeon who will perform robotic surgery using the specific retractor must also perform the endoscopy. The main criteria assessed during preoperative endoscopy are the anatomical location and the size of the tumor, the mouth opening, and the maxillo-mandibular anatomy. The presence of a small mouth opening and/or a large tongue base are contraindications that only the robotic surgeon can evaluate. Thus, with this preselection, a very small number of patients are ineligible due to poor exposure. Only 13 patients out of 129 cases had inadequate exposure in a multicenter study by Weinstein et al. [7].

The FDA has provided approval for TORS only in cases of T1–T2 tumors of the oropharynx, larynx, and hypophar-

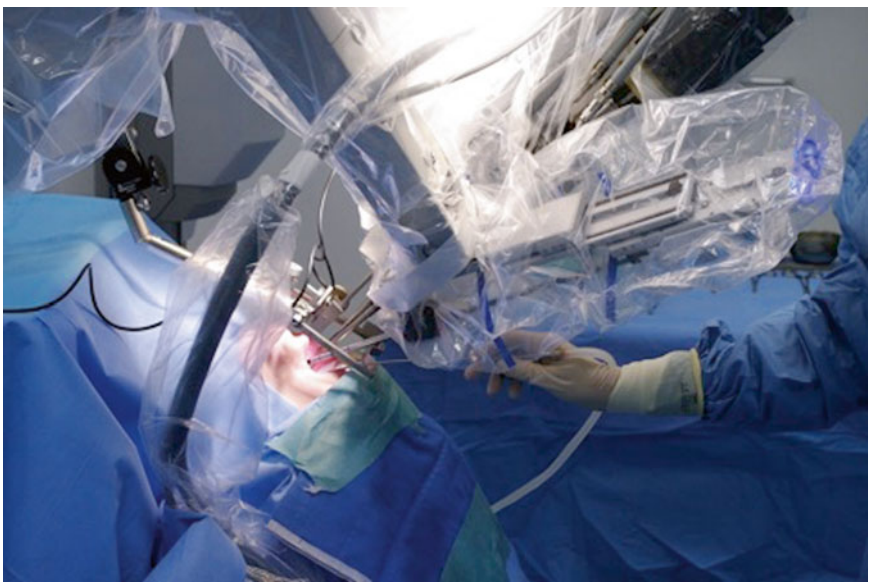

Fig. 22.1 Robotic arms and mouth gag setting during a transoral robotic surgery

ynx. The lack of force feedback makes palpation impossible with the robotic instruments. Therefore, highly invasive tumors are ineligible for this procedure, in our experience. The size of the 5-mm robotic instruments is too large to work in the endolarynx, and endoscopic laser surgery is preferred in these locations.

22.4 Learning Curve

The start of robotic surgery cannot be improvised and must be planned so that the whole team is properly informed before initiating the first case. Health institutions that invest in an expensive robotic system should routinely offer this training. Ideally, the planning of the first case should occur within 15 days of this training. In addition, the first case should be easy (small tumor of the tonsil) and supervised by an experienced TORS surgeon. Under these conditions, the learning curve is quite fast. Several publications [8, 9] have shown that the durations of TORS procedures performed by a given surgeon decreased significantly after the first 10 patients. The surgical team must follow a progression in the programming of cases, beginning with lesions of the oropharynx, followed by the supraglottic larynx, and finally, the hypopharynx.

22.5 Anesthesia and Operative Specificities

The anesthesia required for TORS is not different from that required for other endoscopic surgeries. We prefer a nasal intubation to avoid placing the probe in the oral cavity. Weinstein et al. performed oral intubation by placing the probe in the contralateral labial commissure [7].

The quality of resection margins is an important prognostic factor in local control. The use of frozen section is highly recommended when there are short margins.

In a series of TORS from a group of surgeons from France [10], the neck dissection was performed during the same operation in most cases. However, for larger tumors with a risk of cervical fistula, the neck dissection can be offset by 15 days. Where there is a significant risk of bleeding intraoperatively during tumor resection (risk of injury to the lingual artery), the node dissection can be completed first to control and bind the branches of the external carotid that may be injured.

22.6 Functional Results

The TORS should allow early oral feeding and decrease the number of tracheotomies required (Table 22.1). In a study by Boudreau et al. [11], 45 % of the patients (13/29) required a nasogastric tube after hospitalization. Factors associated with dependence on a nasogastric tube were advanced age ($p=0.02$), a laryngeal location ($p<0.001$), and the size of the lesion ($p=0.02$). In most patient series, 70 % of patients subjected to TORS had no feeding tube at the 7th day. Genden et al. [12] reported no cases of tracheotomies for 18 patients who underwent TORS. In a study by Hammoudi et al. [13], two groups of patients who received TORS or conventional surgery (CC) were matched according to TNM, age, and comorbidities. A tracheotomy was performed in three cases out of 26 in the TORS group and 18 out of 26 cases in the CC group.

However, the tracheotomy must be performed to protect the upper respiratory tract in cases that present a high risk of bleeding or edema [14].

22.6.1 Oncological Results

Considering the recent development of TORS, it is not possible to assess the long-term oncological results. The major retrospective series in the literature report negative margins in 85–100 % of the cases [7, 10, 12]. Weinstein et al. reported a series of 47 patients treated for stage III or IV cancer of the oropharynx with a mean follow-up of 26 months [5]. These authors describe only one positive margin (2.1 %). Local, regional, and metastatic controls were 46/47 (97.9 %), 45/47 (95.7 %), and 43/47 (91.5 %), respectively. Specific survival

Table 22.1 Percentages of nasal drip, tracheotomy, bleeding, and hospitalization duration less than 7 days in the postoperative period of transoral robotic surgery in the different series of the literature

	Nasal drip < 7j (%)	Tracheotomy (%)	Bleeding (%)	Hospitalization <7 days (%)
Iseli et al. 2009 [14], $n=54$	70	10	6	62
Boudreaux et al. 2009 [11], $n=35$	62	3	6	80
Weinstein et al. 2012 [7] $n=192$	–	12.4	7.8	–
Hammoudi et al. 2014 [13], $n=26$	55	11.5	3.8	72

at 1 and 2 years was 97.8 % (45/46) and 90.0 % (27/30), respectively. A study of Hammoudi et al. [13] found no significant difference in disease-free survival at 3 years between the TORS group (89 %) and the CC group (85 %). These are very good results, especially for a significant number of advanced tumors, and must now be compared with chemoradiotherapy. Several prospective randomized trials are ongoing (ORATOR, RTOG 1221) to allow us to clarify the indications of TORS.

22.7 Conclusion

The large number of publications regarding TORS confirms the growing role of this new technology for the surgical treatment of head and neck cancers. Team training, assessment of tumor exposure, and respect for oncological rules are essential criteria for this less invasive surgery. The contribution of technical innovations is expected to partially compensate for the lack of force feedback. The use of reconstruction surgery by local or free flaps is also under development. Finally, the future of robotic surgery in our discipline lies in the development of new systems dedicated to TORS with articulated thinner arms and flexible endoscopes. Several projects are under way and expected to be available in the coming years.

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Multidisciplinary Management of Skull Base and Superstructure Tumors

23

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Abstract

Malignant tumors of the paranasal sinuses are rare, accounting for only 3 % of all the head and neck malignancies. Moreover, only a small part of them involves the superstructure and the skull base. As a consequence, no report of a randomized clinical trial about different treatments has been published, and the chance to perform such a trial is remote. However, the combination of surgery and (chemo)-radiotherapy seems to offer better local control than radiotherapy alone.

The treatment of skull base tumors is, by definition, a multidisciplinary work. Even in cases where surgery may be the only treatment, at least a neurosurgeon and a head and neck surgeon must collaborate to reach good results avoiding complications. A neurosurgeon must be quickly available also when an endoscopic resection is performed by an otolaryngologist. Plastic and reconstructive surgeons, radiologists, anesthesiologists, critical care and rehabilitations experts, and nurses are also indispensable. Moreover, the quite steady indication for pre- or postoperative (chemo)-radiotherapy involves the involvement of medical oncologists and radiotherapists in the therapeutic team.

This chapter demonstrates in detail the abovementioned principles, mentioning the more recent papers on this topic and our own large experience in the treatment of malignant skull base tumors. Moreover, we will take into consideration the most frequent histologic types and their different etiology and standard or experimental treatment.

Keywords

Sinonasal cancer • Skull base • Paranasal sinus • Occupational tumors • Reconstructive surgery

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23.1 Introduction

Malignant tumors of the paranasal sinuses account for only 2–3 % of the head and neck carcinomas and about 0.5 % of all malignancies. Most tumors originate in the maxillary sinus or nasal cavity, and only 20–25 % originate in the ethmoid sinus or involve the superstructure and the skull base [1]. The low incidence and great variety of histologic types means that there are no large studies on management of these tumors. No randomized clinical trials about different treatments have been published, and the chance to perform such a trial is remote.

23.2 Etiology

A possible occupational etiology of sinonasal cancers was first hypothesized in 1890, when a maxillary tumor was detected in a worker exposed to chrome [2]. An increased risk of sinonasal cancer has been demonstrated among workers exposed to formaldehyde, nickel, and chrome. Tobacco and alcohol are not considered major risk factors, even though heavy smokers have an increased risk of squamous cell carcinoma (SCC) [3].

The most interesting paranasal sinus tumor, for which there is an indisputable occupational etiology, is ethmoid adenocarcinoma, mainly Intestinal Type Adenocarcinoma (ITAC). Wood dust exposure as a risk factor for sinonasal cancers was recognized in 1968 by Acheson et al. [4]. Several papers have since been published on the occupational etiology of these tumors [5–9], including leather dust as a major risk factor [8]. These papers have a possible bias for properly classifying the histology and site of tumor. Some of the studies use the generic terms "nasal cancer" [4, 8], "nasal and sinonasal cancer" [9], and "sinonasal cancer" [3, 7]. Only one paper correctly stated in the title both the histology (adenocarcinoma) and location of the tumor (ethmoid sinus) [6]. Hadfield [5], who analyzed 92 patients with sinonasal cancer (34 SCC, 35 adenocarcinomas, and 23 anaplastic carcinomas), found that the tumor appeared to originate in the ethmoid sinus in all 35 patients with adenocarcinoma. This fact was confirmed in a later paper [10].

Taking advantage of our large sample of patients with malignant paranasal sinus tumors we sought to determine the impact of the workplace etiology of these tumors, primarily for ethmoid adenocarcinomas and wood and leather dust exposure, and whether there was any difference in occupational etiology between the various types of adenocarcinomas. We carefully assessed the histology and tumor origin of 646 patients with sinonasal malignant tumors treated at the Istituto Nazionale dei Tumori of Milan between 1987 and 2007 [11]. Adenocarcinomas were classified according to the latest pathologic classification of head and neck tumors by the World Health Organization, which divides sinonasal adenocarcinomas into two histologic forms: ITACs and non-ITACs [12]. Of the 345 patients with ethmoidal tumors, 169 (48.9 %) had adenocarcinoma and ITAC was the most frequent histologic type (153/169). Of the 301 patients with maxillary tumors, 20 (6.6 %) had adenocarcinoma and no ITAC was found among them.

We found an exposure to organic dusts in 148 of 153 patients (96.7 %) with ethmoid ITAC (91 wood, 55 leather, 1 textile, and 1 rice). One patient reported an exposure to asbestos. Four patients did not report any specific exposure. Regarding non-ITAC ethmoid adenocarcinoma, 3 patients were exposed to organic dusts (2 to leather and 1 to wood), whereas 13 of 16 patients (81.3 %) did not experience any exposure. For patients with ethmoid malignant tumors other than adenocarcinoma, we found an exposure to possible carcinogenic agents in 10 of 176 patients (5.7 %): 3 wood, 2 leather, 2 textile, 2 concrete, and 1 asbestos. For non-ITAC adenocarcinomas of the maxillary sinus (20 cases), we found an exposure to wood dust in 1 patient (5.0 %). Among patients with other histologies (281), only 4 (1.4 %) were exposed (2 to wood, 1 to leather, and 1 to asbestos). Highly significant ($p < .0001$) were the associations between ITAC histology and tumor site and between ITAC histology and wood/leather exposure.

The period of exposure was between 25 and 55 years for the majority of exposed individuals. However, 16 patients with ITAC had experienced a very early and limited exposure, followed by a long interval between the end of exposure and the onset of the ITAC. The mean interval was 33 years (range, 23–46), and the mean duration of exposure was 7.5 years (range, 4–18).

The different role of hardwoods and softwoods in tumor development remains largely unknown. Some authors [9, 13] in Northern Europe (where furniture industries employ mainly softwoods) highlighted a minor and different carcinogenic power of softwoods compared to the hardwoods that are more often employed in Southern Europe. The authors found an association between hardwood dust exposure and adenocarcinoma, while softwood dust exposure alone was associated with epidermoid and anaplastic carcinomas. However, there is a general consensus about the danger posed by a working environment with over 5 mg/m^3 of wood dust, while some [14] suggest a lower dust level of 1 mg/m^3.

Sinonasal tumors treated with an anterior craniofacial resection had different histological compositions in Europe compared to North America. The rate of adenocarcinomas in European countries is very high: Roux [15] (France) 74 %, Suarez [16] (Spain) 53 %, Cantu [17] (Italy) 49 %, and Cheesman [18] (United Kingdom) 27 %. Conversely, the rates are much lower in American studies: McCutcheon [19] (USA) 17 %, Bentz [20] (USA) 12 %, Donald [21] (USA) 6 %, and Irish [22] (Canada) 5 %. Bridger [23] (Australia)

reports 37 % of sinonasal tumors were adenocarcinoma, consistent with the UK study. While no definitive explanation for these discrepancies exists, Blot et al. [24] hypothesize the following:

- While the commonly accepted threshold for the level of wood dust in the air is 5 mg/m^3, many European artisan furniture factories and joinery may have exceeded that threshold.
- Hardwoods, which are more dangerous than softwoods, are probably more widespread in Europe than in America.
- America adopted safety measures, such as masks and aspiration devices, earlier than Europe. Given that these tumors have a latent period of about 30–40 years between the beginning of exposure and clinical presentation [25], there will probably be a reduction in the incidence of this disease in Europe over the next decades resulting from the improved factory conditions.

Polymorphisms in xenobiotic metabolizing enzymes play an important role in the gene–environment interaction and may contribute to a high degree of variance in the individual susceptibility to cancer development. Pastore et al. investigated the role of polymorphisms in the CYP1A1 and GSTM1 genes in 30 ethmoid ITAC patients and 79 healthy blood donors [26]. The results revealed that patients with the CYP1A1 codon 461 polymorphism may be at an increased risk of developing ITAC and that this risk increases in the presence of both the polymorphism at this CYP1A1 codon and the GSTM1-null genotype. This study strongly suggests that these genotype investigations may be useful in determining the exposed individuals who are at risk for developing ethmoid ITAC.

23.3 Pathology and Natural History

Excluding the nasal cavity, the maxillary sinus is the most frequent site of tumor origin (70–75 %), followed by the ethmoid sinus (20–25 %). Primary tumors in the frontal or sphenoid sinus are unusual, even though these sinuses are sometimes involved in large neoplasms. The most common histologic type in maxillary sinus is SCC, more or less differentiated, followed by tumors affecting minor salivary glands: adenocarcinoma (ADE), adenoid cystic carcinoma (ACC), and mucoepidermoid carcinoma (MEC). Sarcomas (malignant fibrous histiocytoma, malignant peripheral nerve sheath tumors, chondro-, osteo-, fibro-, leiomyo-, and angiosarcomas) are rare. Rhabdomyosarcomas are more frequent, particularly during childhood [27]. In the ethmoid sinus, in addition to SCC and ITAC, other common histologies include sinonasal undifferentiated carcinomas (SNUC), melanomas, and sinonasal neuroendocrine tumors: esthesioneuroblastomas (ENB), neuroendocrine carcinomas (NEC), and small cell carcinoma neuroendocrine type (SCCNET) [27].

These tumors often grow silently, meaning that patients often present with advanced-stage disease. The air-filled sinus cavities do not offer resistance to tumor growth, and the tumor becomes symptomatic only after it erodes the bony walls. A tumor of the maxillary sinus may affect the hard palate and alveolar ridge inferiorly, the orbit superiorly, the cheek anteriorly, or the pterygoid plates posteriorly. These tumors may also invade the pterygopalatine and infratemporal fossa, the greater wing of the sphenoid, and the middle cranial fossa. A tumor of the ethmoid may spread inferiorly into the nasal cavity, laterally into the orbit, posteriorly into the sphenoid sinus and nasopharynx, or superiorly into the anterior cranial fossa (after eroding the cribriform plate). The medial periorbita provides an effective barrier against tumor invasion, but the natural holes in this structure (lacrimal duct, anterior and posterior ethmoidal arteries) are roads for tumor invasion into the orbital contents. Although the dura is resistant to tumor growth, the olfactory nerves allow for the tumor to spread intradurally.

The lymphatics from the anterior part of maxillary sinus drain through the facial lymphatic vessel into the nodes at levels I and II. Lymphatics from the ethmoid and posterior part of maxillary sinus drain into the lateral retropharyngeal nodes, which lead to the deep cervical chain.

Neck metastases are an unfavorable prognostic factor [28–34], although the incidence of neck metastases at presentation is low. The meta-analysis by Dulguerov et al. [28] reported about 12 % of patients presented with neck metastases, although the incidence of nodal metastases during the follow-up period was around 13 %.

In a previous paper [35], we reviewed the medical records of 704 consecutive patients surgically treated for paranasal sinus malignant tumors (305 ethmoid sinus tumors and 399 maxillary sinus tumors). Nodal metastases from ethmoid tumors were very rare, both at presentation (1.6 %) and during follow-up (4.3 %). Moreover, the majority of subsequent neck metastases appeared with a recurrence of the primary tumor. Only patients with SNUC, NEC, or SCCNET had a high rate of regional recurrence (25 %), and these tumors probably behave similarly to nasopharyngeal undifferentiated carcinoma in this regard. In the maxillary sinus, the rate of neck metastases for non-squamous cell carcinomas was very low at presentation (6 %). Subsequent nodal metastases were rare, except in SNUC (13 %) and ADE (22.2 %). Actually, ADE of maxillary sinus originates in the minor salivary glands and acts like ADE of the major salivary glands. This type of cancer is very different from ITAC of the ethmoid sinus, which rarely metastasized regionally.

Only 16 of the 156 patients with SCC of the maxillary sinuses presented with nodal lesions (10.3 %), of which 11 patients were staged as T2, one was as T3, three were

considered T4a, and one was stage T4b. All five of the patients with T3–T4 tumors had involvement of the oral mucosa as well. Four of the 26 (15.4 %) patients with SNUC presented with nodal lesions, as did 13 of the 217 (6 %) patients with other histologic types. These data strongly suggest that a higher percentage of stage T2 tumors present with cervical metastases than stage T3–T4 tumors. By definition, a T2 tumor involves the floor of maxillary sinus (with possible mucosal invasion of the hard palate and upper gum) and/or the inferior nasal cavity, both of which have a more expansive lymphatic network than the mucosa of paranasal sinuses. Therefore, in terms of lymph node metastases, these tumors have a behavior more similar to oral cancers than paranasal cancers. The fact that paranasal sinus carcinoma behaves differently than other head and neck carcinomas was first recognized in 1937 by del Regato [36] and has been confirmed by numerous authors [28, 33].

23.4 Symptoms

While tumors affecting the hard palate or nasal cavity may cause symptoms early, superstructure tumors are asymptomatic for a long time, making an early diagnosis difficult. When the tumor is located in the ethmoid sinus or the upper part of the nasal cavity, patients may present with only unilateral nasal obstruction. Epistaxis generally occurs only in vascular tumors (hemangiopericytoma and esthesioneuroblastoma), with the patient often complaining of blood-stained secretions. More advanced tumors that have invaded the nasolacrimal duct and orbit may cause epiphora, proptosis, and diplopia. The tumor may also invade the orbital apex posteriorly, causing ophthalmoplegia and visual loss, the sphenoid sinus, and the nasopharynx. Anterior involvement of the nasal bones produces a characteristic broadening of the upper nasal region. Although few patients report anosmia as a first symptom, almost all patients remember some loss of smell when specifically asked. Incredibly, tumor invasion of the anterior cranial fossa is generally silent. Invasion of the infraorbital nerve, leading to dysesthesia and pain at the level of the cheek and upper lip, is often misdiagnosed as trigeminal neuralgia. A tumor invading the infratemporal fossa may infiltrate the third branch of the fifth cranial nerve at the foramen ovale, causing dysesthesia, pain, and anesthesia of the chin, inferior teeth (mandibular nerve), and omolateral tongue (lingual nerve). In our series, some patients had these symptoms for over a year prior to diagnosis, particularly with slow-growing tumors like adenoid cystic carcinoma. A tumor can infiltrate the pterygoid muscles, causing trismus, and it may also erode the greater wing of the sphenoid, spreading into the middle cranial fossa.

23.5 Staging

Establishing a consistent prognostic staging system for each extension of paranasal sinus carcinoma has proven difficult, as demonstrated by the numerous classification schemes previously published [37–42]. All systems only considered tumors of the maxillary sinus and assigned a higher stage for tumors with posterosuperior extension. In 1906, Sebileau [43] realized that the prognosis of tumors differed depending on their location, either inferiorly or superiorly in the paranasal sinuses. He divided the upper jaw with two horizontal parallel "*imaginary lines*" into "*infrastructure, mesostructure*, *and suprastructure*." In 1933, Öhngren [44] recognized that Sebileau's system did not address posterior extension of the tumor and proposed a classification system based upon a hypothetical plane passing through the inner canthus and the mandibular angle. The "*malignancy plane*" divided the upper jaw into an infrastructure ("*topographically more benign tumors*") and a suprastructure ("*tumors of more malignant character*"). Öhngren's plane, which was incorrectly called "line," was the basis for the division between T1–T2 and T3–T4 maxillary sinus carcinomas in the first four versions of the American Joint Committee on Cancer (AJCC) classifications [45–48]. According to these guidelines, the maxillary sinus was "the only site to which the following classification applies. The ethmoid sinus and nasal cavity may ultimately be defined similarly with further study." While the AJCC partially staged paranasal sinus carcinoma from the beginning, the International Union Against Cancer (UICC) did not stage paranasal sinus tumors in the first three editions of its manuals. A classification of maxillary sinus carcinoma, similar to that of the AJCC, appeared only in the fourth edition in 1987 [49].

Several studies of the AJCC-UICC classification of maxillary sinus carcinoma have demonstrated its prognostic value, with a progressive worsening of the prognosis from T1 to T4. The absence of a universally accepted classification of ethmoid cancer led to an obvious lack of disease staging in the literature. Sisson [50] wrote: "The ethmoid cancers were not staged because there is no generally accepted staging system for this site." Similarly, after having staged tumors of the maxillary sinus, Spiro [51] wrote: "As there is no widely accepted staging system for the remaining sinuses or the nasal cavity, no attempt was made to stage tumors arising in these sites." In fact, some authors have tried to stage nasoethmoid tumors. Kadish [52], Biller [53], and Dulguerov [54] proposed a classification for esthesioneuroblastomas. Ellingwood [55] and Roux [56] published a classification for tumors of the nasal cavity and ethmoid–sphenoid sinuses. Despite their historical significance, these classification systems were never tested in large-scale studies to determine their prognostic value. For example, the so-quoted Kadish's

Table 23.1 INT classification of ethmoid tumors

T1	Tumor involving the ethmoid and nasal cavity but sparing the most superior ethmoidal cells
T2	Tumor with extension to, or erosion of, the cribriform plate, with or without erosion of the lamina papyracea and without extension into the orbit
T3	Tumor extending into the anterior cranial fossa extradurally and/or into the anterior two-thirds of the orbit, with or without erosion of the anteroinferior wall of the sphenoid sinus, and/or involvement of the maxillary and frontal sinus
T4	Tumor with intradural extension, or involving the orbital apex, the sphenoid sinus, the pterygoid plate, the infratemporal fossa, or the skin

classification was based on only 17 cases. In 1997, the fifth edition of both the AJCC and UICC guidelines contained an unambiguous staging system for cancers of the maxillary sinus, nasal cavity, and ethmoid sinus. Even if the terms "*infrastructure*" and "*suprastructure*" formally disappeared, the concept of tumors divided by Öhngren's plane having differing prognosis was present in the fifth and sixth edition of the AJCC-UICC guidelines.

In the absence of a universally accepted staging system, we presented in 1997 an original classification for malignant ethmoid tumors [57] based on the most commonly accepted prognostic factors, including involvement of dura mater, intradural extension, involvement of the orbit (particularly the apex), invasion of maxillary, frontal and/or sphenoidal sinus, and invasion of the infratemporal fossa and skin (Table 23.1). In 1999 and in 2005, we tested our original classification for ethmoid tumors (*INT*—Istituto Nazionale Tumori) in terms of prognostic performance versus the fifth and sixth AJCCUICC classifications [58–61]. Both the 1997 and 2002 AJCC-UICC classification systems seemed to have limited prognostic value. In contrast, our INT classification demonstrated the progressive worsening of prognosis with different tumor classes for the overall series, when applied separately to untreated and recurring cases, and when applied only to adenocarcinomas, the most frequent histologic type in our series [62, 63].

In 2006, Dulguerov et al. [64] stated that "while the evolution of TNM staging is a work in continuous progress, the T staging of ethmoid and nasal primaries needs an urgent revision." Nevertheless, the seventh AJCC-UICC classification of nasal cavity and ethmoid sinus tumors published in 2010 remained unchanged [65].

23.6 Imaging

All patients with a malignant tumor of the superstructure must undergo a high-resolution contrast-enhanced computer tomography (CT) in axial and coronal planes and/or a multiplanar magnetic resonance imaging (MRI) enhanced with gadolinium. CT is helpful in determining the erosion of the bones surrounding the paranasal cavities and the involvement of the skull base. Although CT soft tissue windows are essential to evaluate intracranial or intraorbital extension of the tumor, MRI allows a better distinction of tumor from the adjacent soft tissue (orbital contents, dura, brain, cavernous sinus, infratemporal fossa, and carotid artery). Although neck node metastases are unlikely for these tumors, CT or MRI must be extended to the neck, and chest CT or positron emission tomography (PET scan) may be useful to exclude distant metastases.

23.7 Histologic Diagnosis

A biopsy is mandatory for a histologic diagnosis. The biopsy must be made in representative tissue, avoiding necrotic vegetations. An endoscopic approach, sometimes in the operating room, is almost always sufficient for a proper biopsy. An open procedure should be avoided, except in cases where an endoscopic approach is impossible.

We recommend all histologic slides be read separately by two experienced pathologists. Cohen et al. [66] report a high rate of misdiagnosis of olfactory neuroblastoma, as the diagnosis was changed by the pathologists at the M.D. Anderson Cancer Center in 10 out of 12 cases. There were two cases of melanoma, three cases of NEC, three cases of pituitary adenoma, and two cases of SNUC. Eight of 10 patients in whom lesions were misdiagnosed required significant alteration in the initially proposed treatment plan. In our experience, the rate of changing diagnosis is not as high, with our pathologist changing the previous diagnosis in about 20 % of cases. Because the treatment regimens and prognosis of tumor types are often significantly different, the correct diagnosis should be confirmed before initiating treatment to provide the optimum therapy and spare the patient from needless and potentially toxic treatment.

23.8 Prognostic Factors

Significant prognostic factors include the histologic findings of the primary tumor, the presence of neck node metastases, the status of surgical margins, and the extent of intracranial and intraorbital involvement. Tumor histology is statistically related to outcome. Patients with mucosal melanoma and undifferentiated carcinoma (SNUC, NEC, and SCCNET) have the worse outcome, whereas those with minor salivary

gland tumors, esthesioneuroblastomas, and low-grade sarcomas have the best outcomes [28, 67]. However, one must remember that tumors like adenoid cystic carcinoma and esthesioneuroblastoma may recur after a long period of time, so the common reported 5-year survival may be misleading. Patients with ITAC have a better disease-specific survival than those with squamous cell carcinoma [35, 67, 68].

Although neck metastases are rare, their presence, whether upon presentation or later, worsens the prognosis for patients with ethmoid and maxillary sinus tumors. In the ethmoid sinus group of our series, 5-year survival rates were 45.3 % in patients with N0 tumors versus 0 % in those with N+ (N1, N2, or N3) tumors. In the maxillary sinus group, the corresponding 5-year survival rates were 50.6 and 16.8 % [35]. No patients with ethmoid malignant tumors and nodal metastases, either at presentation or during follow-up, survived. For patients with maxillary sinus tumors, the situation was similar, although slightly less dramatic.

Because local failure is the most common cause of death, the status of surgical margins is an important prognostic factor [67, 69, 70]. As tumors of the superstructure often involve the skull base and orbit, patients with these extensions have a worse prognosis. Therefore, craniofacial surgical techniques are mandatory to try to reach negative surgical margins.

23.9 Treatment

The treatment of tumors of the superstructure is by definition a multidisciplinary field. A wide variety of management approaches have been advocated and practiced in the past, and there is currently no standard treatment. The most common approaches involve some combination of surgery, radiation, and chemotherapy. The timing and combination of these three therapeutic means is dictated by the histology, locations, and extensions of the tumor. As surgery often entails a craniofacial approach (open or endonasal-endoscopic), this treatment may also be dictated by the expertise of the surgical team.

Given the rarity of malignant tumors of paranasal sinuses, particularly tumors of the superstructure, the retrospective studies published by individual institutions are often based on a small number of patients with a diversity of histologic findings and tumor extension. Most studies also have selection bias, as higher proportions of patients with favorable lesions are found mainly in the surgery groups, whereas most patients with advanced disease, unfavorable histology, and/or unresectable tumors are found in the (chemo)-radiation groups.

Nevertheless, the combination of surgery and (chemo)-radiotherapy seems to offer better local control than radiotherapy alone, as "the meta-analysis confirmed that surgery and combined surgery and radiation offer better local control and cure rates than radiotherapy alone" [28]. Another study concluded that "surgery and postoperative radiation therapy may result in improved local control, absolute survival, and complications when compared with radiation therapy alone" [29]. Surgery and postoperative (chemo)-radiotherapy is considered the treatment of choice in most centers, even if some continue to prefer primary radiotherapy [71].

23.9.1 Surgery

For many years, surgical treatment of paranasal sinus cancers remained little more than a partial piecemeal resection. Lizars of Edinburgh, in 1826, proposed entirely removing the superior maxillary bone and performed the first resection in 1829. He accurately described the procedure, although he could not remove the posterior portion of the tumor around the pterygoid process [72]. The goal of oncologic surgery is complete resection of the malignant tumor with negative margins, possibly *en bloc*. Unfortunately, given the frequent extensions of these tumors into the orbit, infratemporal fossa, and middle and/or anterior cranial fossa, tumors involving the superstructure were considered unsuitable for a radical resection until the 1960s. Innovative surgical approaches into the pterygomaxillary and infratemporal fossa for tumors with posterior extension were introduced by pioneers such as Conley [73] and Crockett [74]. In 1970, Dingman and Conley [75] wrote, "In the standard maxillectomy, the posterior chisel cut is made in the pterygomaxillary sulcus, thus freeing the maxilla from the lateral process of the pterygoid lamina. Examination of a skull shows that this margin is inconsistent with good tumor management for many maxillary cancers with posterior extensions. Failure at this margin is often responsible for failure to effect local control of the maxillary cancers and has led many clinicians away from surgery as a method of primary treatment. The obvious extension of the maxillectomy operation is the inclusion of the pterygoid plates and muscles to form the posterior margin of the specimen. When the surgeon attempts this by the anterior or Weber-Fergusson approach, he finds that he must develop this critical margin in a cavity filled with blood, within several mm of the internal carotid artery." After this publication, the anterolateral approach became the standard treatment for tumors involving the pterygomaxillary fossa.

Similarly, paranasal sinus tumors invading the skull base (middle or anterior cranial fossa) continued to be considered unresectable. Some isolated reports in the 1950s discussed a craniofacial approach to tumors of the frontal sinus [76, 77]. However, in 1963, Ketcham [78] was the first to report a remarkable series of patients with tumors involving the anterior skull base who were treated with a combined transcranial and transfacial approach. Today, anterior craniofacial

resection continues to be the standard treatment for these tumors, and the prognostic factors have been quite well established [17, 67, 69]. Ketcham, a head and neck surgeon, began his enterprise with Van Buren (a neurosurgeon) and they published articles [79] stressing the importance of this collaboration: "Although some may consider a neurosurgeon helpful but not necessary for this surgical undertaking, his preoperative evaluation and intraoperative handling of the skull, dura, and sometimes the brain contributes to a lower rate of complications and a greater cure rate."

Given the concept of a double approach (Fig. 23.1), surgical resection must be tailored to the tumor's specific extension. For an ethmoid tumor involving the anterior cranial fossa but sparing the maxillary sinus and the orbit, a total ethmoidectomy with medial maxillectomy is the standard treatment. The anterior and inferior walls of the sphenoid sinus and the lamina papyracea must always be removed to allow for a radical resection (Fig. 23.2). For tumors with intracranial extension, the dura should always be resected and reconstructed, especially when infiltrated. Intradural invasion is usually a contraindication for surgery. In our series of anterior craniofacial resections for superstructure malignant tumors, only some patients with esthesioneuroblastomas and intradural extension survived [17].

When the tumor has invaded the lamina papyracea, the medial periorbital layer should be resected, even if it is uninvolved. An orbital exenteration is required if the tumor has invaded the orbit deeply. Sometimes the orbital contents may be preserved, but the medial and inferior walls of the orbit must be removed. In these cases, alloplastic materials and free bone grafts are not a good choice for reconstruction as most of these patients will undergo postoperative radiotherapy, with probable extrusion of these materials. In spite of reconstruction with vascularized flaps, patients may complain of possible dysfunction of the eye, especially if postoperative radiotherapy is used [80].

For tumors involving the anterior cranial fossa, the posterior wall of the maxillary sinus, and the infratemporal fossa, a combined anterior craniofacial and infratemporal approach is mandatory, as the pterygoid plates and muscles must be removed. Sometimes the greater wing of the sphenoid may also be infiltrated requiring an anterolateral craniofacial resection [81] (Fig. 23.3). Following these resections, especially orbital exenterations, a vascularized free flap is required for a good functional and cosmetic reconstruction.

In the last decade, a number of papers have discussed endoscopic resection of malignant tumors involving the anterior skull base. While most include a small number of

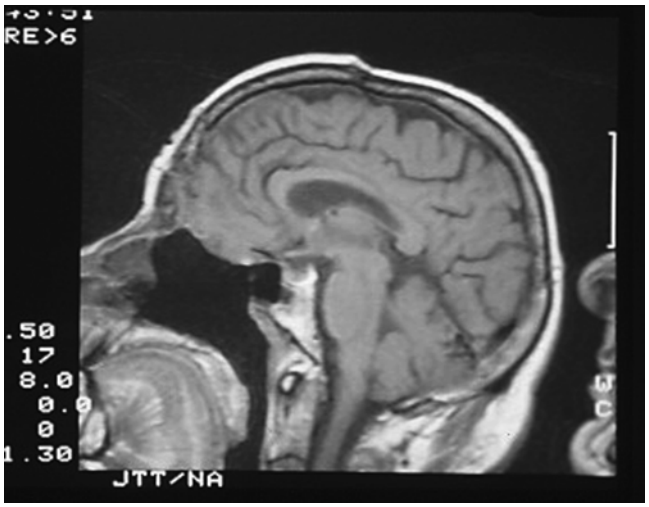

Fig. 23.2 Sagittal postoperative MR image showing total ethmoidectomy with resection of the anterior wall of the sphenoid sinus

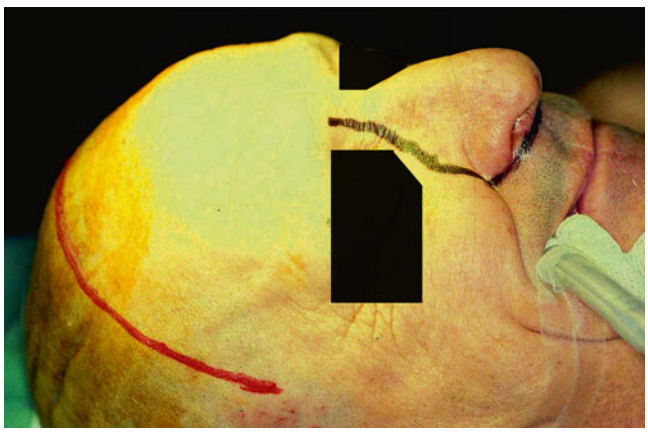

Fig. 23.1 Our standard coronal and lateral rhinotomy incision for an anterior craniofacial resection. The lateral rhinotomy incision without lip-splitting provides adequate exposure for total ethmoidectomy and medial maxillectomy

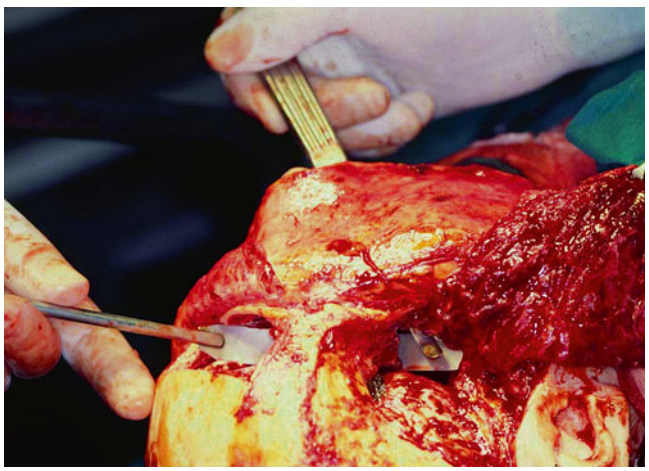

Fig. 23.3 Anterolateral craniofacial resection for a superstructure tumor involving both anterior and middle cranial fossa. After the resection of the tumor, the surgical instruments, introduced through the transfacial and anterior transcranial approaches, cross in the infratemporal fossa where the temporal lobe is exposed

patients with brief follow-up, one paper from two Italian university hospitals reports a number of purely endoscopic resections for T1–T2 ethmoid adenocarcinoma (12 cases) and squamous cell carcinoma (4 cases), with a median follow-up of 47 months. The 5-year disease-specific survival of these patients was 93 % [82]. In a following paper from the same institutions, 134 patients were treated with an exclusively endoscopic approach (EEA), while 50 cases underwent a combined cranioendoscopic approach (CEA) [83]. The 5-year disease-specific survival was 91 % for patients treated with EEA and 58 % for those treated with CEA. Tumor size differed between the two groups, with the larger tumors requiring CEA. Nevertheless, the authors conclude that when properly planned and completed by an experienced surgeon, endoscopic surgery is a valid alternative to standard surgical approaches for the management of selected malignancies of the sinonasal tract.

Hanna et al. [84] presented a series of 120 patients with biopsy-proved malignant neoplasm of the sinonasal region who were treated with endoscopic resection between 1992 and 2007: 93 (77.5 %) were treated with EEA and 27 (22.5 %) with CEA. Only 10 % of the tumors had an intracranial epicenter, most commonly around the olfactory groove. Tumors extended to or invaded the skull base in 20 % and 11 % of the patients, respectively. In summary, only 41 % of tumors involved the anterior skull base. An intracranial epicenter and extension to or invasion of the skull base were significantly more common in patients treated with CEA than in those treated with EEA. Actually, the T-stage distribution was significantly different between the EEA group and the CEA group. Approximately two-thirds (63 %) of the patients treated with EEA had a lower (T1-2) disease stage, while 95 % of patients treated with CEA had a higher (T3-4) disease stage. The 5- and 10-year disease-specific survival rates were 87 % and 80 %, respectively. Disease recurrence and survival did not differ significantly between the EEA group and the CEA group. The authors' conclusion was: "Our results suggest that, in well-selected patients and with appropriate use of adjuvant therapy, endoscopic resection of sinonasal cancer results in acceptable oncologic outcomes."

In order to state the possibilities and limits of the EEA, a group of internationally recognized experts from many disciplines have been invited by the European Rhinologic Society to contribute to an Advisory Board, which has considered the present knowledge and published evidence concerning endoscopic techniques in the management of tumors affecting the nose, paranasal sinuses, and adjacent skull base. The conclusions of this Advisory Board have been published in an outstanding paper [85] where we may find some important questions and precise definitions: "Is *en bloc* resection necessary in sinonasal tumors? Can tumor-free margins be achieved during endoscopic resection with the same degree of accuracy as conventional open approaches? Questions which could and should be answered are the survival rates in both groups in relation to morbidity and to determine the most relevant stratification variables."

We agree totally with this conclusion and believe that regardless of method, resection of the sinonasal component of the tumor must be radical, especially with intestinal type adenocarcinomas. As mentioned above, ITAC is a professional disease involving the whole ethmoid sinus. As the metaplastic transformation of ethmoidal mucosa to enteric-type epithelium precedes the development of enteric adenocarcinoma [86, 87], pre-neoplastic or neoplastic foci may be present in macroscopically uninvolved sites of ethmoid. In some cases, we found small tumor localizations in the contralateral ethmoid [11]. These foci were separate from the apparent primary tumor and undetected by CT, MRI, and PET. As ITAC is a locally aggressive tumor that easily infiltrates the underlying bone [27], we believe that a total ethmoidectomy must always be performed. In the 1980s and 1990s, we resected many "relapses" of ITAC after an incomplete ethmoidectomy performed with only a paranasal incision. In the 2000s, we began to operate a lot of "relapses" after an unsuitable and incomplete endoscopic resection (Fig. 23.4).

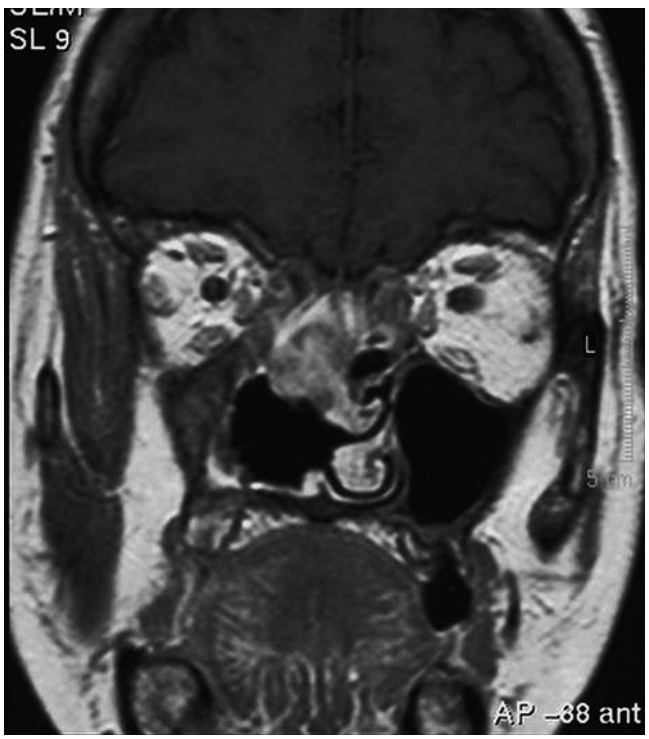

Fig. 23.4 Coronal MR image of the relapse of an ITAC after an incomplete endoscopic resection

23.9.2 Radiotherapy

There are few large-scale studies of patients with paranasal sinus malignant tumors treated with radiotherapy alone, and especially superstructure tumors. The majority of papers looked at a small number of patients and included those who received postoperative radiotherapy and those treated with radiotherapy alone, but received surgery if radiotherapy failed. Almost all these papers reported that combined surgery and radiotherapy worked better than RT alone. Katz et al. [29], discussing their experience in treating malignant tumors of the nasal cavity, and paranasal sinuses (excluding the nasal vestibule and the maxillary sinus), state that "until approximately 17 years ago, most nasal cavity and paranasal sinus tumors were treated with high-dose irradiation alone at the University of Florida. On the basis of our experience, a change in treatment philosophy has occurred such that most patients undergo resection followed by postoperative irradiation. Surgery alone may be acceptable for very early cancers of the nasal cavity. Radiation therapy alone is used in patients with unresectable disease." Another paper on sinonasal undifferentiated carcinoma from the same institution makes a similar statement: "Our current guidelines are to treat patients with apparently resectable tumor with craniofacial resection and postoperative RT" [88]. Guntinas-Lichius et al. [89] report on 229 patients with nasal and paranasal sinuses cancer treated at a single institution. Although the study suffers from selection bias, patients treated surgically had higher overall survival rates than patients who only received radiotherapy. The multivariate analysis for overall survival revealed that the type of therapy was an independent risk factor. Surgery combined with radio(chemo)therapy achieved better results in comparison to radio(chemo)therapy alone.

Tanzler et al. also wrote that "one advantage associated with combined surgery and RT is that it may be possible to reduce the RT dose and thus reduce the risk of RT-induced optic neuropathy" [88]. Regarding the use of modern radiotherapy techniques in the postoperative setting, the same authors wrote "Hyperfractionated RT is employed to further reduce the risk of injury to the visual apparatus. Intensity modulated radiotherapy (IMRT) and/or proton beam therapy may be useful to produce a more conformal dose distribution to reduce the dose to normal tissues and, thus, late toxicity" [88]. A paper from the Memorial Sloan-Kettering Cancer Center draws a similar conclusion: "Complete surgical resection followed by adjuvant RT is an effective and safe approach in the treatment of paranasal sinus cancer. Emerging tools, such as three-dimensional conformal treatment and, in particular, intensity-modulated RT for paranasal sinus tumors, may minimize the occurrence of late complications associated with conventional RT techniques" [90].

Regarding neutron radiotherapy, Douglas et al. [91] report a 5-year actuarial local-regional control of 59 % of tumors that do not involve the cavernous sinus, base of skull, or nasopharynx. The local-regional control was significantly lower for patients with tumors involving these sites (15 %). In a following paper [92], the same authors stated that "variables associated with decreased local-regional control in the patients with gross residual disease as determined by multivariate analysis included base of skull involvement and biopsy only versus an attempted surgical resection prior to treatment." For proton beam radiation, Pommier et al. [93] concluded that tumor involvement of the sphenoid sinus and clivus are adverse prognostic factors. In a review on proton therapy in clinical practice, Brada et al. [94] concluded that "the lack of available evidence in favor of protons does not mean that protons may not be useful in selected tumors. It should be a stimulus for more research, particularly in the form of appropriately designed and powered prospective studies."

More recently, hadrontherapy in oncology attracted a large interest. Hadrontherapy is an innovative form of radiotherapy, based on high-technology equipment using proton or carbon ion beams to destroy tumors. Carbon ions are specifically characterized by superior biological efficacy (relative biological effectiveness from 1.5 to 3), overcoming the radiation resistance of certain cancers to photons and even protons. Indeed, carbon ion beams when compared to X-rays represent a distinct advantage for the treatment of highly radiation-resistant tumors (68 skull base tumors) [95]. In June 1994, the world's first clinical center offering carbon ion radiotherapy (Heavy Ion Medical Accelerator in Chiba, HIMAC) opened at the National Institute of Radiological Science (NIRS) in Japan. As of March 2010, 5196 patients have been registered [96]. Between April 1997 and February 2006, 236 patients with locally advanced, histologically proven, and new or recurrent cancer of the head and neck were treated with carbon ions [97]. The 5-year local control rate, by histological type, was 75 % for the 85 patients with malignant melanoma, 73 % for the 69 with adenoid cystic carcinoma, 73 % for the 27 with adenocarcinoma, 61 % for the 13 with papillary adenocarcinoma, 61 % for the 12 with squamous cell carcinoma, and 24 % for the 14 with sarcomas. The 5-year overall survival rate was 68 % for adenoid cystic carcinoma, 56 % for adenocarcinoma, and 35 % for malignant melanoma. The conclusion of the authors is: "Carbon ion radiotherapy for head and neck cancer showed the therapeutic effectiveness for malignant melanoma and adenoid cystic carcinoma without severe morbidity of the normal tissues."

23.9.3 Chemotherapy

Chemotherapy alone is normally reserved for cancers of the superstructure that are too advanced to be treated by surgery

or radiotherapy, patients presenting with metastatic disease, or those with recurrent disease. However, chemotherapy may have a role into complex multimodal treatment plans along with surgery and radiotherapy.

Beginning in 1970, some Japanese authors reported high cure rates with a combination of intra-arterial chemotherapy with 5-fluorouracil (5-FU), necrotomy, and radiotherapy. Using these treatment combinations, Sato et al. [98] and Sakai et al. [99] achieved a 5-year cumulative survival rate of 67 % and 54 %, respectively. Other Japanese authors were unable to reproduce these results, concluding that the addition of intra-arterial chemotherapeutic agents to either surgery [100] or radiotherapy [101] did not improve survival. Shibuya et al. [102] ascribed these contradictory results to the fact that the maxillary tumors receive blood from not only the internal maxillary artery, but also the facial and ethmoidal arteries. These latter arteries arise from the internal carotid artery and are the main feeding vessels of tumor of the ethmoid. This diverse blood flow may cause an irregular distribution of the intra-arterially infused antimetabolites, leading to decreased effectiveness. In order to prevent this situation, physicians have combined superselective intra-arterial chemotherapy with radiotherapy and surgery in the last decade. Studies of this treatment method have reported a 5-year survival of 75 and 53 % [103, 104].

Knegt et al. reported an interesting experience using surgical debulking, low dose of irradiation, topically applied cytostatic drug (5-FU), and necrotomy [105]. The actuarial 5-year survival rate for squamous cell carcinoma and undifferentiated carcinoma of the maxillary sinus was 52 % and 100 % for patients with adenocarcinoma of the ethmoid sinus. A subsequent paper by the same authors reported their experience in treating 62 patients with ethmoid adenocarcinoma. They performed surgical debulking via an extended anterior maxillary antrostomy followed by a combination of repeated topical chemotherapy (fluorouracil) and necrotomy. Eight patients (13 %) required additional radiotherapy for local recurrence, while one patient required surgery for regional lymph node metastases. Adjusted disease-free survival at 10 years was 74 % [106]. However, we only know of one other reported on this approach to ethmoid adenocarcinoma [107].

There are few reports on the use of systemic chemotherapy in paranasal sinus carcinoma, and sinus squamous cell cancer is not included in many head and neck prospective randomized trials on chemotherapy and/or radiotherapy. The most often applied schedules were platinum based, with a response rate ranging from 36 to 84 % [108]. The combination of primary chemotherapy, surgery, and postoperative (chemo)radiotherapy achieved very high cure rates [109], particularly in cases with pathologic complete remission (pCR) after neoadjuvant chemotherapy [110, 111].

The ability to predict complete response to primary chemotherapy by analyzing predictive biomarkers, such as TP53, is critical to determining the usefulness of chemotherapy. In National Cancer Institute of Milan, 30 patients with ethmoidal ITAC have been enrolled in a phase II study using cisplatin, fluorouracil, and leucovorin (PFL) followed by craniofacial resection and radiation. On surgical specimens, absence of viable tumor cells was defined as pCR. The TP53 status and p53 function, analyzed on pretreatment biopsies, were retrospectively correlated with pathologic results and patient outcome. In patients with wild-type (wt) TP53 or functional p53 protein, pCRs were seen in 83 % and 80 % of patients, respectively. However, only 11 % of patients with mutated TP53 achieved pCR, whereas no patients (0 %) with an impaired p53 protein had pCR. At a median 55-month follow-up, all pCR patients were disease free, while 44 % of nonresponsive patients experienced relapse. These results indicate that differences in TP53 mutational status or protein functionality strongly influence pathologic response to primary chemotherapy and ultimately prognosis. PFL seems to be highly effective in patients with a functional p53 protein, even when encoded by a mutated TP53 gene. However, ITAC patients carrying a dysfunctional p53 protein will not respond to PFL [112, 113]. The fact that less than 50 % of ITAC patients have a functional p53 protein diminishes the enthusiasm over these results.

23.10 Conclusions

The actual prognosis for malignant tumors of the superstructure is still difficult to determine. The reported 5-year local control and survival rates are somewhat unreliable, as these studies include patients with different histologies, localizations, extensions, and treatment strategies. In spite of the best modern treatments available, the prognosis of these tumors continues to be disappointing. Many patients present with advanced-stage tumors and with intracranial and intradural extension. In our studies of ethmoid tumors [17, 68], the prognosis of adenocarcinomas and esthesioneuroblastomas was better than for the other histologic types. In particular, the prognosis was very unfavorable for melanomas. Epidermoid carcinomas also had a poor prognosis due to a large number of undifferentiated types. Patients with adenoid cystic carcinomas had a good overall survival, but only a short disease-free survival, as these patients may survive for a long time after local recurrence or lung metastases. Untreated patients had better results compared to patients with relapses after previous treatment, suggesting that for these tumors, the first treatment is often the only treatment. The cure rates of patients with a tumor involving the middle cranial fossa are very low. For

these patients, we may only perform surgery to improve the quality of their remaining life [81].

In conclusion, we must employ multidisciplinary treatments for these tumors, and translational research must continue to help improve how and when such treatments are used.

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Multidisciplinary Management of Oral Cavity and Maxillary Sinus Cancers

24

Alexander D. Rapidis

Abstract

During the last 30 years the belief that oral/head and neck cancer management is based on team work has been established. The functions of tumor boards and combined clinics is a common contemporary practice with an exceedingly large number of medical, surgical, and other specialties being part of comprehensive, multidisciplinary therapeutic head and neck teams. The basic treatment modalities remain surgery, radiotherapy, and chemotherapy.

Basic surgical techniques have not changed dramatically over the last 30 years. Among the major changes are the variations in the surgical management of the neck of both clinically negative and clinically positive neck patients, as well as the management of the mandible especially in the early invasion of oral squamous cell carcinoma in the mandibular bone. The revolution in the surgical treatment of oral/head and neck cancer is the introduction of reconstructive techniques with both pedicled locoregional flaps and free tissue transfer. These reconstructive techniques allowed for safer and wider resections with adequate disease-free margins and functional reconstruction of the created surgical defects.

Contemporary radiotherapeutic treatment has very little similarities with that of the late 1970s. Modern technology with the institution of new forms of radiation and the application of sophisticated computerized methods have enhanced the therapeutic effectiveness of irradiation with an equal important reduction in the sparing in irradiation of normal surrounding tissues. This has led to an increased therapeutic dose in the tumorous site and a decreased severity of radiation-induced injuries. Alterations in the fractionations have also shown to produce better therapeutic results in selected cases.

The era of methotrexate, the leading chemotherapeutic agent of the 1970s, was followed by the institution of platinum-based chemotherapies with or without the addition of 5 Fu. Adjuvant and neoadjuvant schemes coupled with pre- or postoperative radiotherapy started in the late 1980s and showed a distinct survival benefit over radiotherapy alone. This major breakthrough was followed by the institution of various and diverse chemoradiation regimes tested over a large time period for their survival benefits. The introduction of taxanes and the development of molecular targeted therapies during the last 5 years have revolutionized the concept of chemoradiation. Induction chemotherapy and chemoradiation coupled with epidermal growth factor receptor antagonists proved to have a survival benefit in patients with locally advanced or recurrent squamous cell carcinoma of the head and neck. Other biological agents against tumor angiogenesis or restoring cell apoptosis are being tested in various phase I or II trials.

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Perhaps the most promising noninvasive therapeutic method for squamous cell carcinoma of the oral mucosa is immunotherapy. The clinical applications so far are very limited but the research into these pathways vast and extended.

Keywords
Oral squamous cell carcinoma • Head and neck tumors • Oral cavity cancer • Head and neck cancer • Treatment of the oral cavity cancer • Maxillary carcinoma • Chemoradiation • Induction chemotherapy • Targeted therapies • Combined treatments

24.1 Introduction

Cancer of the oral cavity comprises nearly 30 % of all malignant tumors of the head and neck. Oral cavity cancers include primary tumors of the lip, floor of the mouth, oral tongue, lower and upper alveolar ridge, retromolar trigone, hard palate, and buccal mucosa. Squamous cell carcinoma represents approximately 90 % of the cases [1], while the remaining 10 % represents rare malignancies (unusual forms of squamous cell carcinoma, minor salivary gland tumors, melanomas, lymphomas, sarcomas) and a variety of malignant tumors of odontogenic origin. Lifestyle, habits, and demographic as well as genetic factors influence geographic variations in the incidence of disease. In North America, common risk factors for the development of cancer of the oral cavity include tobacco and alcohol use. Outside of North America, dietary habits, like chewing beetle, areca nut, and tobacco, represent additional risks for the development of oral cancer. Beyond these risks, there is little evidence linking dietary factors or nutritional deficiencies to the development of oral cavity cancer especially low fruit and vegetable consumption and high fat and/or sugar intake. The highest rates of incidence of cancer of oral cavity are observed in Pakistan, Brazil, India, and France [2]. While the use of alcohol and tobacco independently represents risk factors for the development of oral cavity cancer, the synergistic effect of these risk factors has been well documented. It has been suggested that the use of alcohol suppresses DNA repair following exposure to nitrosamine compounds; however, the exact mechanism of the observed synergy remains poorly defined. Human Papillomavirus (HPV) is strongly associated with the development of oropharyngeal cancer and a small percentage of oral cavity cancers [3]. Over the past 30 years, the proportion of potentially HPV-related oral cancer in the United States has increased, possibly due to changing sexual behaviors especially in the young population. This probably explains the increasing number of patients with oral carcinoma who had never been exposed to tobacco or alcohol.

During the last 30 years, there has been an explosion of accumulated knowledge and evidence in our understanding of the biological phenomenon of oral carcinogenesis as well as in the technological advances in the diagnosis of the disease in both the histopathological and clinical levels. An equal abundance of knowledge has been achieved in the therapeutic management of the disease from the combined uses of surgery, radiotherapy, and chemotherapy. Despite all these developments, the 5-year overall survival of the disease has remained in the range of 50–60 %. The quality of life though of the patients, which has become a major issue, has undoubtedly improved during these 30 years [4].

24.2 Principles of Oral Cavity Cancer Management

The treatment of primary tumors from different head and neck subsites often overlaps. Treatment for oral cavity cancer in general is highly complex, not only because of the variety of tumor subsites, but also because of the anatomic constraints of the head and neck region, and the importance of maintaining organ function after treatment.

The factors that influence the choice of initial treatment are those related to the characteristics of the primary tumor, those related to the patient, and those related to the therapeutic team (Tables 24.1, 24.2, 24.3, 24.4, 24.5, and 24.6) [5]. They are therefore classified under tumor, patient, and treatment factors. In the selection of optimal therapy for oral carcinoma, one should consider these three sets of parameters in primary treatment planning. The ultimate goal of treatment of cancer of the oral cavity is to eradicate disease, preserve or restore form and function, minimize the sequelae of treatment, and finally prevent the development of any subsequent new primary cancers. The tumor factors that affect the choice of initial treatment of oral cancer represent the clinical and histopathological characteristics of the tumor and, more specifically, the anatomical site, size (T stage), location (anterior versus posterior), proximity to bone (mandible or maxilla), status of regional cervical lymph nodes, previous treatment, and histology (type, grade, and depth of invasion). The ability of the patient to tolerate an optimal therapeutic scheme is similarly an important factor influencing the choice of initial treatment. The patient's acceptance of and compliance with the proposed treatment are similarly important considerations in designing an optimal treatment strategy.

Table 24.1 Staging for tumors of the lip and oral cavity

T (primary tumor size)
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor 2 cm or less in greatest dimension
T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3 Tumor more than 4 cm in greatest dimension
T4a Lip Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face (i.e., chin or nose)[a]
Oral Cavity Tumor invades through cortical bone, into deep extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face
T4b Tumor involves masticator space, pterygoid plates, or skull base and/or encases internal carotid artery

[a]Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify as T4.
Based on data from Ref. [5]

Table 24.2 Staging for tumors of the nasal cavity and paranasal sinuses

T (primary tumor size)
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
Maxillary sinus
T1 Tumor limited to the maxillary sinus mucosa with no erosion or destruction of bone
T2 Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T3 Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
T4b Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve V2, nasopharynx, or clivus
Nasal cavity and ethmoid sinus
T1 Tumor restricted to any one subsite, with or without bony invasion
T2 Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3 Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
T4a Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4b Tumor invades any of the following: orbital apex, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx, or clivus

Based on data from Ref. [5]

Table 24.3 Staging for all head and neck sites except the nasopharynx and thyroid

N (regional nodal status)
Nx Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2 Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3 Metastasis in a lymph more than 6 cm in greatest dimension

Based on data from Ref. [5]

Table 24.4 Staging for head and neck tumors

M (distant metastasis)
Mx Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Based on data from Ref. [5]

Table 24.5 Stage grouping for all head and neck sites except the nasopharynx and thyroid

Stage group	T stage	N stage	M stage
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
IVB	T4b	Any N	M0
	Any T	N3	M0
IVC	Any T	Any N	M1

Based on data from Ref. [5]

Table 24.6 Algorithm of stage status in cancer of the oral cavity

Staging of oral cavity cancer				
	N0	N_1	N_2	N_3
T_{1S}	**Stage 0**			
T_1	**Stage I**			
T_2	**Stage II**			
T_3		**Stage III**		
T_{4a}			**Stage IVA**	
T_{4b}				**Stage IVB**
Stage IVC any T any N when M1				

Additionally, the performance status, the previous medical history, and the presence of additional comorbidities should also be taken into consideration. The factors related to the therapeutic team are also important and are related with the experience, dexterity, ability, and availability of technical support of the surgical team and its environment. Expertise in various disciplines including surgery, radiotherapy, chemotherapy, rehabilitation services, dental, and psychosocial support are all crucial in bringing about a successful outcome of the therapeutic program.

For the purpose of providing an overview of treatment strategies in oral cancer patients, it is mandatory to group the oral squamous cell cancers into early-stage disease (stages I and II; no apparent lymph node involvement) and advanced disease which includes cancer metastatic to cervical lymph nodes (regionally advanced) and locally advanced primary tumors (stages T3 andT4).

24.3 Early-Stage Disease

Approximately 30–40 % of patients with oral cavity cancer present with early (stage I and II) disease. In general, these patients are treated with curative intent using either surgery or radiotherapy (RT). Because both modalities result in similar rates of local control and survival, the choice is usually based

upon an assessment of competing morbidities, functional outcomes, and accessibility. One advantage of RT over surgery is the ability to electively encompass areas at high risk for subclinical involvement (i.e., cervical lymph nodes). Prophylactic treatment of the clinically negative neck (i.e., no evidence of pathologic lymphadenopathy either by clinical examination or radiographic study) is somewhat controversial. However, in general, prophylactic neck irradiation or lymph node dissection is recommended if the likelihood of neck recurrence at a specific site exceeds 15 %. Generally in tongue cancer, the incidence of nodal metastasis depends upon the stage of the tumor. T1, T2, and T3 tongue cancers are associated with 30 %, 50 %, and 70 % respective incidence of microscopic nodal metastasis. Selective neck dissection can be used to effectively treat clinically positive nodal disease in selected patients [6, 7].

As surgical cures can often be achieved rapidly and with minimal morbidity, surgery has become the gold standard for management of early cancers of the oral cavity. Tumors involving the oral tongue can usually be managed through a transoral approach. While radiotherapy is equally effective for the treatment of early disease, the rates of long-term sequelae including xerostomia, dysphagia, and osteoradionecrosis are unacceptably high. Other advantages of surgery include the duration of treatment. Surgical therapy requires a single intervention, while RT requires daily therapy over a period of several weeks in addition to possible catheter implants and the use of chemotherapy. Therefore, in resectable patients RT is usually reserved for those patients who are unable to undergo surgery [8].

24.4 Advanced-Stage Disease

Advanced disease (stages III and IV) of the oral cavity is best managed with multimodality therapy. Surgery coupled with preoperative or postoperative RT is often utilized for advanced disease. Although preoperative radiation has been proposed to decrease the tumor mass and therefore increase the "resectability" of the tumor, it is common practice to surgically resect the tumor based on the pre-radiation margins because islands of viable tumor may persist in the initial peripheral margins. Additionally, preoperative radiation is associated with a higher rate of postoperative complications. For these reasons, most centers perform surgery followed by postoperative radiation [9, 10].

24.5 The Role of Radiotherapy (RT) and Chemoradiotherapy (CRT) as Treatment Modalities in Oral Cancer

The current standard technique for delivery of RT to tumors involving the oral cavity is three-dimensional conformal RT (3D-CRT). As opposed to the historically two-dimensional planning which relied on simulation X-ray films, treatment planning with 3D-cRT is based upon three-dimensional information that is obtained on simulation CT scans. The radiation dose distribution is shown in three dimensions and doses to the treatment target as well as various organs are more accurately calculated. Modification of beam properties can be performed if needed to produce a conformal dose distribution to the treatment target [11].

Although primary surgical management has been advocated for advanced (T4) oral cavity cancers, recent evidence suggested that primary CRT may be an effective treatment approach for selected patients with T4 lesions, with comparable rates of locoregional control, survival, and complications associated with primary surgical management and postoperative RT [12].

Xerostomia is the most common late side effect of radiotherapy to the head and neck. Compared with conventional radiotherapy, intensity-modulated radiotherapy (IMRT) can reduce irradiation of the parotid glands. Nutting et al. [13] in a randomized controlled trial assessed the hypothesis that parotid-sparing IMRT reduces the incidence of severe xerostomia. The trial compared conventional radiotherapy (control) with parotid-sparing IMRT. The findings from this study showed that sparing the parotid glands with IMRT significantly reduces the incidence of xerostomia and leads to recovery of saliva secretion and improvements in associated quality of life. Over the last few years, IMRT has been implemented in most radiation oncology centers and is becoming a dominant treatment technique for head and neck cancer. With the assistance of advanced computer technology, IMRT is capable of delivering radiation doses that are highly conformal to the target, with rapid dose falloff outside of target volumes. This technique permits high doses of RT to be delivered to tumors which lie in close proximity to critical normal organs [14]. The newest technology, image-guided radiation therapy (IGRT), is being introduced into radiation therapy practice. A CT scanner is incorporated into the linear accelerator, allowing target position verification in the treatment position. The capacity for near real-time imaging during treatment permits tumors to be treated with greater precision and accuracy than is possible with conventional IMRT, further reducing toxicity to normal tissues.

For conventional fractionation RT, the dose for all gross disease (primary and nodal) is 70–72 Gy in 2 Gy fractions over 7 weeks. Subclinical regions of the neck are electively treated to 50 Gy in 25 fractions, while nodal regions with adjacent gross disease may receive 60 Gy in 30 fractions. IMRT also allows for the delivery of smaller radiation doses to the major salivary glands, thus reducing the risk of permanent post-irradiation xerostomia.

Most oral cavity tumors as with the majority of head and neck cancer typically present with advanced-stage locoregional disease (stage III or IV) for which local and regional control with surgery and/or radiation has been the mainstay

treatment. After the publication of the trials on larynx preservation strategies in both Europe and the United States [15, 16], there was a rapid proliferation of non-site-specific trials to further investigate organ preservation protocols in the treatment of advanced head and neck squamous cell carcinoma. Over 70 divergent randomized trials compared traditional locoregional treatments of surgery and radiation versus locoregional treatment plus chemotherapy. Unfortunately, this enthusiasm was plagued by small sample sizes and a lack of statistical power to confidently detect even modest effects on survival, leading to mixed results and an obscured clinical picture [17–19].

Concomitant CRT may represent an acceptable alternative in selected advanced stages of oral cancer patients. In addition to the optimal combination of drugs, the role of altered fractionation RT schedules is also under active study [20]. Two main strategies of altered fractionation have been explored in order to increase the effective dose of RT delivered without magnifying toxicity. Hyperfractionation that delivers smaller doses of RT twice daily (1.1–1.2 Gy fractions compared to conventional daily 1.8–2.0 Gy fractions) allows higher doses of RT to be administered (thereby improving local control) without a significantly higher risk of late complications [21].

Because delayed long-term toxicity of normal tissues is dependent on the size of the individual fractional dose, decreasing the size of each radiation fraction should permit utilization of higher total doses without increasing late morbidity [22]. In practice, multiple daily treatments with smaller than conventional fraction sizes are given over approximately the same treatment duration. Typically 1.1–1.2 Gy/fraction two fractions per day to total doses of 74–80 Gy have been employed. Accelerated fractionation RT schedules deliver the total dose of RT in shorter treatment duration. This seems to reduce the rapid tumor repopulation that is thought to occur during treatment interruptions [21].

A benefit for hyperfractionated compared to conventional fractionation RT in patients with locally advanced head and neck cancer has been shown in at least three prospective, randomized trials [22–24] and in meta-analyses of these trial data [15, 21].

Even in the absence of chemotherapy, significantly higher local control rates have been documented with both strategies compared to conventional fractionation RT alone, although demonstrating a survival benefit from either approach has been more difficult [25]. Taken together, these data support the view that accelerated treatments using split-course RT schedules or reduced total doses do not improve locoregional tumor control or overall survival. Accelerated treatments that employ continuous (rather than split-course) RT schedules, without compromising the total dose, improve local control [22]. However, whether the added mucosal toxicity is justified by meaningful gains in survival remains an open question. Altered fractionation RT is considered by some to represent a standard approach for patients who are receiving RT alone as definitive treatment for oral cancer.

However, it is important to clarify that the indications for postoperative RT directed to the primary site are different from the indications for postoperative radiation directed at the neck. The goal of a surgical excision is to achieve a complete resection of the tumor with tumor-free margins. In cases where there are positive or close margins (tumor within 5 mm of the surgical margin), surgical re-resection is usually recommended. In cases where a re-resection is performed, if there remains evidence of microscopically positive margins, radiation directed at the primary site should be considered. In cases where there is neck disease that is N2 or greater, or the histopathological characteristics of the primary tumor demonstrate an aggressive behavior [26], radiation therapy to the neck is warranted, usually administered with concurrent chemotherapy [27, 28].

Definitive RT, usually administered with cisplatin-based chemotherapy, is the treatment of choice for patients with potentially resectable locoregionally advanced oral cancer who desire organ preservation, for those who have surgically unresectable disease, or who are medically inoperable. Although direct comparative data are lacking, combined use of chemotherapy and RT appears to produce similar locoregional control and survival rates as does surgery, while providing the opportunity for function preservation [25].

Chemotherapy can be administrated before, at the same time, or after locoregional treatment corresponding to induction, concomitant, or adjuvant chemotherapy. There are several other potential advantages to giving neoadjuvant rather than postoperative (adjuvant) chemotherapy. These include the delivery of chemotherapeutic drugs through an intact vasculature which is optimal to enhance its therapeutic effectiveness before surgery or radiation. The neoadjuvant treatment is more likely to treat micrometastases, thus diminishing the chances of developing gross metastatic disease. Finally, the reduction in tumor size and healing prior to definitive RT may improve functional outcomes.

The response to chemotherapy may be an important predictor of survival, as various studies have shown that patients with a good response to induction chemotherapy have a better overall survival [4, 29, 30]. A thorough meta-analysis of randomized trials showed that adding cisplatin concurrently to radiotherapy improved progression-free survival (PFS), overall survival (OS), and organ preservation, but only approximately 50 % of patients survived more than 5 years [31]. Moreover, radiation-cisplatin regimens induce severe acute and late morbidity [32]. These observations inspired the search for alternative therapy approaches.

A greater benefit (8 %) was observed in trials that gave CT concomitantly to RT. Effect of concomitant CT on survival did not differ significantly between the group of trials

with postoperative RT or curative RT with conventional or altered fractionation. No significant difference was also seen between mono- and poly-chemotherapy. In the poly-chemotherapy group, the effect of chemotherapy was not significantly different between the different subgroups: with cisplatin or carboplatin (platin) and 5-fluorouracil (5-FU), with either platin or 5-FU, or with neither [31, 33]. As might be expected, the proportion of deaths not due to head and neck cancer increases progressively with age from 15 % in patients less than 50 to an impressive 39 % in patients 71 and over. The survival benefit resulting from the addition of CT to RT is confirmed to be around 4 %. This benefit is larger for concomitant CT, whereas there was no clear evidence of a benefit for induction and adjuvant CTs. Another important issue is that the benefit of concomitant CT appears to be similar irrespective of whether the RT is given conventionally or using altered fractionation. Finally, the magnitude of the benefit of concomitant CT is less in older patients, a feature that has also been observed with altered fractionation compared to conventional RT in head and neck cancer [21] and also when combining anti-EGFR agents (cetuximab) with radiotherapy [34–36]. One strategy to improve the efficacy of treatment is to add molecular targeted agents to classical chemoradiotherapy regimens. Cetuximab, the first targeting strategy to demonstrate survival advantage for patients with HNSCC, has emerged in the context of epidermal growth factor receptor (EGFR) biology [34, 37]. In a recent meta-analysis, the comparison of the benefit associated with concomitant versus induction CT was examined. It is interesting that both the indirect and the direct comparisons were consistent on survival, event-free survival, and locoregional failure, showing a clear advantage in favor of concomitant CT [38, 39].

Combining cisplatin or cetuximab with radiation improves OS of patients with stage III or IV head and neck carcinoma. Cetuximab plus platinum regimens also increase OS in metastatic head and neck carcinoma. The Radiation Therapy Oncology Group launched a large phase III trial to test the hypothesis that adding cetuximab to the radiation-cisplatin platform improves PFS [40]. Of 891 analyzed patients, 630 were alive at analysis (median follow-up, 3.8 years). Cetuximab plus cisplatin-radiation, versus cisplatin-radiation alone, resulted in more frequent interruptions in radiation therapy (26.9 % vs. 15.1 %, respectively), similar cisplatin delivery (mean, 185.7 mg/m^2 vs. 191.1 mg/m^2, respectively), and more grade 3–4 radiation mucositis (43.2 % vs. 33.3 %, respectively), rash, fatigue, anorexia, and hypokalemia, but not more late toxicity. Adding cetuximab to radiation-cisplatin did not improve outcome, and hence, the authors stated that should not be prescribed routinely. This large phase III trial stemmed from strong previous phase III data showing that combining cisplatin or cetuximab concurrently with radiation improved PFS and OS of patients with locally advanced head and neck carcinoma and that adding cetuximab to platinum-based chemotherapy improved OS of patients with recurrent or metastatic head and neck carcinoma. Therefore, it was disappointing to discover that adding cetuximab to the radiation-cisplatin platform had no significant impact on PFS, OS, LRF, or DM [40]. This study reported conflicting findings from a number of previous studies on the same subject. More specifically, in a phase III study in locally advanced HNSCC, it was demonstrated that cetuximab increased OS when combined with radiotherapy alone, while not enhancing local toxicities [37]. In addition, following a proof-of-concept study in the recurrent metastatic setting, the Erbitux in First-Line Treatment of Recurrent or Metastatic Head & Neck Cancer (EXTREME) study showed that addition of cetuximab to platinum-based chemotherapy with fluorouracil improved OS, PFS, and response rates [35, 41]. Both studies attempted to intensify treatment in the locally advanced setting by incorporating cetuximab into concurrent chemoradiotherapy regimens in unselected populations. RTOG-0234 was a randomized phase II study in the postoperative setting in patients with high-risk pathologic features. It was designed to select one of two chemoradiotherapy regimens for further testing against standard high-dose cisplatin-based chemoradiotherapy in a phase III trial [42]. The two chemoradiotherapy regimens, docetaxel–radiation–cetuximab triplet and weekly cisplatin–radiation–cetuximab triplet, were compared in terms of disease-free survival (DFS) to the historical cohort treated with chemoradiotherapy in RTOG-9501 [27]. Both arms performed better than historical RTOG-9501 results, and the docetaxel arm appeared better than the cisplatin arm. RTOG-9501 randomly allocated high-risk postoperative patients to either radiation alone or radiation with concurrent high-dose cisplatin. No significant impact on distant control was noted, although the addition of cisplatin did increase acute severe adverse events [43]. However, the EXTREME trial was conducted in an unselected population and showed improvement in survival, even though the cetuximab-sensitive population was diluted as a result of the lack of a predictive test. Such a synergistic effect of cetuximab with chemotherapy did not emerge in RTOG-0522, possibly because of a lack of feasibility of the cisplatin–cetuximab–radiation triplet [40].

Postoperative RT with or without concomitant chemotherapy is reserved for those cases in which the risk of recurrence is high. Defining the "high-risk" patient has been the topic of controversy. This decision is made after a careful evaluation of the various patient and disease factors. The findings can be summarized as follows: extracapsular extension and/or microscopically involved surgical margins are the only risk factors for which the impact on survival of adding chemotherapy to RT is statistically significant. There is a trend toward improved survival in favor of CRT in patients who had stage III and IV disease, perineural infiltration, vascular embolisms, and/or

clinically enlarged level IV and V lymph nodes secondary to tumors arising in the oral cavity or oropharynx. The differences though were not statistically significant. Patients with two or more histopathologically involved lymph nodes without extracapsular extension did not seem to benefit from the addition of CT. The problem with CRT in head and neck cancer is that the schedules are often rather toxic and associated with a substantial morbidity which in turn influences the compliance with treatment. Obviously this morbidity is to some extent outnumbered by the benefit of the combined treatment, resulting in an improved survival, but we must not forget that many patients do not comply with treatment, and patients who do not fulfill a planned course of RT due to morbidity with the interacting drug are in fact in a worse situation condition than the ones who are treated with RT alone.

24.6 Site-Specific Treatment

The anatomic boundaries of the oral cavity extend from the skin–vermilion junction of the lips to the junction of the hard and soft palate above and to the line of circumvallate papilla of the tongue below. Specific sites of tumor origin include the lips, floor of the mouth, oral tongue, lower alveolar ridge and retromolar trigone, upper alveolar ridge and hard palate, and the buccal mucosa [44]. The maxillary sinus carcinomas will also be included.

24.7 Lip Cancer

The lip is the most common primary site within the oral cavity, accounting for approximately 25 % of cancers at this site. The majority of lesions occur on the lower lip and 95 % occur in males [45] (Fig. 24.1). Basal cell carcinomas (BCCs) may arise from the skin and cross the vermilion border to invade the lip, while squamous cell cancers (SCCs) most frequently develop at the vermilion margin. BCCs are more common on the upper lip. The similar local control and cure rates that can be achieved with surgery or RT in stage I lower lip tumors make either treatment acceptable. Surgery is the treatment of choice for early-stage lesions and is preferred because of better cosmetic results and lower morbidity rates compared to RT. Defects that involve less than two-thirds of the lip usually can be closed primarily. Defects involving two-thirds of the lip can be reconstructed with full thickness pedicled flaps ("Abbe or Estlander") from the upper or lower lip [46]. Many reconstructive options are available for defects larger than two-thirds of the lip, ranging from local nasolabial flaps to hair-bearing free flaps. The facial artery musculomucosal flap has shown application and success in upper and lower lip reconstruction [47]. Radiation

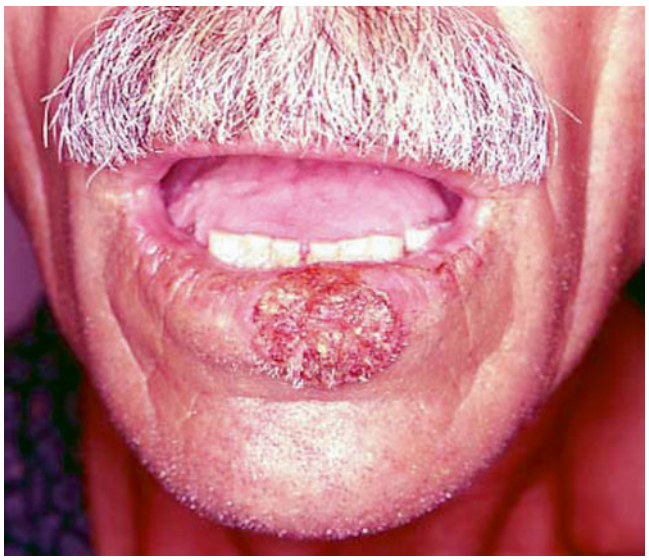

Fig. 24.1 Clinical photograph of a 60-year-old male with an ulcerated lesion in the middle part of the lower lip. A biopsy revealed a moderately differentiated squamous cell carcinoma

therapy is generally reserved for recurrent tumors, for nodal disease, and for patients who cannot tolerate surgery.

Maximum tumor thickness is a predictor of metastatic spread to the regional nodes and is therefore important for treatment planning and assessment of prognosis in patients with squamous cell carcinoma [48, 49]. Among patients who have a clinically negative neck, those with T2 or larger tumors that are treated surgically should undergo ipsilateral neck dissection [49]. Upper lip and commissure tumors are more aggressive, tend to grow more rapidly, ulcerate sooner, and metastasize earlier than those of the lower lip. Carcinomas in these sites may give regional metastases to preauricular and submandibular nodes.

24.8 Oral Tongue Cancer

The incidence of tongue cancer exceeds all other sites in the oral cavity, excluding lip cancer, accounting for almost 30 % of oral cancer patients. The median age for patients with SCC of the tongue is 60, and, similar to other disease sites, the male to female ratio is 3:1. Cancers of the mobile tongue have a high incidence of occult and clinical cervical lymph node metastases.

Tongue cancer has been considered to have a more aggressive course in younger patients. However, more recent studies have found no difference in staging or survival among patients under the age of 40 as compared to a group of patients aged 60–70 [50, 51]. Those receiving neck dissection for prognostic or therapeutic purposes have significantly better 5-year survival rates than those who do not receive a

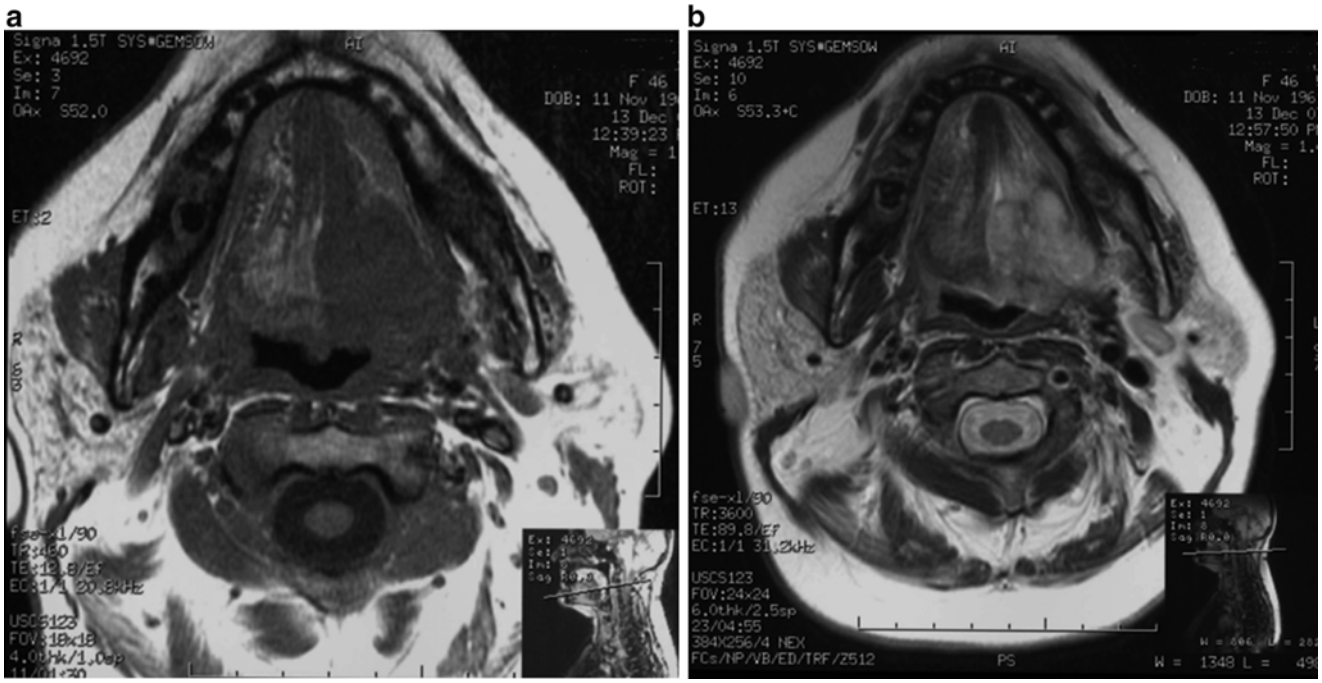

Fig. 24.2 Squamous cell carcinoma of the tongue in a 48-year-old female patient. The MRI shows the lesion extending and occupying the right side of the tongue. T1 weighting (**a**) and T2 weighting (**b**)

neck dissection as part of their primary treatment. Surgery is recommended for small, anterior, and well-lateralized lesions. Radiation therapy is preferred for large T1 lesions and for T2 tumors where resection would result in impairment of normal speech and/or swallowing (Fig. 24.2).

Most stage I and II lesions can be resected via an intraoral approach with ample surgical margins. Due to the small size of these early tumors in relationship to the usual bulky mass of the tongue, most T1 and T2 cancers of the oral tongue can be excised without permanent speech or swallowing deficits. Excision usually entails a partial glossectomy (Fig. 24.3).

Adequate margins (greater than 1 cm) and elective treatment of the clinically negative neck are extremely important in the treatment of early tongue cancer. The 5-year survival rate, in patients with stage I or II disease, after appropriate surgical treatment, approaches 90 %.

Elective neck dissection is recommended in patients with T2-4 tumors and a clinically negative neck because of the high incidence of occult cervical nodal disease [52–54]. More than 25 % of patients undergoing elective neck dissection will be found with pathologically node positive (N+) [53]. The staging information provided by the neck dissection is crucial for defining necessity for and type of postoperative additional treatment.

It is more difficult to define the role of elective neck dissection in patients with T1 disease and a clinically negative neck. There are no randomized trials examining this issue. The 5-year survival rates for patients undergoing synchronous (prophylactic) neck dissection, no dissection, or a metachronous dissection (at the time of clinical neck recurrence) are 81, 60, and 45 %, respectively. This finding supports the concept that prophylactic neck dissections offer improved survival compared to the "wait and see" policy and emphasizes the need for a more aggressive approach to the neck at primary tumor presentation [55]. The best pathologic predictors for the presence of occult neck metastases are depth of invasion above 5 mm, depth of muscle invasion, double DNA aneuploidy, and poor histologic differentiation. It is therefore recommended that elective neck dissection must be considered in patients with T1N0 cancer undergoing surgical treatment of the primary who have aneuploid tumors, depth of muscle invasion >4 mm, or a poorly differentiated cancer [55].

As oral cavity cancer rarely metastasizes to neck level V, a radical or modified radical neck dissection of all five nodal levels is not necessary for patients with N0 neck. Selective neck dissection of levels I–III ("supraomohyoid neck dissection") is the procedure of choice for elective neck dissection of the neck. Most of the relatively small numbers of isolated metastasis to level IV are from primary tumors of the tongue, which are known to produce "skip metastases." Thus, an "extended supraomohyoid neck dissection" of levels I–IV is recommended for elective treatment of the neck in tongue cancer in patients with T2 and above and N0 necks [56]. A number of recent prospective multi-institutional studies have demonstrated that sublevel IIB is rarely involved with isolated metastasis from oral cavity primary tumors, except from some tongue cancers [57–61]. Thus, it is justifiable to

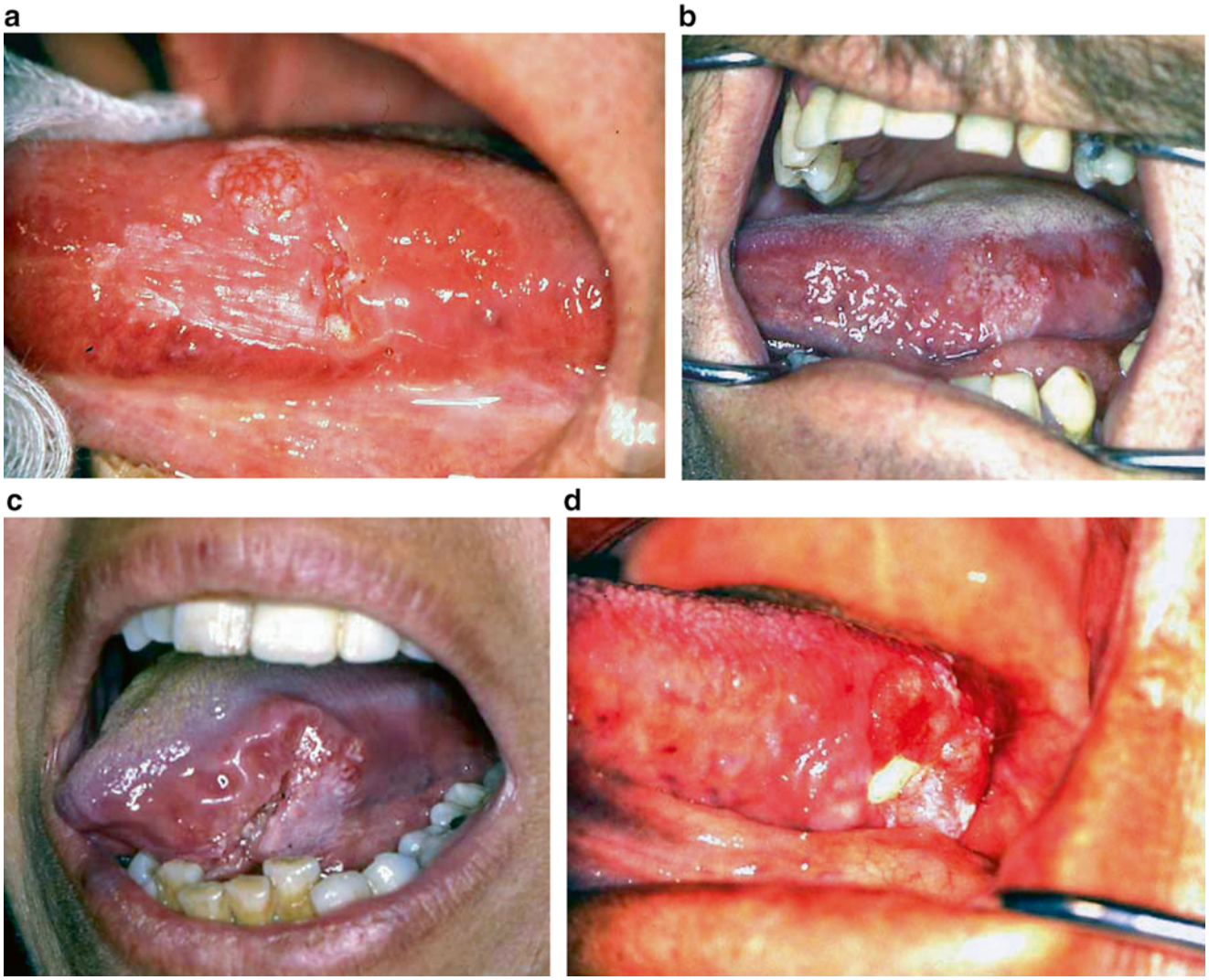

Fig. 24.3 (**a**) Clinical photograph of a 69-year-old female patient. On the left border of the tongue there is a well-demarcated speckled lesion, indurated on palpation. There is also an area of leukoplakia. The patient had noticed the change on the left tongue border for the first time about 3 months earlier. A biopsy revealed a well differentiated oral squamous cell carcinoma. (**b**) An early, T1 carcinoma of the middle third of the tongue in a 65-year-old male smoker patient. A slightly raised, erythematous superficially ulcerated area can be noted. (**c**) Clinical photograph illustrating an ulcer in the left anterior two-thirds of the tongue in a 43-year-old female patient. She had no tobacco or alcohol habits. The lesion measured 4.3 cm in its widest dimension. This carcinoma is therefore staged as T3. A submandibular lymphadenopathy was detected. Incisional biopsy showed a deeply invasive squamous cell carcinoma. (**d**) This photograph shows a non-healing ulcer in the posterior third of the tongue corresponding to a T2 squamous cell carcinoma. The patient, a 55-year-old male was a smoker and reported a history of regular alcohol consumption. No regional lymph nodes were palpable

omit dissection of sublevel IIB in elective treatment of most cases of oral cavity cancers. In this way injury to the spinal accessory nerve is avoided [62].

It is recommended that elective neck dissection is performed for all patients with T2 or larger tumors if surgery is used to treat the primary tumor [54]. Ipsilateral neck dissection is generally sufficient for most T1/T2 tumors. However, bilateral node dissection should be considered for patients with anterior or midline lesions, as well as for those with more advanced-stage disease (Fig. 24.4).

24.9 Floor of Mouth Cancer

The floor of the mouth is rich in neural and vascular structures including the lingual and hypoglossal nerves, the submandibular duct, and the sublingual glands. SCCs of the floor of the mouth are aggressive oral cavity neoplasms. They typically present as painful infiltrative ulcerative lesions that may bleed (Fig. 24.5). The lack of any substantial fascial barrier means that early tumors of the floor of mouth can quickly invade into the underlying structures and

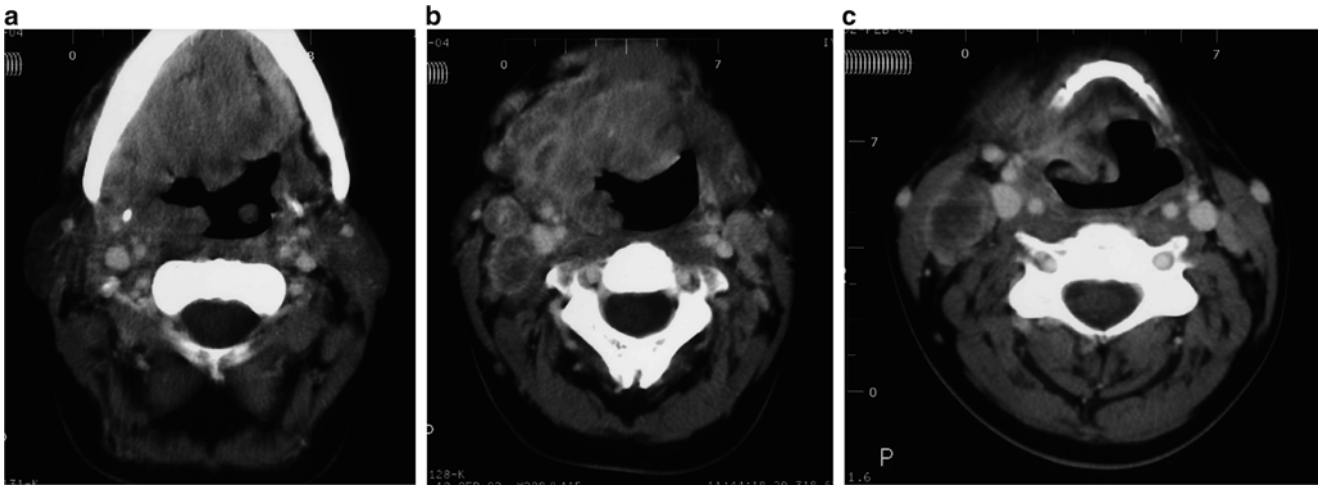

Fig. 24.4 Squamous cell carcinoma of the tongue in a 55-year-old male patient. The CT shows the lesion occupying the entire musculature of the left side of the tongue. Regional node metastases are also present. (**a**) At the level of the floor of the mouth. (**b**) At the level of the base of the tongue. Multiple nodal metastases with central necrosis can be seen. (**c**) At the level of the hyoid bone. A large nodal block can be seen under the sternocleidomastoid muscle

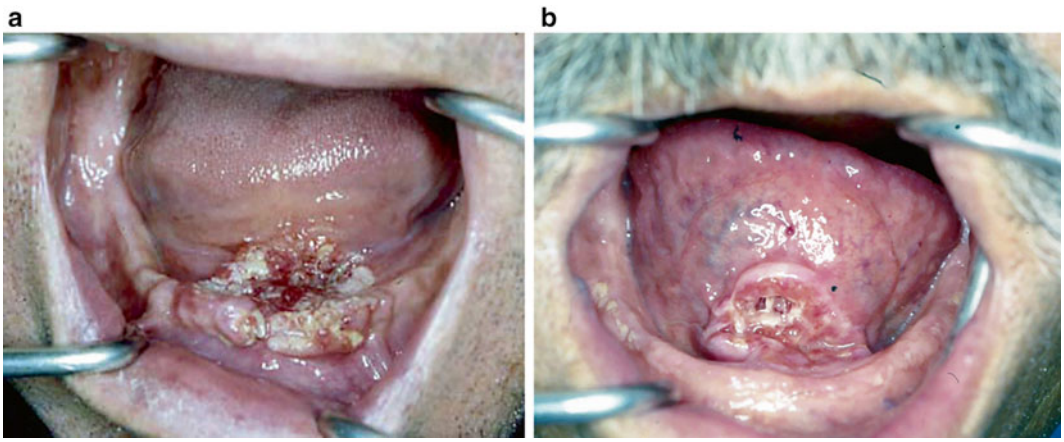

Fig. 24.5 (**a**) Clinical photograph of a 67-year-old edentulous male patient with a heavy smoking history. A carcinoma of the floor of the mouth is noted. The lesion extends also toward the alveolar ridge of the anterior mandible. (**b**) An ulcerated lesion in the floor of the mouth in a 76-year-old male smoker can be seen. The lesion also extends toward the ventral side of the tongue

metastasize to the first echelon lymph node basin (neck levels I and II). They have a high incidence of cervical nodal metastases which are detectable clinically in 30–60 % of patients at presentation. The incidence of occult cervical metastases is also high [63].

Treatment approaches include surgery and RT. Due to the risk of radiation-induced bone necrosis, surgery is usually the preferred treatment approach in operable patients. Local control of these tumors can be difficult because of their proximity to the mandible and the lack of a good mechanical barrier to tumor spread at this site. Surgery is generally preferred with an emphasis on negative margins, which can be technically difficult without rim mandibulectomy due to the proximity of and/or occult invasion into the mandible. The outcome of surgical treatment for patients with cancer of the floor of the mouth varies directly with tumor size and the status of the surgical margins. In early-stage T1 and T2 disease, the 5-year survival can be higher than 80 % [63, 64].

Due to the high incidence of occult nodal disease in all but the earliest superficial carcinomas (i.e., those limited to less than 5 mm invasion) of the floor of the mouth, prophylactic neck dissection is recommended at these sites [52, 63]. For T1 or T2 lesions, an ipsilateral supraomohyoid (levels I–III) dissection is generally advocated as the surgical procedure of choice; bilateral selective dissections are indicated for more anterior/midline lesions [65]. Because of the density

of neurovascular structures in the floor of the mouth, frequent metastasis occurs to the sublingual, submandibular, and level II lymph node basins.

Postoperative radiation (in some cases, with concomitant chemotherapy) is indicated for patients who have positive resection margins (if not re-resected), mandibular bone erosion, or pathologically positive lymph nodes after elective neck dissection. Postoperative RT should also be considered if there is vascular or perineural invasion in the primary tumor [66]. For resectable tumors in nonsurgical candidates, RT (usually a combination of external beam RT and brachytherapy) achieves similar local control rates [66].

24.10 Tumors Invading the Mandible

Tumors within the oral cavity may invade the mandible and gain entrance into the mandibular canal through several routes. Not uncommonly, SCC of the oral epithelium will travel along the surface mucosa until it approaches the attached gingiva where the tumor cells may come into contact with the periosteum of the mandible. This can be done in both dentate and edentulous patients. In the dentate patient, tumor cells demonstrate a tendency to migrate into the dental sockets because this area represents a pathway of minimal resistance. In edentulous patient, tumor cells will migrate onto the occlusal surface of the alveolus and enter the mandible through dental pits, which are cortical bone defects at the location of prior dentition. SCCs of the floor of the mouth may also extend to invade the neighboring mandibular bone. Less commonly, tumor may enter the mandible through mental or mandibular canals. Finally, adjacent tumor may erode through the cortical bone directly into the mandibular canal (Fig. 24.6).

Plain radiography has been used in the past for the diagnosis of tumor invasion of the mandible. The introduction of orthopantomogram or panoramic radiography, CT, and MRI scans has increased the accuracy of preoperative imaging and staging (Fig. 24.7). Significant debate still exists regarding the optimal modality or combination of modalities recommended for preoperative assessment of mandibular invasion by oral SCC. While CT is a very accurate method for identifying gross bone invasion, prior work has suggested that bone invasion may be missed in as many as 27 % of patients with preoperative CT scans [67]. The CT scan renders an excellent view of both the soft tissue and bone of the mandible; however, it has several limitations, the most significant being artifacts caused by dental amalgams and prosthetic metal bridgework. Dental amalgams commonly create a shadow leading to artifact that can obscure invasion of the mandibular cortex. Additionally, the CT scan may misleadingly detect defects in the cortex secondary to irregular tooth sockets or periapical lesions of inflammatory origin.

In light of these shortcomings, several investigators have reported on the use of a Dentascan. The Dentascan was introduced in the early 1980s to assist oral maxillofacial surgeons in planning for osseointegrated implants. The Dentascan images are derived by reformatting standard axial CT scans in two views, panelliptical and parasagittal. This reformatting permits assessment of the buccal and lingual cortices. The diagnostic accuracy of the Dentascan is high, yielding a sensitivity of 95 % and a specificity of 79 % with a positive predictive value of 87 % and a negative predictive value of 92 % [68]. The Dentascan is therefore an accurate method for preoperative evaluation of mandibular invasion in patients with SCC of the oral cavity (Fig. 24.8).

While the CT scan and Dentascan may offer excellent methods for assessing bone, MRI offers the advantage of imaging soft tissue and potentially the medullary bone space. Several studies have examined the use of MRI in assessing mandibular invasion and it has been concluded that MRI is superior for evaluating the medullary space of the mandible [69] but inadequate for assessing mandibular invasion. Shaha [70] examined the value of various studies including

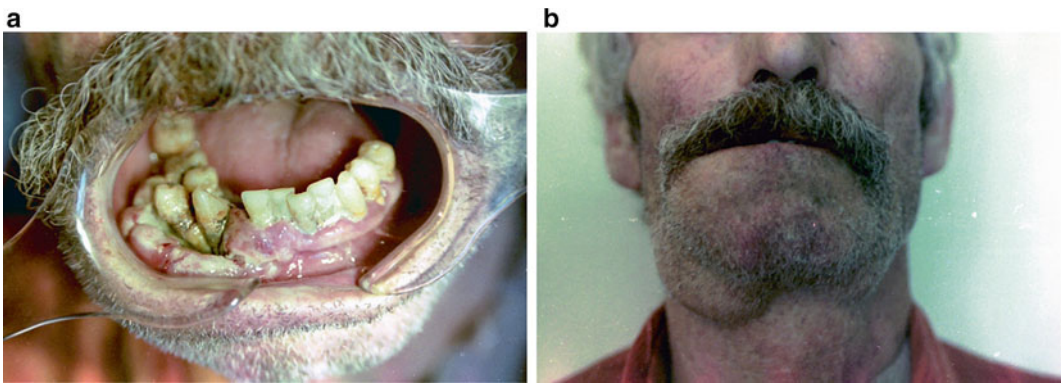

Fig. 24.6 (**a**) Clinical photograph of a 58-year-old male patient with a large (T4) squamous cell carcinoma of the right mandibular parasymphysis. The patient, a heavy smoker and alcoholic, reported a 2 years presence of the tumor which had completely invaded the mandibular bone. (**b**) There was a marked regional lymphadenopathy with fixation of the nodes in the mandible

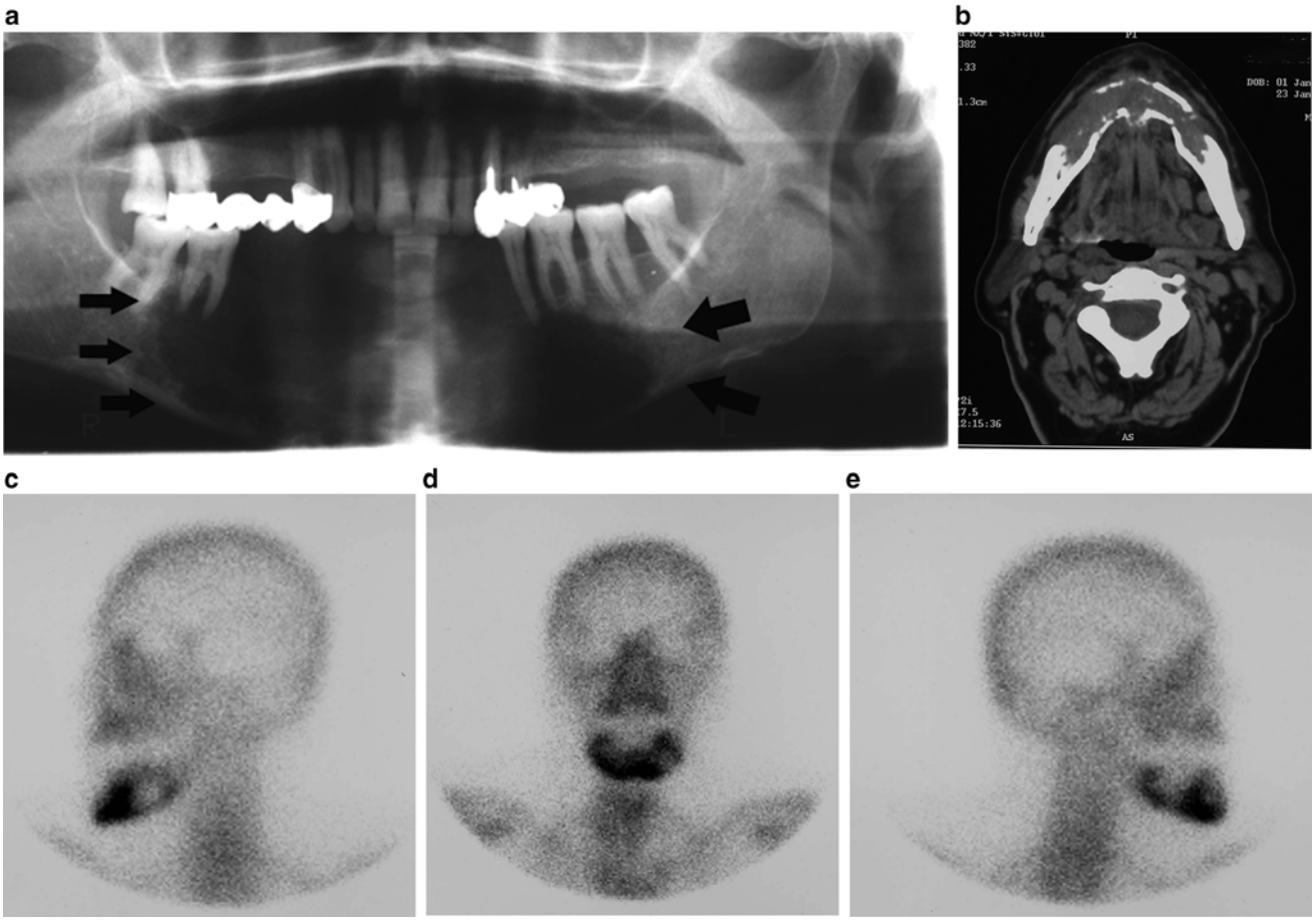

Fig. 24.7 Squamous cell carcinoma of the anterior part of the mandible in a 60-year-old female. (**a**) Orhtopantomogram showing the lesion to extend from the right premolars area of the mandible to the left one (*arrows*). (**b**) CT of the mandible shows the extensive distraction of the osseous architecture of the mandible extending to the buccal and lingual cortical bone. (**c**, **d**, **e**) Bone Scan with Tc 99 m shows a pathological uptake of the radionucleade in the anterior part of the mandible. The uptake corresponds to the extent of the lesion

panoramic X-rays, dental films, routine mandible films, bone scans, CT scans, and MRI and found that CT scanning was not very helpful mainly because of the presence of irregular dental sockets and artifacts. Many suggest that clinical evaluation is the most accurate in determining the presence of bone invasion and the optimal method of resection, marginal versus segmental [71].

Most centers consider the combination of a CT scan and a panoramic X-ray acceptable for preoperative imaging of the mandible and maxilla; however, the most accurate measure of bony invasion is determined clinically at the time of surgery. Unless there is frank invasion of the bony cortex, periosteal stripping followed by frozen section examination at the time of surgery is often the most reliable measure of bone invasion. Recent studies have shown that technetium (Tc) 99 m bone scintigraphy in the form of planar views or as SPECT provides a high diagnostic accuracy for mandibular invasion by oral SCC of the alveolus in both edentulous and dentate patients [72, 73].

Among all investigations and evaluations of the extent of disease in the oral cavity in relation to involvement of the mandible, the best investigation continues to be routine clinical evaluation and intraoperative evaluation of the proximity of the tumor to the inner border of the mandible. Even though the tumor may not involve the mandible directly, a marginal mandibulectomy may be necessary for appropriate oncologic margins and resection of part of the mandible due to close proximity. This decision is best made using clinical judgment.

Tumors invading the mandible can be managed either with a marginal resection or a segmental resection. The decision regarding the optimal method of tumor resection is largely dependent on the degree of invasion. It has been suggested that tumor invasion of the periosteum or cortical bone, without invasion of the medullary cortex, can be appropriately managed with a marginal resection. Tumors that erode into the medullary canal, however, require a segmental resection. It has been shown that once a tumor gains access to the medullary canal, tumor may travel through the canal via the neurovascular bundle. The inability to obtain frozen section assessment of the mandible intraoperatively represents a management dilemma because decalcification of the

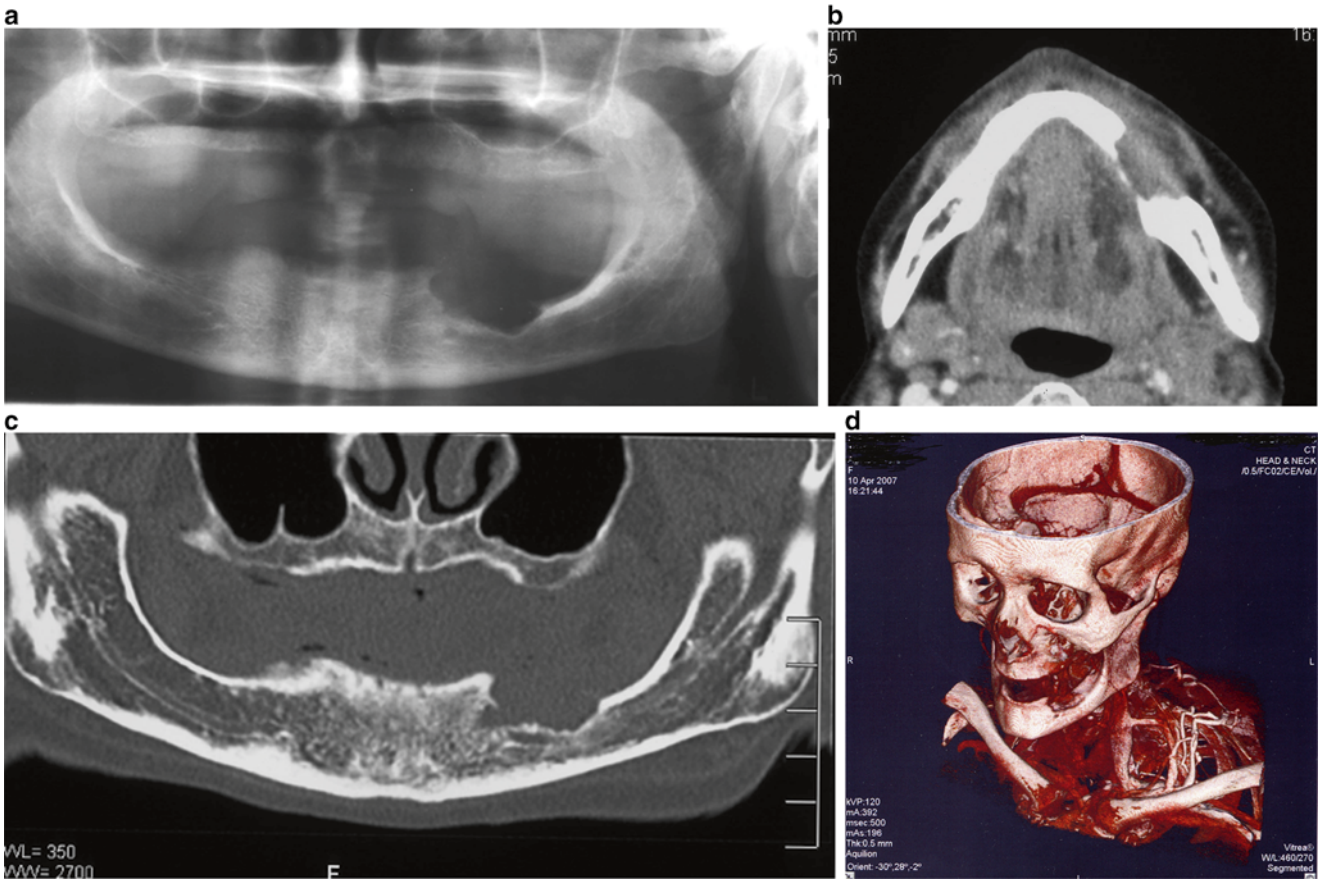

Fig. 24.8 Squamous cell carcinoma of the left body of the mandible in a 68-year-old male patient. (**a**) The orthopantomogram shows a lytic lesion in the left body of the mandible extending to the inferior dental canal. (**b**) The CT shows complete destruction of the entire width of the mandibular body. (**c**) The Denta Scan CT depicts the erosion of the cortical bone and the extension of the tumor to the medullary part of the mandible. (**d**) Threee-dimensional reconstruction of the CT of the mandible

mandible specimen in preparation for definitive histopathological analysis can take as long as 2 weeks.

The periosteum is relatively resistant to cancer invasion. With the exception of the tooth sockets, the periosteum acts as a dense barrier to the invasion of adjacent tumor. In spite of the protective periosteum, aggressive and long-standing tumors erode the periosteum and invade the adjacent mandible through a variety of pathways. Two distinct histological patterns of tumor invasion have been identified. The first pattern is referred to as *infiltrative* and is characterized by fingerlike projections of tumor which advance independently and invade the cancellous spaces without the intervening connective tissue layer and possess very little osteoclastic activity. The second pattern is referred to as *erosive*. In contrast to the infiltrative pattern, the erosive pattern is characterized by a broad front with a connective tissue layer and active osteoclast activity. The significance of the erosive and infiltrative patterns has been demonstrated in several reports, and it has been demonstrated that patient survival is significantly impacted by the pattern of invasion [74]. It has been suggested that the pattern of invasion is a reflection of the biologic aggressiveness of the tumor and may impact the approach to ablative therapy. While most tumors that invade the mandible mandate postoperative external beam radiation, some have suggested that superficially invading tumors may not benefit from postoperative radiation. Given the aggressive behavior of the infiltrative pattern of invasion, we recommend postoperative RT for all patients with this pattern of bone invasion.

While the superficial invasion of the periosteum or cortical bone may be managed with a marginal mandibulectomy, once the tumor has eroded into the medullary cavity and mandibular canal most advocate a segmental resection. Determining the presence of bone erosion and the extent of bone erosion represents an ongoing clinical dilemma. The poor predictability associated with preoperative imaging has led many to rely on preoperative clinical assessment as the primary method for determining the presence of mandibular invasion. Several groups have studied this issue and found that clinical evaluation of mandibular bone erosion is more sensitive than radiographic evaluation; however, radiographic assessment may be more specific and provide a higher reliability index [75].

There are a few studies reviewing the impact of clinical assessment alone in determining the extent of mandibular invasion. This likely represents the difficulty in quantifying a clinical exam. However, most agree that clinical assessment

for invasion is paramount. Several studies have evaluated the role of periosteal stripping as an indicator for tumor invasion of the mandible and found that periosteal stripping at the time of resection represented an accurate predictor of the presence of mandibular invasion [76]. Without clear preoperative evidence of mandibular invasion, a marginal resection followed by periosteal stripping and inspection is an adequate approach. In the event that microscopic evidence of invasion at the rim is discovered, the marginal mandibulectomy is converted into a segmental mandibulectomy.

24.11 Lower Alveolar Ridge and Retromolar Trigone Cancer

The retromolar trigone is a small mucosal space that begins at the third molar of the mandible and extends cranially to the maxillary tuberosity. It is directly continuous with the buccal mucosa, upper and lower gingiva, maxillary tuberosity, anterior tonsillar pillar, soft palate, and the floor of the mouth (Fig. 24.9).

Squamous cell cancers arising in the retromolar trigone and lower alveolar ridge comprise approximately 10 % of all oral cancers and exhibit the same 3 or 4:1 male predominance of other head and neck cancers. The presenting symptom is typically pain, which is exacerbated by chewing.

Treatment options include RT and surgery. The local recurrence rate is higher with these tumors than for other sites in the oral cavity due to microscopic extension to the mandible and maxilla (for retromolar trigone tumors). In addition, the probability of occult regional lymph node metastases is higher than with most other oral cavity tumors, with the exception of tongue cancer and floor of mouth cancer [69]. Thus, elective neck dissection is usually recommended for patients with a clinically negative neck.

Surgical treatment involves wide local excision. Marginal or horizontal "rim" mandibulectomy may be required in order to achieve tumor-free margins. Due to the normally thin overlying mucosa and the close proximity to the mandible, alveolar ridge and retromolar sites have a propensity for early invasion of this bone, as well as the maxilla for retromolar trigone lesions [77, 78]. Consequently, lesions that are clinically staged T1/T2 and treated with rim mandibulectomy may become pathologic stage T4 after histologic confirmation of bony invasion. Segmental or composite resection is reserved for those tumors that are deeply invasive or that wrap around the mandible [67]. In addition, segmental mandibulectomy may be necessary for early-stage lesions in the thin, edentulous mandible in order to achieve negative margins.

It is extremely important to determine the true invasive margin, which may extend grossly or microscopically beyond the tumor front [69]. Determining this invasive margin is challenging. For oral cavity lesions in general, computed tomography (CT) scans may be helpful for identifying bone invasion. The sensitivity of CT scan for bone involvement of the retromolar trigone is approximately 50 % with a negative predictive value of 60 %; however, the positive predictive value is approximately 90 %. It has been concluded that while the CT scan is accurate when bone erosion is clearly identified, its negative predictive value is unacceptably low and therefore an inaccurate indicator of bone invasion at the retromolar trigone. In one report of 127 patients with oral cavity or oropharyngeal carcinoma treated with composite (segmental) resections, CT scan findings suspicious for bone invasion and primary tumor location (alveolus, retromolar trigone, tonsil, and sulcus) were the only independent variables that predicted for the presence of bony invasion [72, 77, 79]. However, in one report, preoperative CT scan failed to identify bone invasion in one-half of

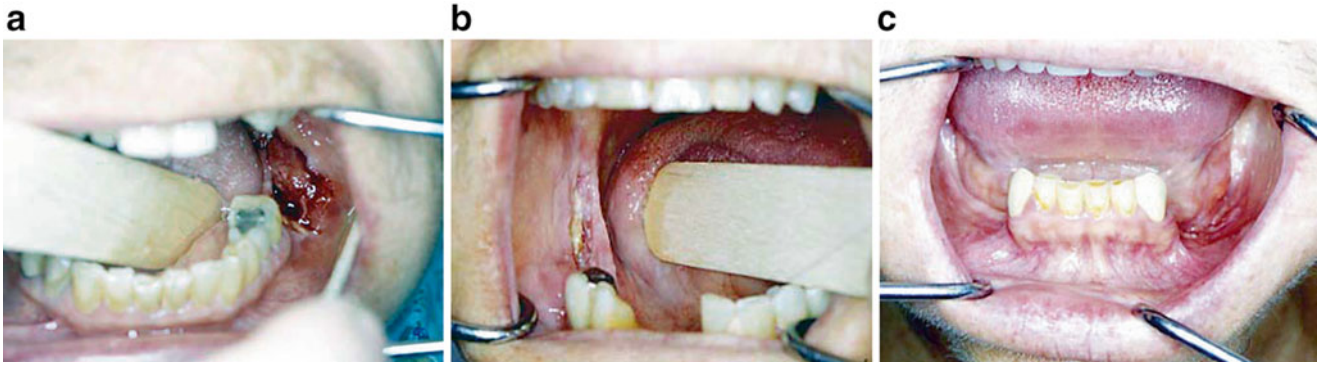

Fig. 24.9 (**a**) Squamous cell carcinoma of the left retromolar area of the mandible in a 47-year-old male patient. The lesion was diagnosed after a dental extraction when the tooth socket failed to heal after 6 weeks. (**b**) Clinical photograph of a ulcerative lesion in the right retromolar trigone of a 52-year-old male patient. The superficial ulceration after biopsy proved to be a moderately differentiated squamous cell carcinoma. (**c**) Clinical photograph illustrating a carcinoma of the alveolar bridge in a 60-year-old partially edentulous female patient. The patient reported an ill-fitting denture that produced diffuse local pain

retromolar trigone lesions that histologically invaded bone [80]. Potential reasons for this low sensitivity include the thickness of CT sections, the lack of bone windows and coronal imaging, and the presence of distortion from dental artifact.

A resection margin of at least 1 cm in all directions is recommended [81]. At least for tumors involving the retromolar trigone, the optimal extent of surgery is controversial [63, 82]. In addition to stage, outcomes are dependent on the presence of bone invasion, deep infiltration of the masticator space, nodal involvement, and treatment modality [78, 83, 84].

Among the patients with stage I and II disease, survival exceeds 75 % at 5 years. In a later series of 99 patients treated with definitive RT or surgery followed by RT, local control rates were better in surgically treated patients (approximately 71 vs. 48 %) [83, 85]. Among all patients treated for stage I–III disease (RT or surgery plus RT), 5-year rates of cause-specific and overall survival were 70 and 58 %, compared to 57 and 42 % for those treated for stage IV disease. Notably, in multivariate analysis, both cause-specific and overall survival were significantly better in the group undergoing RT in addition to surgery.

For early lesions of the lower alveolar ridge and retromolar trigone, selective neck dissection in levels I–III is recommended as tumors are characterized by early invasion of the mandible and high rates of regional metastases.

24.12 Tumors Invading the Buccal Mucosa

Buccal cancer comprises less than 10 % of oral cavity cancers, and when it occurs, it commonly arises from a preexisting leukoplakia [86, 87] (Fig. 24.10).

SCCs arising within the buccal mucosa are notable for their locoregional aggressiveness. For early-stage disease, treatment with either surgery or definitive RT is reasonable, although in most circumstances surgery is favored. Surgical treatment can be compromised by anatomic difficulties in obtaining adequate margins. For locally advanced but resectable tumors, surgery followed by postoperative RT is the treatment of choice.

The principles of management of buccal cancer are no different than those of other subsites within the oral cavity. Surgical therapy is the preferred method of management. In early disease, surgical excision can usually be accomplished transorally. The buccal space has poor anatomic boundaries and it is difficult to obtain a clear surgical margin. Even patients with early-stage disease have potential microscopic invasion through the buccinator muscle into the buccal fat and buccal space.

Although more aggressive surgery including exenteration of the buccal space and parotidectomy may improve surgical results, the resulting disfigurement and morbidity of these procedures nay be considerable. Tumors that invade the buccinator muscle and tumors that present with nodal disease or with poor prognostic features should be managed with postoperative radiation therapy. Negative surgical margins are paramount, and in an effort to achieve this goal, careful preoperative planning is essential to determine the extent of the tumor. While early tumors of the buccal mucosa commonly present as an irregular mucosal mass, more than half of buccal tumors will present as deeply invasive tumors that may track along the parotid duct, masseter muscle, or into the palate. The proximity of the buccal mucosa to the parotid duct requires that the duct be traced retrograde and sampled to ensure a negative margin.

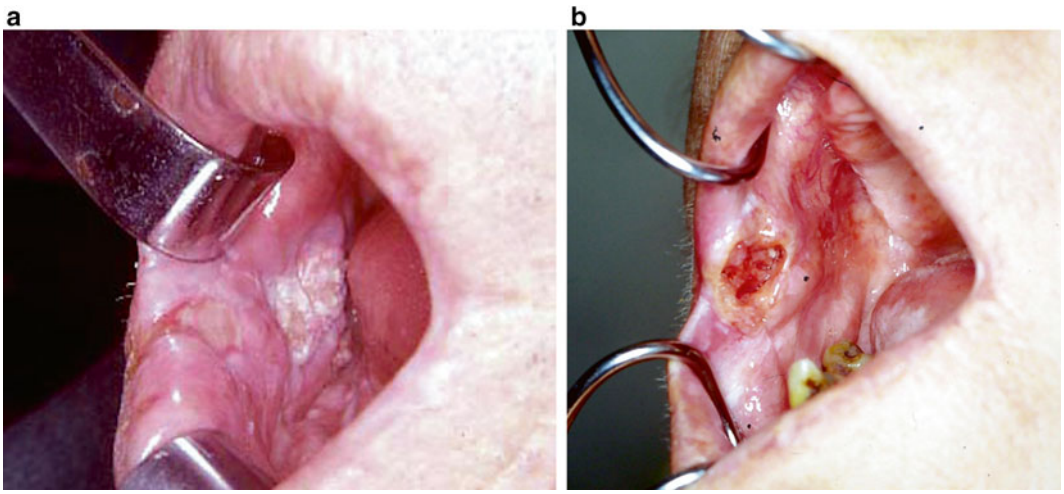

Fig. 24.10 (**a**) Squamous cell carcinoma developed in a preexisting leukoplakia of the right buccal mucosa in a 56-year-old male smoker patient. (**b**) Deep ulcerative lesion in right buccal mucosa and the corner of the mouth in a 56-year-old female patient

Deeply invasive lesions may break into the buccal fat pad. When this occurs, it is advisable to resect the entire fat pad because negative surgical margins in this area are difficult to confirm. The rich lymphatic network, characteristic of the buccal region, and the high rate of lymph node metastasis mandate that the neck be carefully evaluated and, in most cases, treated. Smaller tumors can usually be managed through a transoral approach; however, more advanced tumors may require a midline labiotomy incision. Cancer of the buccal mucosa is a highly aggressive form of oral cavity cancer that is associated with a high rate of locoregional recurrence and poor survival.

Surgery is generally preferred for managing small lesions. The tumor can usually be excised using a transoral approach. Five-year survival rates are approximately 75 % for patients with stage I disease and 65 % for patients with stage II lesions [88–90]. However, local recurrence rates with surgery alone are high, particularly with surgical margins less than 2 mm [88, 89, 91].

Treatment of the clinically negative neck is controversial. Elective neck dissection is not routinely recommended in all patients. For those with small (T1) lesions, cervical lymph node metastases occur in less than 10 % and the neck can be observed. Selective neck dissection of levels I–III should be considered for larger lesions [89].

24.13 Upper Alveolar Ridge and Hard Palate Cancer

Malignant neoplasms of the upper alveolar ridge and hard palate comprise approximately 5 % of oral cavity malignancies and have a male to female ratio of 8:1. Only about two-thirds of hard palate malignant neoplasms are SCCs; the remainder are minor salivary gland carcinomas and other rare malignancies. Unlike other areas of the oral cavity where SCC makes up the overwhelming majority of pathology, the palate is rich in minor salivary glands and therefore is the site of both benign and malignant salivary gland tumors (Fig. 24.11).

Most upper alveolar ridge and hard palate SCCs are managed with primary surgery. RT can be used for small, superficial lesions, or tumors with extensive involvement of the hard and/or soft palate. Combined modality therapy provides better locoregional disease control than single modality therapy [83, 84]. Postoperative RT (in some cases with concomitant chemotherapy) is indicated for patients with positive resection margins, bone erosion, or pathologically positive lymph nodes after elective neck dissection [83, 84]. Others recommend that postoperative RT also be considered if there is vascular or perineural invasion in the primary tumor [66].

The principles of management of tumors of the palate are similar to those of mandible; obtaining tumor-free margins is essential to achieving a good outcome. Lateral tumors may represent a risk to invasion and perineural spread via the palatine or trigeminal neurovascular bundle. The depth of invasion will dictate the extent of the surgical resection. Superficial lesions of the palatal mucosa are best managed with a wide surgical resection including the underlying palatal periosteum. The periosteum serves as an early barrier to spread; however, as tumors become more invasive, tumors can vertically invade the nasal vault or maxillary sinus.

Tumors of the hard palate rarely metastasize to the neck and therefore a neck dissection is rarely warranted in the absence of demonstrable regional disease. One exception is when there is tumor erosion through the posterior or posterior lateral maxillary sinus into the pterygopalatine fossa.

Most lesions of the upper alveolar ridge and hard palate are managed with primary surgery. Lesions with extensive involvement of the hard and/or soft palate can also be initially

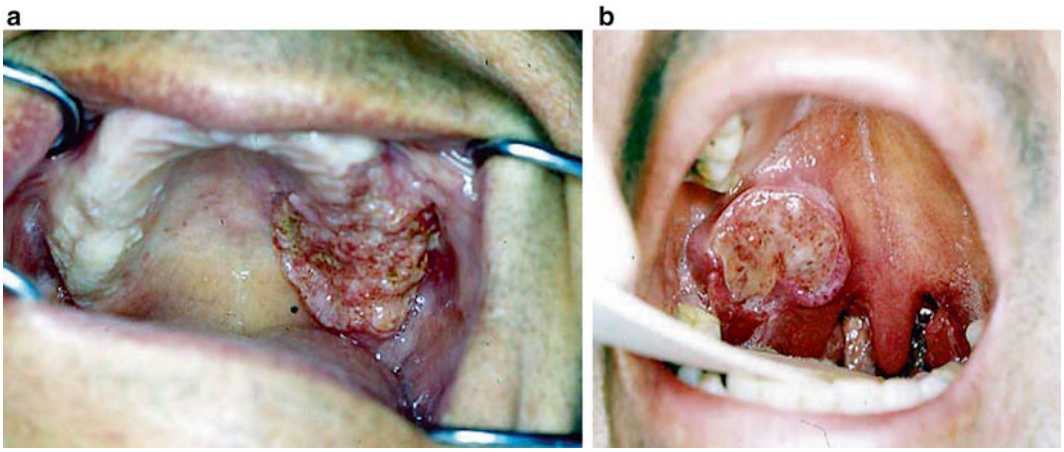

Fig. 24.11 (**a**) A large, T3 squamous cell carcinoma of the alveolar ridge and the palatal mucosa in a 72-year-old male edentulous patient. (**b**) Exophytic ulcerative tumorous lesion in the hard palate in a 63-year-old female patient. The lesion extends to the soft palate causing dysphagia to the patient

treated with primary RT. In patients initially treated with surgical resection, the 5-year survival rates are 70 and 45 % for patients with stage I and II disease [92].

Selective neck dissection with removal of level I–III nodal groups is adequate for early disease of the hard palate in patients with clinical positive nodes at presentation. If disease extends beyond the hard palate, however, elective treatment of the neck is indicated even in No neck patients.

24.14 Maxillary Sinus Cancer

Paranasal sinus cancer is rare, accounting for just 3 % of upper aerodigestive tract malignancies [93]. The incidence is higher in males than in females (2:1) with a peak incidence at 50–59 years of age. Lesions of the maxillary sinus are most common, followed by the ethmoid, sphenoid, and frontal sinuses. These tumors are generally slow-growing and tend to remain asymptomatic until late in the course. As a result, most patients present with locally advanced disease. SCCs constitute the majority of paranasal malignancies (45–80 % of cases). This is followed by malignancies of salivary gland origin, of which adenoid cystic carcinomas predominate [94–96], followed by adenocarcinomas and mucoepidermoid carcinomas. The most common symptoms in patients with paranasal sinus cancer include facial or dental pain, nasal obstruction, and epistaxis [97]. Oral symptoms (e.g., ill-fitting dentures) occur in 25–30 % of patients. Pain with unilateral nasal obstruction or ocular symptoms can be seen in 50 and 25 % of patients with antral-ethmoidal disease, respectively (Fig. 24.12).

A classic triad of facial asymmetry, palpable/visible tumor in the oral cavity, and visible intranasal tumor occurs in 40–60 % of patients with advanced disease. At least one of these signs is present in 90 % of cases [98].

As disease progresses, symptoms and signs depend upon the involved site. The bony structures between the nasal cavity, sinuses, orbits, and cranial vaults are thin and offer little resistance to cancer spread (Fig. 24.13).

Regional nodal metastases are uncommon, occurring in less than 20 % of patients, lower if they have adenoid cystic tumors [94, 99–102]. The incidence of lymph node involvement increases as tumors extend locally to adjacent sites, especially with extension into the oral cavity. The retropharyngeal nodes comprise the first echelon lymphatic drainage for sinus malignancies. Other regional nodes that may be involved with lymphatic spread are the periparotid and level Ib nodes. Patients with clinically positive nodes will have their necks treated with surgery and/or radiotherapy. Much more controversial is the strategy to be adopted for patients with a N0 neck. Some authors stress the indication for prophylactic neck treatment, whereas others recommend a wait and see policy especially in patients with small sized or histologically low-grade tumors. In order to investigate this controversial issue, Cantu et al. [103] performed a retrospective study of patients with tumors of the maxillary sinus. The study included 704 consecutive patients with malignant tumors of the paranasal sinuses seen over a 35-year period. Tumor site was classified as maxillary or ethmoid sinus. The series of 704 study patients included 305 patients with tumors of the ethmoid sinus (43.3 %) (ethmoid sinus group) and 399 with tumors of the maxillary sinus (56.7 %) (maxillary sinus group). Eighty patients underwent an orbit exenteration. Surgical resection achieved clean margins in 545 cases (77.4 %); there was macroscopic residual disease in 38 cases (5.4 %) and close margins or microscopic residual disease in 121 cases (17.2 %). The surgical procedure that achieved the highest rate of clean margins was anterior craniofacial resection (88 %). Lymph node recurrences (66 overall) were mostly observed in the maxillary sinus group, with a cumulative incidence significantly higher (12.5 %) than for the ethmoid sinus group (4.3 %) ($P = .001$). They concluded that nodal metastases from malignant tumors of the ethmoid sinus are very rare, either at presentation (1.6 %) or during the postoperative follow-up period (4.3 %). Moreover, most subsequent neck metastases appeared together with a recurrence of the primary tumor. Therefore, in their opinion, in ethmoid sinus malignancies there is no indication for prophylactic treatment of the neck. The problem is more intriguing for maxillary sinus malignant tumors. In non-squamous cell carcinomas, the rate of neck metastases at presentation in this series was very low (6 %). In addition, subsequent nodal metastases were rare. The rate of neck metastases at presentation for SCC was 10.3 %. The percentage of cervical metastases was much higher in T2 tumors than in T3 or T4 tumors. However, among 31 patients who developed node metastases during follow-up, only 1 presented with unresectable nodes, whereas 30 underwent neck dissection with or without radiotherapy and were successfully salvaged [103].

There is no consensus as to optimal treatment for early-stage tumors. Traditionally, surgery has been the primary treatment modality for paranasal sinus cancers involving the maxillary or ethmoid sinuses. However, the limitations of surgery alone are obvious given the frequent presentation of advanced disease [104].

Both surgical technique and the overall approach to management have evolved to incorporate into the decision-making process the histology and tumor size as well as location in relation to the adjacent critical structures. In many cases of maxillary and ethmoid sinus SCC, for example, aggressive local therapy includes en bloc craniofacial resection with or without orbital exenteration, followed by reconstruction and adjuvant RT.

RT may be used, particularly for T1 tumors of the ethmoid, sphenoid, and frontal sinuses, with acceptable results

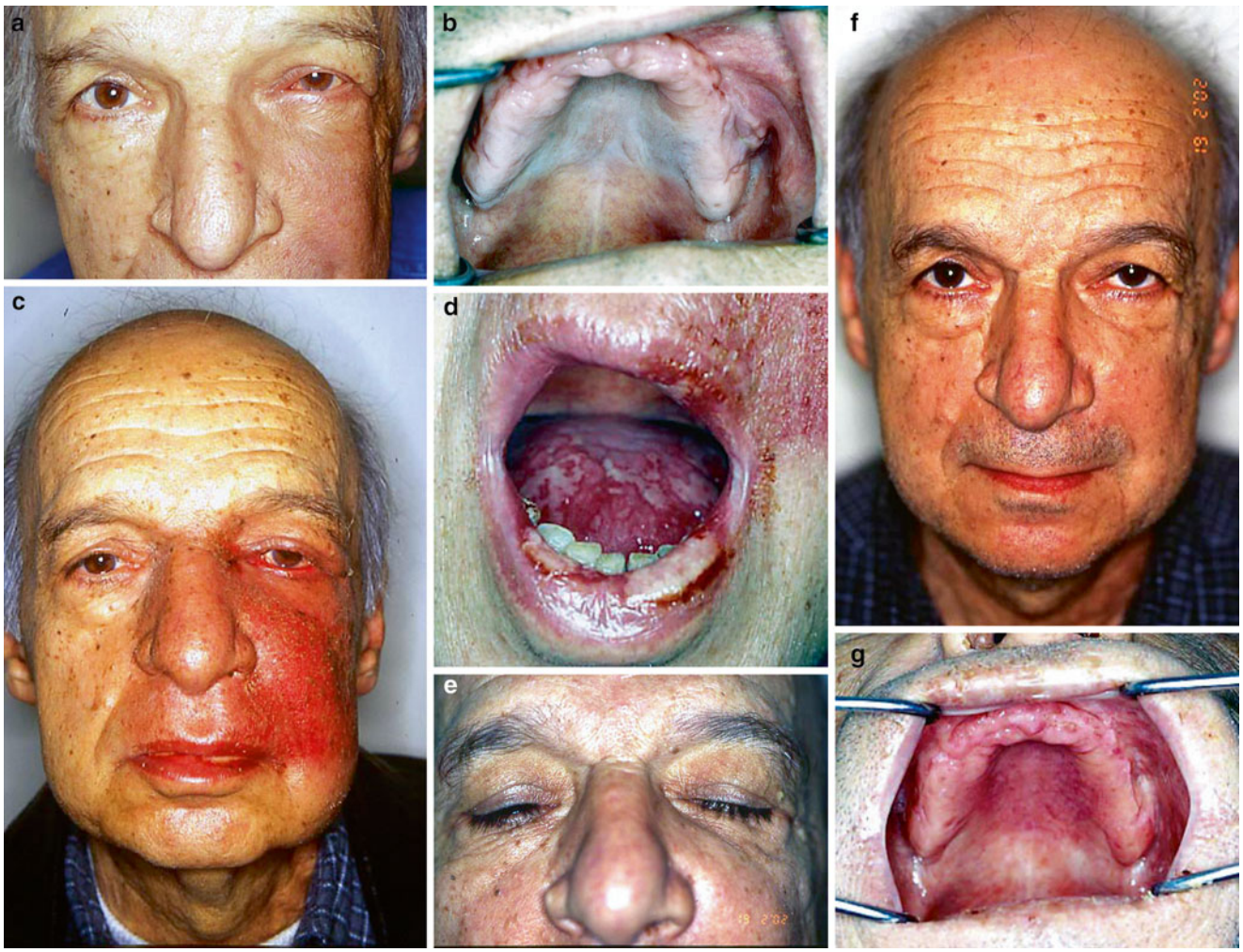

Fig. 24.12 (**a**) Clinical photograph of a 63-year-old male patient. The patient reported an 18 months history of progressive pain and swelling of the left eye causing visual disturbances. Clinical examination showed a painful mild exophthalmus with proptosis of the left eye and ptosis of the upper lip. (**b**) Intraoral examination of the same patient revealed a swelling of the left alveolar ridge of the maxilla with expansion and parts of ulcerations of the overlying mucosa. The edentulous patient reported a progressive inability for his denture to fit in place. Radiographic examinations and intraoral biopsy showed an extensive squamous cell carcinoma of the left maxillary sinus invading the orbital content and extending to the nasal cavity. (**c**) The patient during chemoradiation. A marked erythematous reaction of the skin of the left middle third of the face caused by radiotherapy is evident. (**d**) Chemoradiation also produced a stage IV mucositis. (**e**) Three months after chemoradiation improvement of the clinical signs and symptoms occurred. (**f**) Clinical photograph of the patient 3 years after chemoradiation. The patient shows a complete response and remains tumor free. (**g**) Intraoral photograph showing complete response to the treatment

[105, 106]. However, in practice, RT is rarely used as the sole modality of treatment except for cancers of the frontal and sphenoid sinuses, which are unsuitable for en bloc surgical resection.

Regardless of the surgical margin status, adjuvant postoperative RT optimizes local control. However, even with aggressive surgery and adjuvant RT, the results of treatment for most paranasal sinus cancers are poor with local control rates from 50 to 60 %, and 5-year survival rates ranging from 30 to 60 % [105–113].

Preoperative RT has been explored as a means of making these lesions more amenable to surgical resection [99, 114]. However, given the inherent bias in these nonrandomized studies, it is unclear whether preoperative is superior to postoperative RT in enhancing local control and improving outcome.

The use of postoperative RT and concomitant chemotherapy should be considered in patients with pathologically positive lymph nodes, particularly in cases with adverse prognostic factors such as multiple metastatic lymph nodes or any node with extracapsular spread.

24.15 Conclusions

If one wants to summarize the most notable developments of the last 30 years in the therapeutic management of oral squamous cell carcinomas that have been incorporated into

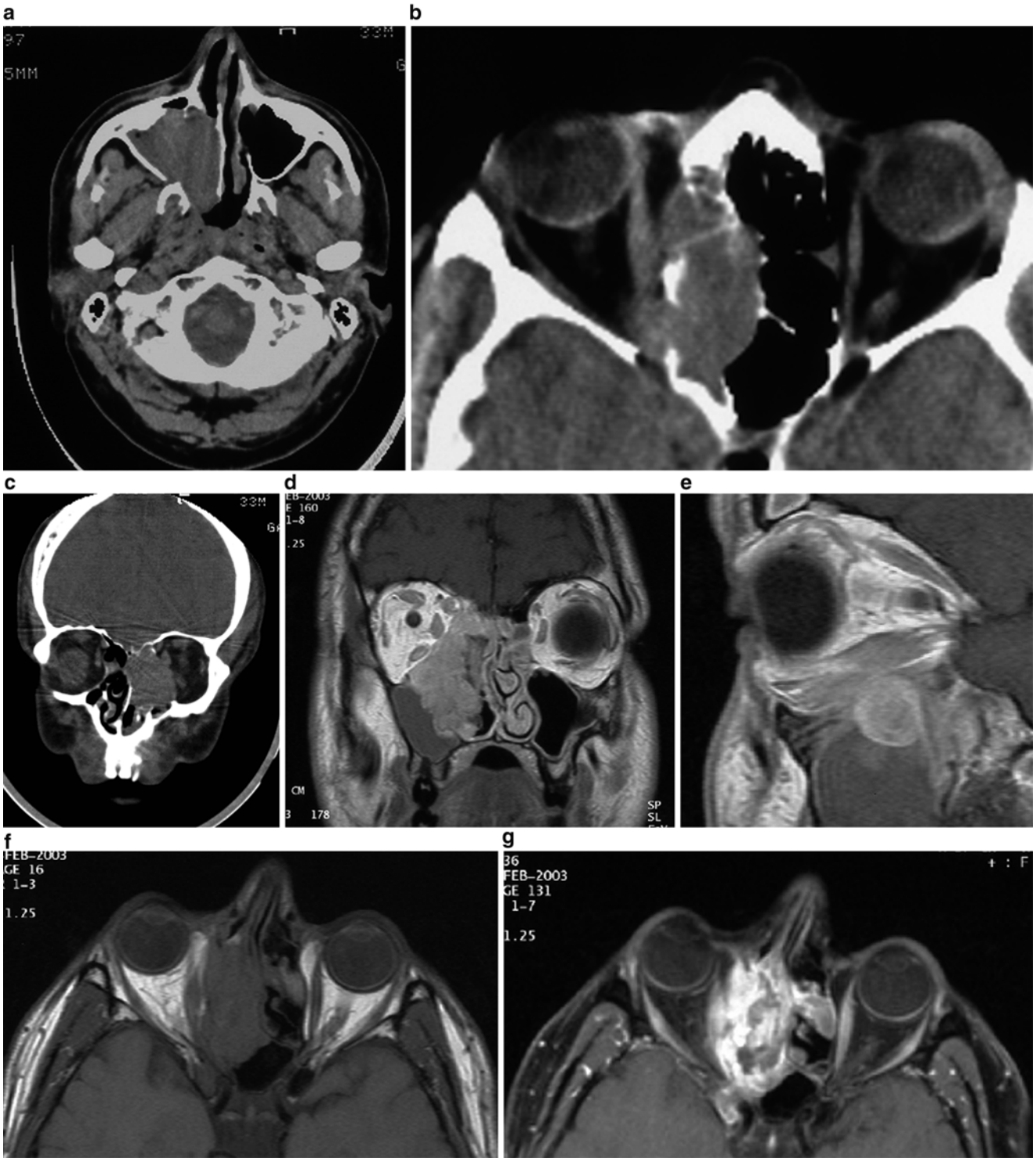

Fig. 24.13 Squamous cell carcinoma of the right maxillary antrum extending in the homolateral orbital cavity, the anterior ethmoids, and the nasal cavity in a 72-year-old male. (**a**) CT shows the lesion occupying the right maxillary sinus. The lesion is confined within the maxillary sinus cavity and does not erode the wings of the sphenoid bone. (**b**) The lesion occupies the anterior ethmoids and erodes the thin lateral orbital wall. (**c**) Coronal section showing the extension of the tumor into the right orbital cavity. (**d**) In the MRI (coronal T1 weight imaging) the tumor extends to the entire right middle third of the face. (**e**) Sagittal T1 weighting image showing the tumor eroding the right orbital floor and extending into the content of the orbital cavity. (**f**, **g**) T1 and T2 weighting images of the tumor invading the anterior ethmoids

everyday clinical practice, he should definitely point out the following key issues.

During the last 30 years the belief that oral cancer management is based on team work has been established. The functions of tumor boards and combined clinics is a common contemporary practice with an exceedingly large number of medical, surgical, and other specialties being part of comprehensive, multidisciplinary therapeutic head and neck teams.

The basic treatment modalities remain surgery, radiotherapy, and chemotherapy. Basic surgical techniques have not changed dramatically over the last 30 years. Among the major changes are the variations in the surgical management of the neck of both clinically negative and clinically positive neck patients, as well as the management of the mandible especially in the early invasion of oral squamous cell carcinoma in the mandibular bone. The revolution in the surgical treatment of oral cancer is the introduction of reconstructive techniques with both pedicled locoregional flaps and free tissue transfer. These reconstructive techniques allowed for safer and wider resections with adequate disease-free margins and functional reconstruction of the created surgical defects.

Contemporary radiotherapeutic treatment has very little similarities with that of the late 1970s. Modern technology with the institution of new forms of radiation and the application of sophisticated computerized methods have enhanced the therapeutic effectiveness of irradiation with an equal important reduction in the sparing in irradiation of normal surrounding tissues. This has led to an increased therapeutic dose in the tumorous bed and a decreased severity of radiation-induced injuries in the neighboring unaffected by the disease normal tissues. Alterations in the fractionations have also shown to produce better therapeutic results in selected cases.

The era of methotrexate, the leading chemotherapeutic agent of the 1970s, was followed by the institution of platinum-based chemotherapies with or without the addition of 5-Fu. Adjuvant and neoadjuvant schemes coupled with pre- or postoperative radiotherapy started in the late 80s and showed a distinct survival benefit over radiotherapy alone. This major breakthrough was followed by the institution of various and diverse chemoradiation regimes tested over a large time period for their survival benefits. The introduction of taxanes and the development of molecular targeted therapies during the last 5 years have revolutionized the concept of chemoradiation. Induction chemotherapy and chemoradiation coupled with epidermal growth factor receptor antagonists proved to have a survival benefit in patients with locally advanced or recurrent squamous cell carcinoma of the head and neck. Other biological agents against tumor angiogenesis or resulting in the restoration of cell apoptosis are being tested in various phase I or II trials with promising results.

Message Box

- In the course of the next decade: oral cancer in nonsmoker nondrinkers will increase.
- The differences in the ratios between males and females will tend to equalize.
- Surgery will remain the prime modality in early (stage I and II) disease.
- Molecular prognosticators will be used to determine optimal treatment.
- Postoperative chemoradiation will remain the treatment of choice for "aggressive" early (stage I and II) disease.
- Organ preservation treatments will prevail in advanced (stage III and IV) disease.
- Surgery will remain the treatment of choice for locoregional salvage surgery.
- The use of stem cells and biomechanical engineering will complement reconstructive surgery.

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Oral Oncology

25

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Abstract

This chapter describes current maxillofacial prosthetic rehabilitation concepts for the head and neck cancer patient and oral complications that can result from oncologic therapy. Head and neck cancer treatment can result in complex oral and dental sequelae. The complications vary by patient and depend on the individual's oral and dental status, malignancy, and treatment rendered. Oral complications can be minimized if patient education is implemented early in intervention and prevention is optimized. Oral oncology specialist can have an important role on the head and neck multidisciplinary team in supportive care therapy and maxillofacial prosthetic rehabilitation.

Keywords

Maxillary Obturator • Mandibular resection prosthesis • Palatal augmentation prosthesis • Radiation stents: Tongue-deviating stent, Tongue-depressing stent • Facial prosthetics: Orbital, Nasal and Auricular • Oral morbidities: Oral mucositis, Xerostomia, Osteoradionecrosis, Oral infections, Medicine-induced necrosis of the jaw

25.1 Introduction

Oral Oncology is a rapidly evolving field in head and neck cancer medicine and maxillofacial science. As new biological, targeted therapies and surgical techniques are developed, there is a continued need for expertise in oral medicine to address the diagnosis, prevention, and management of oral complications related to these therapies. Head and neck cancer therapies can result in complex oral and dental complications. Such complications vary by patient and depend on the individual's oral and dental status, type of malignancy, type of cancer therapy administered, and preexisting prosthetic rehabilitation. In most cases, preexisting conditions strongly influence the development of complications in the oral cavity. Mucosal and oral sequelae as a result of first- or second-line therapy cause significant morbidity (e.g., oral infection leading to systemic sepsis) and can compromise cancer treatment (e.g., oral mucositis leading to treatment delay, decreased dosing, or discontinued agent use). Oral complications during cancer therapy can be minimized, and in some cases eliminated, as well as maximizing prosthetic rehabilitation, if dispositioned and addressed early by the multidisciplinary team [1, 2].

This chapter describes current maxillofacial prosthetic rehabilitation for the head and neck cancer patient and global treatment of select oral complications that can result from head and neck oncologic therapy.

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25.2 Pretreatment Oral Management

Any potential source of oral infection should be eliminated prior to oncologic therapy. Extractions and associated alveoloplasty should be performed as atraumatically as possible

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and should include smoothing of sharp surrounding hard tissue, appropriate irrigation, and attempts at primary closure in order to promote rapid healing [3–5]. To ensure adequate wound healing, extractions should be performed 2–3 weeks before initiation of cancer therapy. Oral treatment plans should also be designed to correct restoration overhangs, rough or sharp edges on teeth, and any other defects likely to cause soft-tissue irritation. Dental implants should be carefully assessed, and their removal should be considered if integration is poor or if maintenance of peri-implant health cannot be reasonably anticipated. Ill-fitting intraoral prostheses should not be worn during cancer therapy.

Periodontal procedures such as scaling and root planning may be necessary before cancer treatment to reduce the oral bacterial load. Daily plaque removal procedures should be emphasized, including brushing with fluoride toothpaste and flossing. Oral hygiene procedures may require modification during cancer therapy [1]. An oral and dental consultation before chemotherapy, radiation therapy, or head and neck surgery is extremely important in the oral management of cancer patients. For patients receiving a tumor-ablative procedure involving the oral cavity, the treating physician should aim to control oral and dental problems before adjunct therapy and during the recovery phase. In the immediate postsurgical planning, the oral cavity should be prepared for appropriate prosthetic rehabilitation to correct postsurgical deficits.

25.3 Maxillofacial Prosthetic Rehabilitation

Advances in surgical technology and reconstructive techniques have enabled surgeons to resect extensive tumors of the head and neck. The resultant postsurgical defects can result in significant functional and aesthetic challenges for the patient. These difficulties can affect the patient's quality of life and overall outcome. The maxillofacial prosthodontist can assist the head and neck surgeon to minimize certain postsurgical challenges and improve functional outcomes and quality of life. These dental specialists are trained in the prosthetic reconstruction of patients who have undergone ablative surgery or those patients who have similar congenital or developmental defects. Close collaboration between the head and neck surgeon, reconstructive surgeon, and the maxillofacial prosthodontist is important in optimizing postsurgical outcomes [6]. The patient's desire for prosthetic reconstruction should be discussed prior to the ablative and reconstruction surgery. Prosthetic reconstruction requires a stable, healthy, non-ulcerating tissue base for success.

Although there are numerous intraoral maxillofacial prostheses that can be described, the most common are the maxillary obturator, mandibular resection prosthesis, palatal augmentation prosthesis, and radiation stents. Each of the above chosen prostheses will be briefly described as well as extraoral prosthetic rehabilitation.

25.3.1 Intraoral Prosthetic Rehabilitation

25.3.1.1 Pre-prosthetic Surgical Enhancements for Maxillary Obturators

Prosthetic reconstruction of the maxillectomy defect is dependent on having healthy tissue for support, retention, and stability. The following are surgical modifications which may improve success [7]:

1. Maintain healthy teeth on the non-affected side
2. Maintain as much hard palate as is possible and strive to maintain the premaxilla
3. Place a split-thickness skin graft on the cheek and in the maxillary defect. This will provide a non-ulcerating, prosthesis-bearing tissue surface with minimal mucous or polypoid formation
4. Removal of the inferior turbinate allows proper extension of the obturator bulb into the defect
5. Maintain healthy abutment teeth

25.3.1.2 Maxillary Obturator

Patients with acquired maxillary surgical (maxillectomy) defects can often be successfully rehabilitated with obturator prostheses. Functionally, patients with a palatal defect have difficulties with their speech, articulation, bolus control, and deglutition, as the speech sounds and food/liquids escape into the defect. The obturator serves to prosthetically close the defect and thus prevent the leakage of food, liquids, and speech sounds into the nasal cavity and maxillary sinus.

The three phases of rehabilitation of the maxillectomy patient include the fabrication of surgical, interim, and definitive obturators. The surgical obturator is placed at the time of the maxillectomy surgery, following resection of the lesion. This prosthesis holds the surgical dressing in position and replaces the lost palatal contours. It is typically held in position with interdental wires, circumzygomatic wires, bone screws, or sutures. This prosthesis allows patients to eat and speak normally in the postoperative period, eliminating the need for a feeding tube. It is thought to reduce the psychological impact of the surgery and may reduce postoperative hospitalization time. Fabrication of a surgical obturator requires the patient be seen by the maxillofacial prosthodontist days prior to the surgery for dental impressions. The resultant dental cast is modified to reflect the proposed surgery, and the surgical obturator is processed on the cast with acrylic resin (Fig. 25.1).

The ligated surgical obturator and packing are removed approximately 6–10 days following surgery. The interim

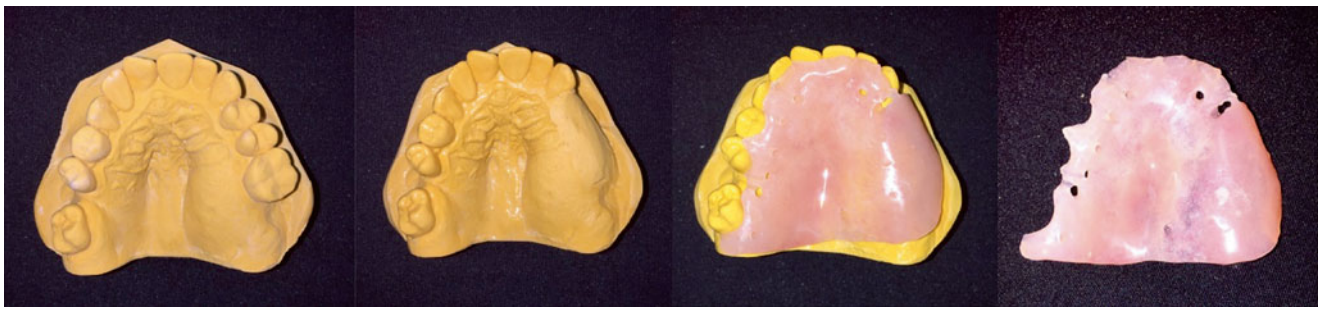

Fig. 25.1 Surgical obturator sequence

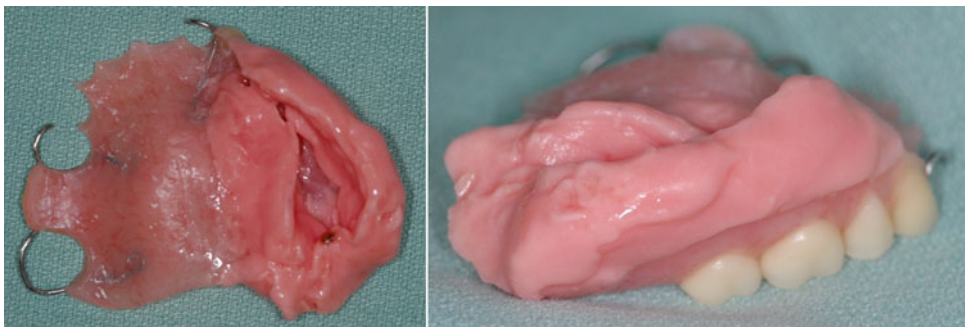

Fig. 25.2 (**a**) Intaglio view obturator. (**b**) Lateral view. Interim obturators have been modified with tissue-conditioning material to form a bulb that closes the maxillary defect when prosthesis is in place

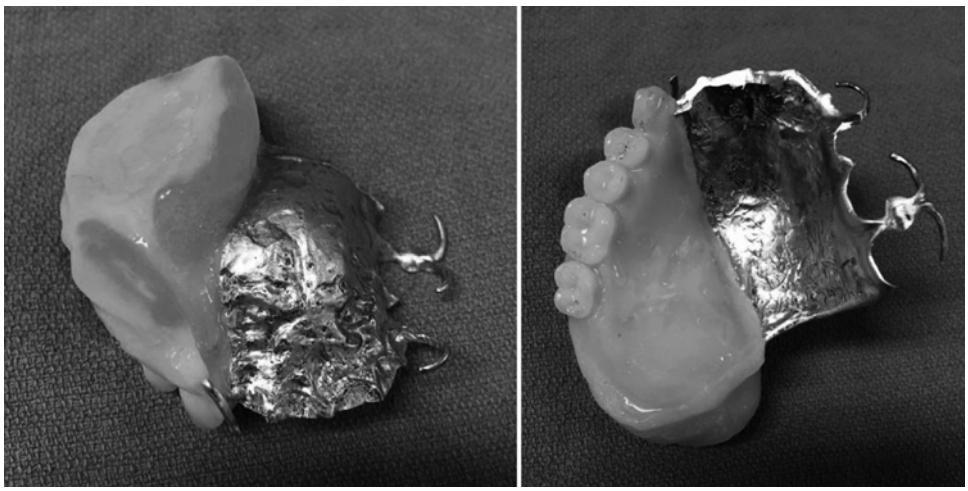

Fig. 25.3 Definitive obturator with metal framework

obturator is then modified and delivered to the patient [8]. This prosthesis is removable and is worn by the patient for 3–6 months as the tissues in the defect heal and mature (Fig. 25.2). The bulb component of the obturator extends into the defect with a soft, pliable tissue-conditioning material which is adapted and molded by the functional movements and anatomy of the defect. As the tissues heal and change, the obturator requires multiple adjustments and modifications. Hypernasal speech and leakage of liquids are common problems during this phase of healing. Frequently, these patients are seen bimonthly for adjustments and modifications.

The definitive obturator is fabricated once the tissues have stabilized and matured. This prosthesis is fabricated to optimize stability, function, and aesthetics and is intended for long-term use (Fig. 25.3). Stability of the obturator is improved with greater contact and adaptation of the remaining soft and hard tissues. Osseointegrated endosteal implants may also aid in the stability and retention of the prosthesis.

25.3.1.3 Mandibular Resection Prosthesis

The mandible provides facial form and contours to the lower part of the face. With its multiple muscle insertions, the mandible provides complex movements which aid in mastication, speech, and deglutition. Resections of the mandible can alter its contours and function. The contours of the defect and the function of the mandible following resection can have significant variability depending on the site, the extent of the

surgery, and the type of reconstruction. The mandibular reconstruction prosthesis attempts to restore mandibular form and function [9–11].

Mandibular resection prostheses require stable, nonmobile tissue for support. The presence of implants or healthy dentition on the unaffected side can greatly aid in retention of these prostheses. Primary closure of mandibular resection defects with the tongue or floor of mouth to the buccal mucosa often precludes prosthetic reconstruction, as the supporting tissue is tethered and mobile. With primary closure, the vestibules are obliterated, and there is limited tongue mobility, with associated speech and swallowing dysfunction. Microvascular flaps and split-thickness skin grafts can be utilized to reconstruct resected areas and eliminate the need for primary closure. The skin graft can provide an ideal surface for prosthetic reconstruction over a marginal mandibulectomy resection (Fig. 25.4). This tissue firmly attaches to the underlying medullary bone providing a nonmobile surface for prosthetic reconstruction.

Discontinuity mandibular resections are difficult to restore to proper function with prostheses. Frequently the mandible deviates to the resected side as well as rotates inferiorly [12]. This causes occlusal disharmony of the remaining dentition and loss of mandibular contours (Fig. 25.5). The ideal treatment for this defect is reconstruction with an osseocutaneous microvascular free flap [13, 14]. Proper postoperative mandibular function and preservation of the occlusal relationships is dependent on maintaining the position and orientation of the non-resected mandibular segments. Bending a reconstruction plate on the non-resected mandible intraoperatively and fixing the plate prior to the resection will maintain the necessary relationship. Alternatively, the reconstruction plate can be prebent on a stereolithographic model of the mandible.

The intraoral tissue provided by an osseocutaneous flap is frequently very bulky and mobile and needs refining prior to prosthetic reconstruction (Fig. 25.6a and b). Debulking of

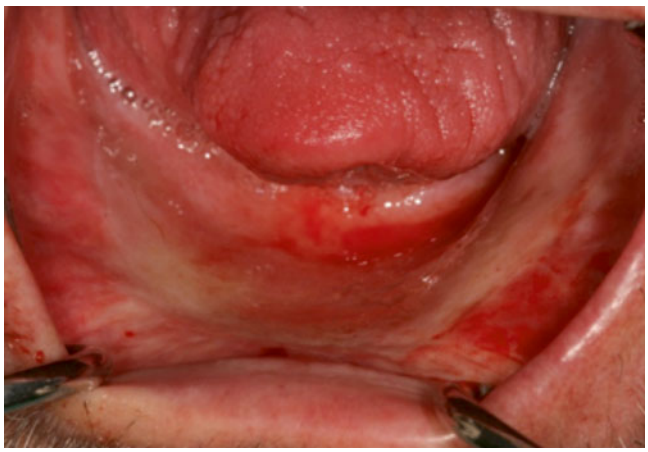

Fig. 25.4 Well-healed skin graft over a marginal mandibulectomy defect providing an ideal surface for prosthetic rehabilitation

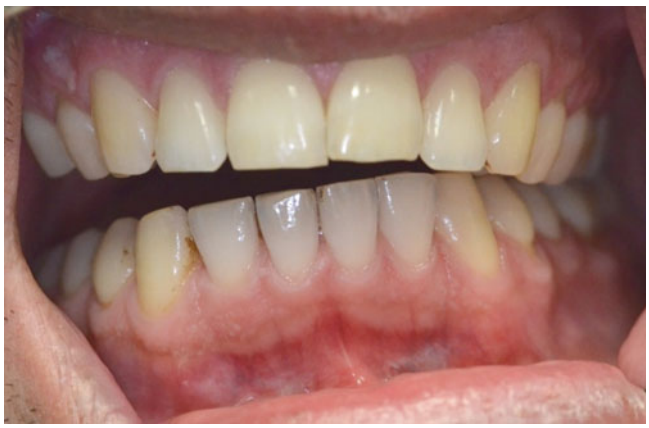

Fig. 25.5 Discontinuity mandibular resection

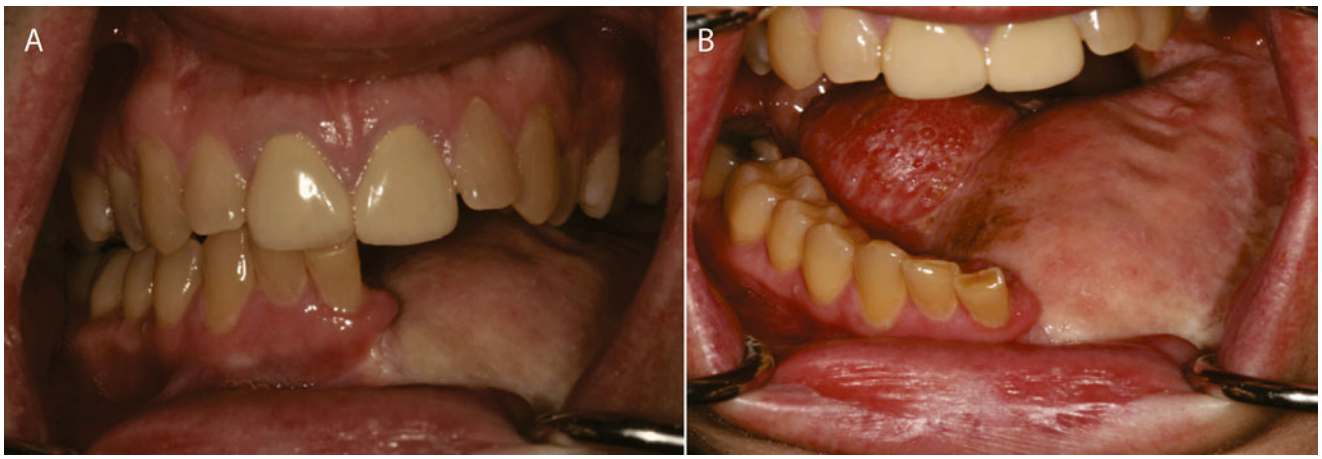

Fig. 25.6 (**a**) Bulky osseocutaneous flap in maximum intercuspation. (**b**) Occlusal indentations on flap

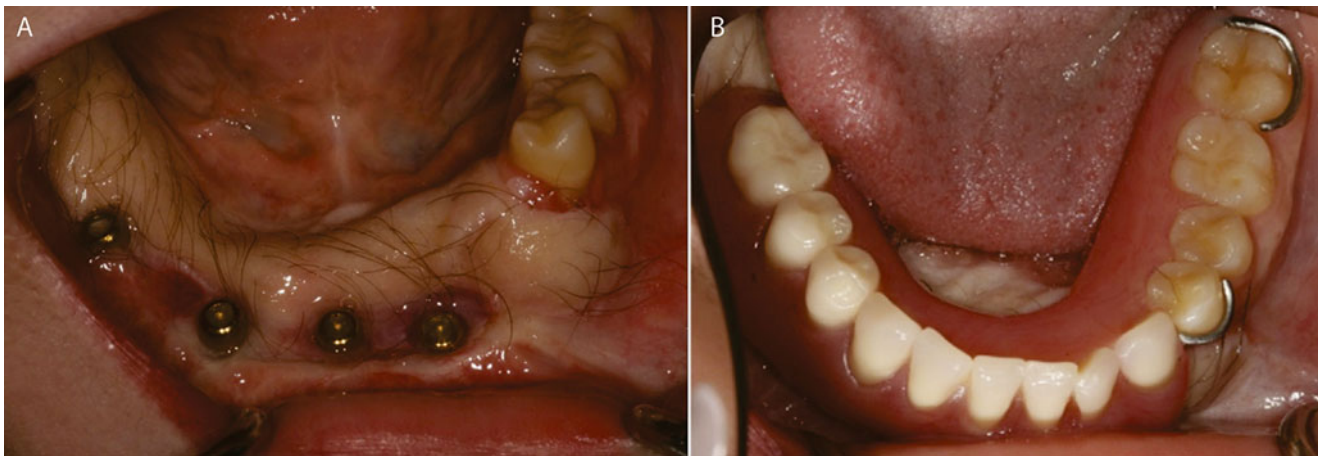

Fig. 25.7 (**a**) Debulked and headed skin graft over a mandibulectomy defect providing an ideal surface for prosthetic rehabilitation. (**b**) Acrylic resin mandibular resection prosthesis in position

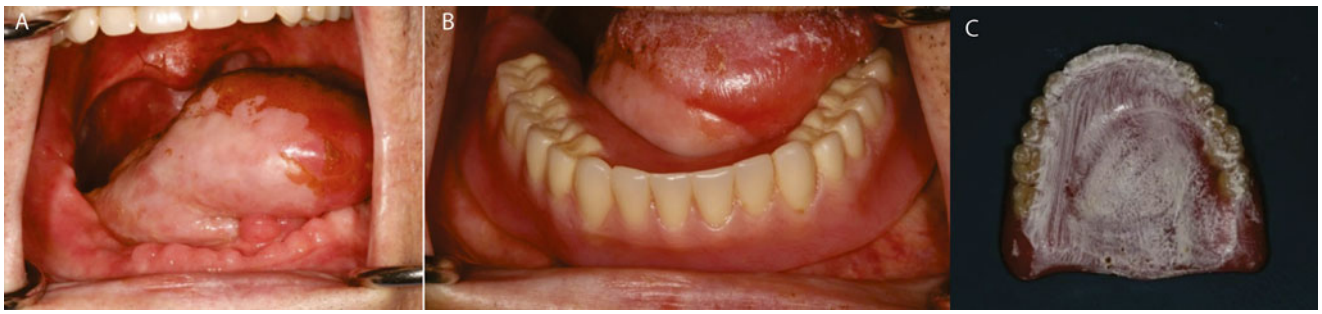

Fig. 25.8 (**a**) Partial glossectomy. (**b**) Mandibular prosthesis in place. (**c**) Palatogram for verification of palatal augmentation prosthesis

the flap and placement of endosteal implants will prepare the tissues for prosthetic reconstruction [15] (Fig. 25.7a and b).

25.3.1.4 Palatal Augmentation Prosthesis

Speech and swallowing functions are highly dependent on the structures of the oral cavity including the tongue, hard and soft palate, lips, and dento-alveolar processes. Patients who undergo glossectomy and floor of mouth and/or mandibular resections frequently have impaired articulation and deglutition. Surgical resection of these oral structures results in altered anatomy and changes in their movement (Fig. 25.8a and b). Alterations in the sensory and motor innervation of these structures may impair function. Imprecise or restricted tongue movements may cause unintelligible speech and difficulties with deglutition and bolus control [16].

The palatal augmentation is a prosthesis worn in the maxilla which prosthetically lowers and recontours the palatal vault. This prosthesis allows a more normal articulation between the resected or reconstructed tongue and neo-palate of the prosthesis. The palatal contour of the prosthesis is developed on a removable acrylic resin plate which attaches to the tissues and teeth of the maxillary arch. A soft pliable tissue-conditioning material is placed on the polished surface of the plate, and this is molded by the movement of the tongue with speech and swallowing functions (Fig. 25.8c). Once the palatal contours are finalized, the tissue conditioner is replaced with acrylic resin [17–19].

25.3.1.5 Intraoral Radiation Stents

Radiation therapy to the head and neck structures is challenging. Its intricate anatomy and numerous vital structures make it difficult to provide tumoricidal doses to target structures while minimizing side effects to adjacent normal structures, i.e., oral mucositis. With the introduction of conformal therapy, i.e., intensity-modulated radiotherapy (IMRT), intensity-modulated proton radiation therapy (IMPT) radiation side effects can be reduced. The use of intraoral radiation stents will also help minimize complications to the normal tissues. Radiation stents are either positional or shielding. Shielding stents incorporate a material (such as Lipowitz alloy) which reduces the transmission of radiation to normal structures. The positional radiation stent displaces normal tissues away from the treatment fields [20]. The most common positional radiation stents are the (1) unilateral or tongue-deviating stent and (2) mouth-opening tongue-depressing stents. Modifications

can be incorporated into these stents in order to customize it for special treatment situations.

25.3.1.6 Unilateral Tongue-Deviating Stent

This stent is fabricated for patients who receive unilateral radiation treatment. It opens the mouth at an inter-incisor distance of 2–4 mm and displaces the tongue contralaterally. By doing so, it positions the oral tongue repeatedly and displaces the tongue and supporting tissues away from the higher dose and, thus, reduces treatment-related morbidities and maximizes uniform position (Fig. 25.9a and b).

25.3.1.7 Mouth-Opening Tongue-Depressing Stent

The mouth-opening tongue-depressing stent (MOTDS) opens the dental arches at an inter-incisor distance of 20 mm and positions the tongue inferiorly in the floor of the mouth. By separating the dental arches, radiation side effects can be minimized to the unaffected arch. If the tongue and floor of mouth is in the target volume, the MOTDS will position the maxillary arch away from the radiation field, thus minimizing the side effects to the maxilla. Conversely, if the maxilla and paranasal sinuses are to be treated, the tongue and mandible may be spared (Fig. 25.9c and d).

25.3.1.8 Fabrication of the Stents

Initially, the stents are fabricated off of casts from impressions of the dentate or edentulous dental arches. A wax interocclusal record is obtained at the desired mouth-opening position and is used to mount the casts on a type 1 dental articulator. The stent is fabricated in wax, and its fit is verified intraorally. Radiation simulation is completed with the wax pattern in place. Following successful simulation, the stent is processed into acrylic resin [21]. The radiation stent must (1) accurately place the oral structures in a repeatable and reproducible position, (2) be easy to insert and remove, and (3) be non-irritating to the tissues. Close collaboration between the radiation oncologist and the prosthodontist is required for successful fabrication and use of these stents.

25.3.2 Extraoral Prosthetic Rehabilitation

25.3.2.1 Facial Prosthetics

Prosthetic reconstruction of facial defects resulting from tumor ablation, trauma, or congenital defects remains an important and challenging aspect of the maxillofacial prosthodontic practice. Surgical reconstruction of these defects can be limited by the availability of tissue, local vascular supply, and the need to perform multiple surgeries to provide acceptable form and function. For some patients, their surgical reconstruction may be delayed by underlying medical conditions or the need to monitor the surgical site for recurrences. Facial prostheses can frequently offer a timely and aesthetic alternative to surgical reconstruction. They provide a great psychological benefit in the rehabilitation of patients as it allows them to return to most of their normal activities.

The most common facial prostheses are the nasal, orbital, and auricular. They are removable prostheses which are attached with adhesives, tapes, or osseointegrated implants. Facial prostheses are custom fabricated from a medical grade elastomeric material and require multiple steps over a 1–2 week period to complete. Initially a moulage impression of the defect and the surrounding tissue is made. The plaster model of the defect is utilized to sculpt the facial contours in wax or clay. Once the form and fit of the wax pattern are verified on the patient, it is processed with a custom-colored silicone. It is delivered to the patient after final fitting and extrinsic coloring [22–24]. Instructions of use and care shall be provided to the patient as well as to look for discoloration of the prosthesis over time [25]. Other issues that may present are inherited to the use of adhesives and their effect on the integrity of the margins of the prosthesis [26]. To help preserve the life of the prosthesis, one can line the tissue surface with a polyurethane liner as described by Udagama [27].

25.3.2.2 Nasal Prosthesis

When tumor ablation involves the resection of the nose or nasal structures, it can necessitate partial or total nasal restoration (Fig. 25.10a and b). At the time of surgery, the nasal spine is left intact, if possible, for stability of the nasal prosthesis. Unsupported tissue tags are removed, as this can make dificult impression-making and can compromise the final prosthesis by hampering the patient in positioning and securing a prosthesis. Rough tissue margins can compromise the concealment of the prosthetic margins and retention. A split-thickness skin graft is placed over the resected bone margins to increase the stability of the nasal prosthesis. Grafts or flaps are used to maintain the position of the midface and upper lip [28]. The nasal prosthesis can help to protect the delicate exposed tissues of the nasal cavity and sinuses from the environmental elements and prevent dessication. The nasal prosthesis can help restore normal speech sounds.

25.3.2.3 Auricular Prosthesis

An auriculectomy can be a difficult rehabilitation as the resection can be exceptionally small as in a subtotal resection or large with a total auriculectomy with surrounding tissue involvement. It is easier to replace a complete ear than a partial ear with a prosthesis due to a clinican's liberty in shape, size, and location (Fig. 25.11a and b). First, the recipient area must be flat or concave as convexity from tissue bulk can hamper aesthetic results. Second, skin devoid of hair provides a good adhesive base, although a split-thickness

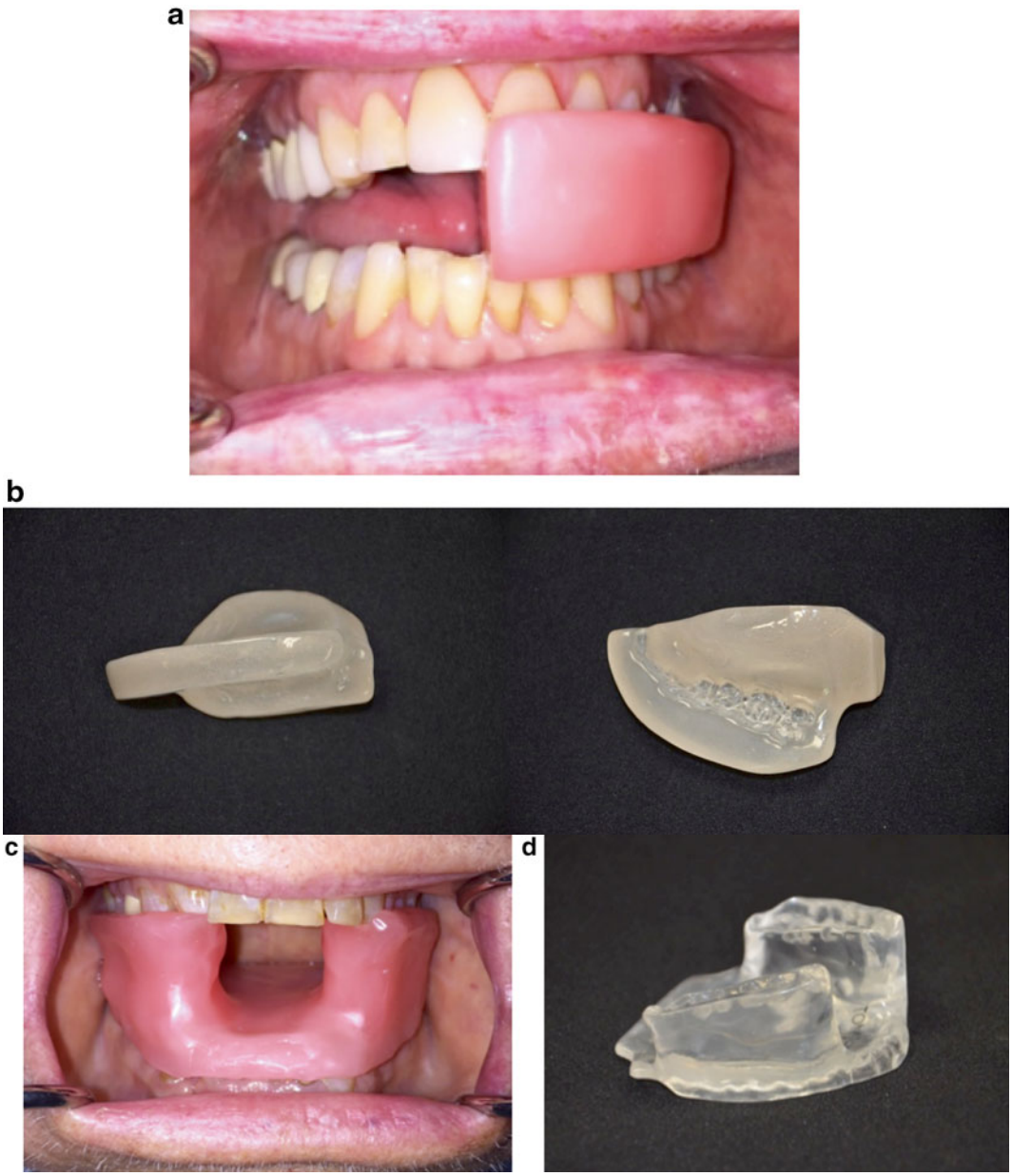

Fig. 25.9 (**a**) An intraoral view of the wax pattern of a tongue-deviating stent prior to simulation and processing. (**b**) An acrylic resin unilateral, tongue-deviating radiation stent used for IMRT external beam radiation therapy. Lateral and occlusal views. (**c**) An intraoral view of the wax pattern of a tongue-depressing stent prior to simulation and processing. (**d**) A tongue-depressing radiation stent used for IMRT external beam radiation therapy

skin graft is better. If tissue can be spared, the tragus is the first choice. It is a good separate landmark that is not easily displaced. The tragus allows the anterior margin of the prosthesis to be hidden behind the posterior flexure. It also aids the patient in proper positioning of the prosthesis by providing a placement reference. The inferior half of the soft-tissue pinna is of little or no use due to lack of cartilaginous support. A preserved portion of the root of the helix is a good landmark and support for eyeglasses. Additionally, this area can help later in vertical support of the prosthesis. The anterior superior helical rim is left in place if possible [28].

25.3.2.4 Orbital Prosthesis

The orbital exenteration can be challenging to the maxillofacial prosthodontist or anaplastologist due to the shape of the final reconstruction or grafted site. Several surgical considerations can improve prosthetic rehabilitation such as maintaining the position of the eyebrow if not required in the initial tumor ablation. Irregular or sharp bony margins should be smoothed and rounded in allowing for a more effective reconstruction. A split-thickness skin graft is placed into the area of the defect to cover exposed bone creating a concavity to house the prosthesis (Fig. 25.12a–c). Sufficient depth of defect is

Fig. 25.10 (**a**) A partial rhinectomy with movable paranasal tissue. Nasal prosthesis secured in place by a bioadhesive. Note the translucent margins. (**b**) A total rhinectomy. Nasal prosthesis secured in place by a bioadhesive

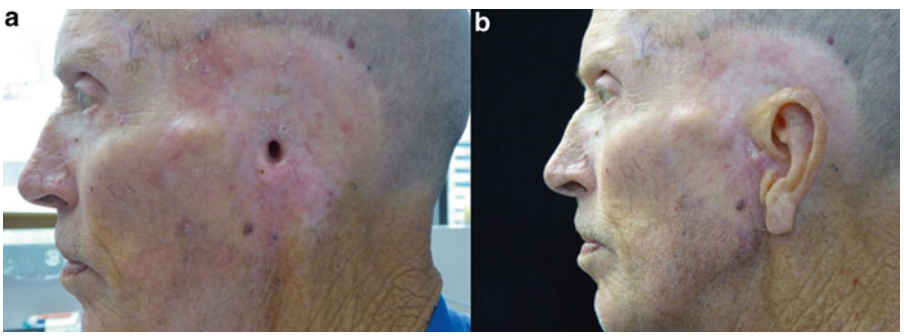

Fig. 25.11 (**a**) A total auriculectomy, post-radiation treatment, with a smooth reconstructed base. (**b**) Auricular prosthesis in position with an excellent aesthetic result

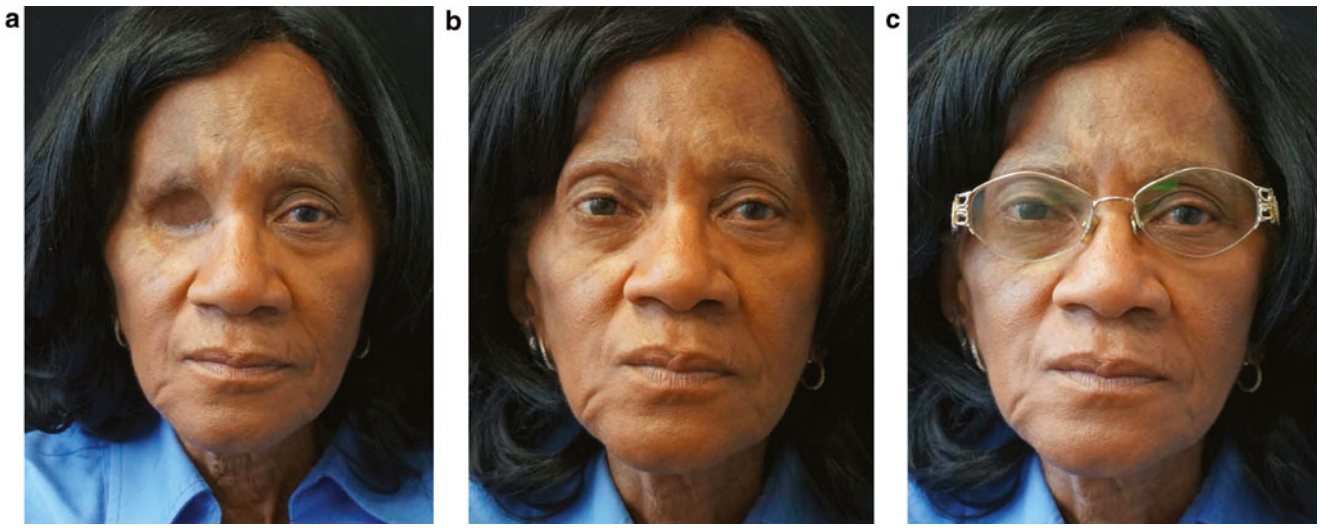

Fig. 25.12 (**a**, **b**, **c**) Orbital exenteration site with an ideal split-thickness skin graft base. Final orbital prosthesis engaged in the concave defect. Eyeglasses help to hide the prosthetic margins

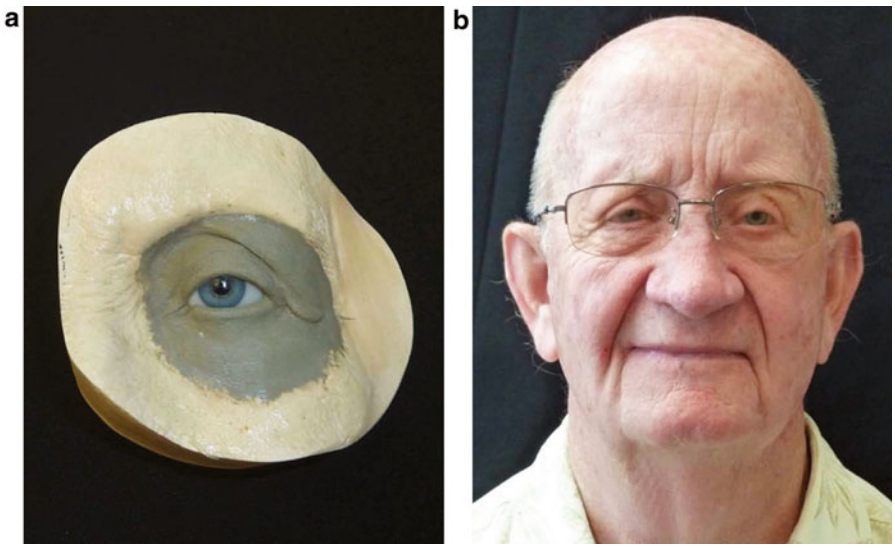

Fig. 25.13 (**a**, **b**) Orbital prosthetic sculpting with a customized ocular prior to final processing. Prosthetic in place

essential in order to fabricate an aesthetic and stable orbital prosthesis as well as markedly improving hygiene [28, 29]. Figure 25.13a and b shows sculpted orbital prosthetic with a custom-painted ocular.

25.4 Treatment-Induced Oral Morbidities

Complications resulting from therapeutic administration of ionizing radiation to the head and neck and cytotoxic or biosensitizing agents as treatment for cancer can be categorized as either acute (e.g., mucositis, infectious stomatitis, alteration of taste or smell acuity, dermatitis, pain, inflammation, and difficulty swallowing) or chronic (e.g., xerostomia, caries, abnormal development, fibrosis, trismus, osteonecrosis, and pain) [2]. The severity of treatment-induced morbidity depends on multiple factors, such as the radiation dose, volume of tissue treated, myelosuppressive treatment, pretreatment performance status, and pretreatment oral condition. Complications arise primarily in three anatomic sites: the mucosa, periodontium, and teeth.

The following is a discussion of five key oral complications: mucositis, xerostomia, osteoradionecrosis, oral infections, and bisphosphonate-induced osteonecrosis.

25.4.1 Oral Mucositis

The term oral mucositis is generally used to describe a mucosal barrier injury or inflammation secondary to chemotherapy or head and neck radiation therapy. The term oral stomatitis is used to describe inflammation secondary to

other causes, e.g., infection, trauma. Indeed, approximately 40 % of patients who receive standard chemotherapy, and almost all patients who receive head and neck radiation therapy, develop varying degrees of oral mucositis [30]. Accumulating data would suggest that the pathogenesis of mucositis is complex and involves the sequential interaction of all cell types of the oral mucosa, as well as a number of cytokines and elements of the oral environment [31].

Sonis has proposed a five-phase model to explain the pathophysiology of oral mucositis: initiation, upregulation and message generation, amplification and signaling, ulceration, and healing [31]. Considerable inter-patient variability exists in the tolerance to chemotherapy regimens [32]. Treatment factors that influence the frequency and severity of oral mucositis include the chemotherapeutic agent used, dosage, delivery schedule, and combination with radiation therapy [33], whereas the severity of radiation-induced mucositis depends on total dose, dose fractionation, volume of tissue irradiated, and type of radiation given [34]. Other factors that may contribute to the severity of mucositis include smoking, use of over-the-counter mouthwashes, and coexistence of collagen vascular diseases or HIV infection [35].

The most consistent symptom of mucositis is pain. The severity of pain correlates with the severity of the mucositis [36]. The pain is constant in nature and is aggravated by drinking, eating, and performance of oral hygiene measures. All intraoral sites may be affected, although non-keratinized surfaces are most severely affected (mucosa of lips, cheeks, floor of mouth, ventral surface of tongue, and soft palate). Erythema is the initial manifestation, followed by the development of white desquamative patches. Epithelial sloughing and fibrinous exudate lead to the formation of ulceration and a pseudomembrane [31, 35]. The complications of oral mucositis include dehydration, malnutrition, local infection, systemic infection, local hemorrhage, and interference with the cancer treatment regimen. The later complication is particularly important, since a delay in completing treatment, or a reduction in the amount of treatment given, may influence the eventual outcome of treatment.

Oral mucositis is a self-limiting condition, with recovery occurring around 2 weeks after a course of chemotherapy and approximately 4–5 weeks after a course of radiation therapy [31, 37]. Preexisting or predisposing factors that challenge wound healing can affect recovery from oral mucositis (e.g., infection) [31].

There is no standard therapy that is effective in the prevention of oral mucositis. The range of medications that have been used is extensive. A recent systematic review identified 21 interventions that had been subjected to randomized controlled trials but found evidence of benefit for only nine of these interventions [38]. The authors concluded that there was some evidence to support the use of allopurinol, amifostine, antibiotics, GM-CSF, hydrolytic enzymes, ice chips, povidone, and oral care. In many instances, the evidence for the effectiveness of the intervention was based on studies performed in specific patient or treatment groups. The mainstay of the symptomatic management of oral mucositis is the use of analgesics. In some cases, topical analgesics will control the pain. However, in most cases, topical analgesics need to be supplemented or replaced by systemic analgesics.

25.4.2 Xerostomia

Salivary gland dysfunction (SGD) is a common problem in patients with cancer, specifically, radiation- and drug-induced xerostomia. SGD may result from a reduction in salivary flow and/or an alteration of salivary composition. The most common cause for salivary gland dysfunction is drug treatment. Several drugs can produce SGD, including chemotherapy agents (e.g., busulfan, procarbazine) and supportive care agents (e.g., analgesics, antidepressants, antiemetics) [34]. Drug-induced SGD is generally reversible, i.e., discontinuation of the drug leads to resolution of the problem.

SGD is a predictable side effect of radiation therapy to the head and neck region. Radiation-induced SGD is generally irreversible. The severity of radiation-induced SGD is influenced by both radiation therapy regimen (volume, dose) and pretreatment salivary gland function [39]. Damage to the salivary glands results in reduced salivary flow, changes in the electrolyte and immunoglobulin composition of saliva, reduction of salivary pH, and a shift of microorganism into a more cariogenic microflora [34]. When the major salivary glands are included in the radiation field, salivary function often decreases by 50–60 % in the first week, with basal salivary flow reaching a measurable minimum 2–3 weeks after 23 Gy of fractionated RT [34, 40, 41]. The extent of glandular change is generally directly related to the dose of radiation to the salivary glands, with the most severe and irreversible forms of salivary dysfunction resulting from damage to or loss of salivary acinar cells.

Individuals with SGD can exhibit innumerable problems, including xerostomia, oral discomfort, taste disturbance, difficulty chewing, difficulty swallowing, difficulty speaking, dental caries, and other oral infections. Salivary gland dysfunction may also intensify, or prolong, the process of oral mucositis [34]. These problems reflect the major functional roles of saliva.

Various pharmacologic strategies have been employed to reduce the impact of radiation therapy on salivary gland function, including salivary gland shielding [39], use of radioprotectors (amifostine) [42], use of cholinergic agonist drugs (pilocarpine, cevimeline) [34], use of prescription fluoride agents to maintain optimal oral hygiene, and use of

antimicrobials to prevent dental caries and oral infection. The options for treating SGD include the use of saliva substitutes, sialagogic agents, or a combination of both to stimulate saliva production from remaining intact salivary gland tissues [41, 43].

25.4.2.1 Osteoradionecrosis

Osteoradionecrosis (ORN) has been defined as "radiological evidence of bone necrosis or persistent bone exposure within the volume of tissue radiated" [44]. ORN has become a relatively uncommon chronic complication of head and neck radiation therapy. The reasons for the decline in the incidence of ORN include improvements in radiation therapy (conformal therapy) and improvements in supportive care (oral and dental care). The underlying mechanisms of ORN relate to the "three-H principle" of irradiated tissue, i.e., hypocellularity, hypovascularity, and hypoxia. In such tissue, the ability to replace normal cellular and collagen loss is severely compromised, with resultant necrosis occurring in relation to the rate of normal or induced cellular death and collagen lysis [45, 46]. The risk of ORN following trauma or oral surgical procedures can be as high as 30 % as noted after dental extractions within the mandible of patients receiving at least 57 Gy [47].

ORN has been associated with a number of different factors, including patient-related factors (poor oral hygiene, post-radiation dental extractions), disease-related factors (tumor size and location), and radiation therapy-related factors (radiation dose, fractionation). ORN can occur at any time following radiation therapy, but commonly occurs within 3 years of the radiation therapy [48], which may be consistent with the fact that a significant number of patients do not survive head and neck cancer. The risk for ORN is lifelong, and when it becomes evident after 3 years, it is usually related to a lack of compliance with oral care.

The mandible is much more susceptible to ORN than the maxilla due to collateral vascularity present in the maxilla. The clinical features are influenced by the stage of the process. Patients with early stage necrosis may be relatively asymptomatic. In contrast, patients with advanced stage are often very symptomatic (pain, discharge). Store et al. have proposed the following classification of ORN:

- Stage 0—exposed bone; no radiological signs
- Stage 1—mucosa intact; radiological signs present
- Stage 2—exposed bone; radiological signs present
- Stage 3—exposed bone; radiological signs present; orocutaneous fistula; localized infection.

The diagnosis of ORN is based on a combination of clinical features and radiological features [41, 48]. Plain radiographs show decreased bone density and may show fractures; however, computed tomography (CT) scans are the imaging of choice as it shows bone abnormalities such as focal lytic areas, cortical breaks, and loss of trabeculation.

The most important aspect of management is prevention. ORN may be avoided if patients receive dental extraction of grossly carious or periodontal involved teeth and appropriate dental maintenance education prior to radiation therapy. Such patients must maintain high standards of oral hygiene following radiation therapy and avoid dental extractions and other types of oral surgery within the highly dosed radiation volumes. If oral surgical intervention is required after radiation therapy, then pre- and postoperative hyperbaric oxygen therapy may increase the potential for healing, while minimizing the risk for ORN [49]. Hyperbaric oxygen therapy increases wound healing capacity by stimulating osteogenesis and angiogenesis. It should be noted that certain dental procedures can be safely done after radiation therapy, including routine restorative procedures, endodontic procedures, and prosthetic procedures.

In most cases, the management of ORN is conservative and involves some or all of the following modalities: removal of loose bone fragments, gentle sequestration, irrigation, topical antiseptics, systemic antibiotics, and/or hyperbaric oxygen [41, 48]. Other modalities that have been reported to be effective include pentoxifylline and vitamin E [50], ultrasound therapy, and electromagnetic stimulation [48]. In advanced (symptomatic) cases, the management of ORN is surgical and involves either radical sequestration or jaw resection and immediate microvascular reconstruction [51, 52].

Figure 25.14a and b shows a patient with past history of squamous cell carcinoma of the sinuses treated with radiation therapy and concurrent chemotherapy. Eight months posttreatment, patient has an injury to the left posterior quadrant resulting in osteoradionecrosis.

25.4.3 Oral Infections

Oral cavity infection is a common problem that can impact the treatment and long-term morbidity of the head and neck cancer patient. It is important that these problems be diagnosed and treated prior to cancer therapy. Oral and radiographic examination by a dentist can eliminate problems such as dental abscesses, gross caries, and advanced periodontal disease. These diseases can cause a pronounced increase in morbidity with treatments such as surgery, radiation, and chemotherapy. In most cases, the treatment of choice is extraction of unrestorable or questionable teeth. In restorable teeth restoration and/or endodontic treatment may eliminate the problem. Oral hygiene is extremely important and must be considered in treatment planning of these patients.

In the surgical patient preexisting oral infection can delay healing and cause contamination to the surgical wound [41,

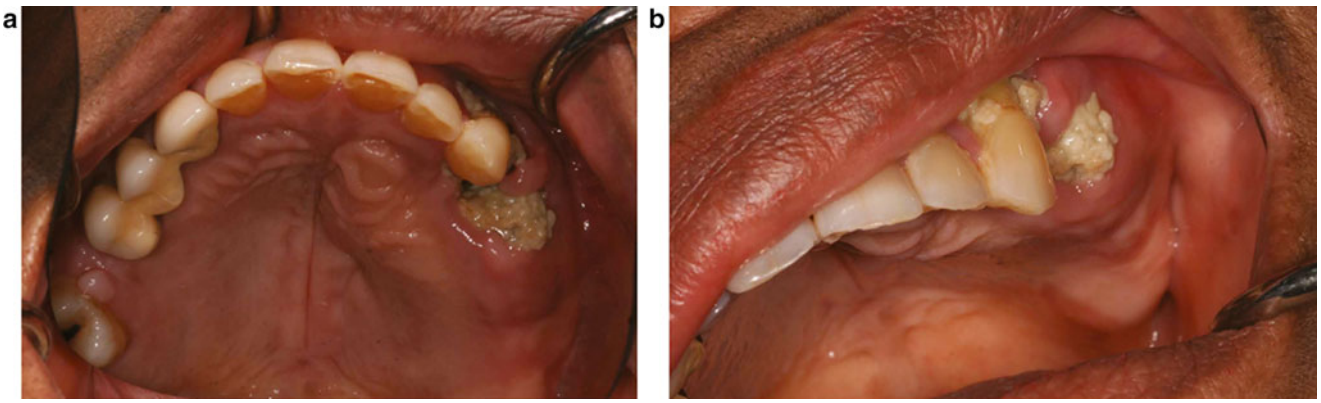

Fig. 25.14 (**a**, **b**) Patient with past history of squamous cell carcinoma of the sinuses treated with radiation therapy and concurrent chemotherapy. Eight months posttreatment, patient has an injury to the left posterior quadrant resulting in osteoradionecrosis

53]. This may prolong hospitalization and antibiotic treatment, thereby increasing the cost of care [54]. Infection can also mimic oral cancer making accurate assessment difficult. Exodontia can be done during the same general anesthesia as the primary ablative procedure.

Patients receiving chemotherapy may develop life-threatening infections from preexisting oral problems not treated prior to therapy. Even removable prostheses such as complete and partial dentures may cause irritation that becomes secondarily infected by bacteria. These prostheses may also increase nausea and vomiting with chemotherapy. Chemotherapy may cause mucositis in the mouth. In some cases these lesions will need to be cultured to rule out viral and bacterial infection. Early detection and treatment of infection improves survival.

Treatment of oral infection in the radiation patient reduces the chances of osteonecrosis with subsequent loss of a portion of the maxilla and mandible. Xerostomia in these patients increases the chance of caries and infection. As in the chemotherapy patient, radiation-induced ulceration must be differentiated from infection by microbiological assessment [53]. The causative organism must be identified and sensitivity testing completed to optimally treat the intraoral bacterial, fungal, viral, resistant organisms, or a combination thereof.

Diagnosis and early treatment of oral infection can reduce morbidity and economic burden of treatment in the head and neck cancer patient. The oncologic dentist has an important role in this process and should be included as a team member in any cancer treatment center.

25.4.3.1 Medicine-Related Osteonecrosis of the Jaws (MRONJ)

New challenges have been developed for those clinicians who participate in the oral care of the oncologic patient. These started to appear over a decade ago and the pathophysiology is poorly understood. The challenges were associated with high relative potent intravenous (IV) bisphosphonate therapy that is used in the oncology setting to reduce skeletal events due to metastatic osseous disease, multiple myeloma, or secondary bone cancer. Individuals considered having medicine-related osteonecrosis of the jaw have common characteristics: current or previous treatment with antiresorptive or antiangiogenic agents, [2] exposed bone in the maxillofacial region that has persisted for more than 8 weeks, and [3] no history of radiation therapy to jaws or obvious metastatic *displacement* to the jaws.

Osteonecrosis of the jaws or medicine-related osteonecrosis of the jaws (MRONJ) slowly emerged into the medical literature recently. In early 2004, an expert panel of medical/dental specialists convened, and reviewed the facts of MRONJ, and published a "white paper" listing risk factors as well as recommendations for patient treatment prior to and during IV bisphosphonate therapy [55]. Recommendations and treatment algorithms were formulated for the treatment of jaw necrosis [55].

At the advent of understanding MRONJ, necrosis was associated with a totally heterogeneous oncology population other than the more well-known and accepted necrosis seen in oral cancer patients treated with radiation (e.g., osteoradionecrosis, ORN). In such patients, the ORN was treated aggressively by local surgical debridement. However, when this was done with MRONJ, healing was poor and slow. The result was only a more profound lack of healing and necrosis. Hyperbaric oxygen therapy did not produce any significant improvement, in contrast to patients with ORN. Finally, after several "cases" it was noted that conservative management was the better approach when MRONJ, developed; specifically, minor surgery produced a better healing response [56]. In addition, with MRONJ, super infection is highly likely necessitating antibiotic therapy [55].

The risk of jaw necrosis is increased with preexisting oral/dental pathology and administration of IV bisphosphonate therapy or others like antiresorptive agents. As significant as the warnings have been, with poor regularity, patients are placed on IV bisphosphonate therapy without regard to the existing oral/dental state. Thus, any oral or dental pathology that needs to be corrected due to infectious risks with oral surgery becomes a high-risk potential for jaw necrosis development.

There are numerous treatment guidelines and algorithms related to patient care of MRONJ associated with IV bisphosphonate therapy use as seen present in the literature regarding oral/dental management, specifically, pre-assessment for risk factors, maintenance of the dento-alveolar complex, as well as treatment modalities if and when jaw necrosis develops [55, 57–60]. Like all phases of medical practice, preventive-interceptive treatment practices are well known to have a significant influence on the course of care, not only for the patient, but for the treating medical and dental practitioners. The treating physician must be assertive to make sure that the patient understands the importance of a healthy dento-alveolar complex prior to IV bisphosphonate therapy and being "cleared" by the dental practitioner before commencing IV bisphosphonate therapy [61]. All efforts are made to prevent surgical wounds to the jaws where a patient starts bisphosphonate therapy as outlined in the new guidelines in the AAOMS update paper [60].

Once the patient has commenced IV bisphosphonate therapy, it is exceedingly important that the patient maintains optimal oral hygiene and dental care. The patient should be taught the importance of tooth brushing after each meal or at least three times a day. Flossing is also an important adjunct in maintaining the health of the periodontal tissues. Patients should selectively floss after each meal to those areas that entrap food debris to maintain the periodontal healthy tissues. It is recommended that the patient be placed on a "fluoride prevention regimen" that will further assist in plague control, tooth sensitivity, and any decay process (i.e., stannous fluoride gel regimen).

The patient is also instructed to maintain regular dental visits that include seeing their family dental practitioner every 6 months with dental cleaning as needed. If the patient is on systemic therapy, any dental treatment must be coordinated with the patient's treating physician. Any invasive oral/dental procedures that will damage the mucoperiosteum or underlying osseous tissues, i.e., extractions, periodontal surgery including implants, or surgical endodontics, is contraindicated due to the substantial risk of developing jaw necrosis.

Bisphosphonates and other antiresorptives such as denosumab inhibit osteoclast differentiation leading to decreased bone resorption and remodeling [60]. The increased remodeling rate in jaws explains the predisposition to osteonecrosis compared to other bones. Risk factors associated with MRONJ include medication-related risk factors, local factors, demographic and systemic factors, and genetic predisposition [55–60].

Management strategies for patients treated with antiresorptives or antiangiogenics include prevention and initiation of appropriate dental care prior to drug therapy, cessation of at-risk medication therapy prior to tooth extraction, or other procedures involving osseous injury. The staging of MRONJ is in four categories: Stage 0 (non-exposed bone variant); Stage 1 (exposed and necrotic bone with asymptomatic presentation), Stage 2 (exposed and necrotic bone with symptomatic presentation), and Stage 3 (exposed and necrotic bone with evidence of infection and pathologic fracture, extraoral fistula, oro-antral communication, osteolysis) [55–60].

Treatment strategies per stage include Stage 0 (systemic management including microbiologic assessment, antibiotics, and pain medicine), Stage 1 (antibacterial mouthwash, follow-up on a quarterly basis, and patient education), Stage 2 (symptomatic treatment with oral antibiotics after microbiologic assessment, antibacterial mouthwash, pain control, debridement to reduce frictional irritation such as with a sequestrectomy), Stage 3 (antibacterial mouthwash, antibiotic therapy after microbiologic assessment and pain control, surgical debridement, or resection) [57–59]. Figure 25.15(a–d) shows a patient on IV bisphosphonates, MRONJ evident on her palate, conservative therapy, and debridement.

Numerous research efforts are under way in investigating MRONJ. Developing valid MRONJ assessment tools is essential in understanding this clinical research. A better understanding of the underlying pathophysiology of MRONJ at the molecular level is critical to improve strategies for the prevention or risk reduction of the oral necrosis [59].

25.5 Conclusions

The oral cavity should be thoroughly evaluated in all patients diagnosed with cancer, as well as in patients undergoing any immunomyelosuppressive therapy. Preventing and treating the oral complications of cancer are important responsibilities of the oral healthcare provider, and anticipating primary and secondary mucosal insults and recognizing oral complications promptly in this setting can decrease the incidence of such complications or ameliorate their morbid side effects. By fostering communication and compliance among mem-

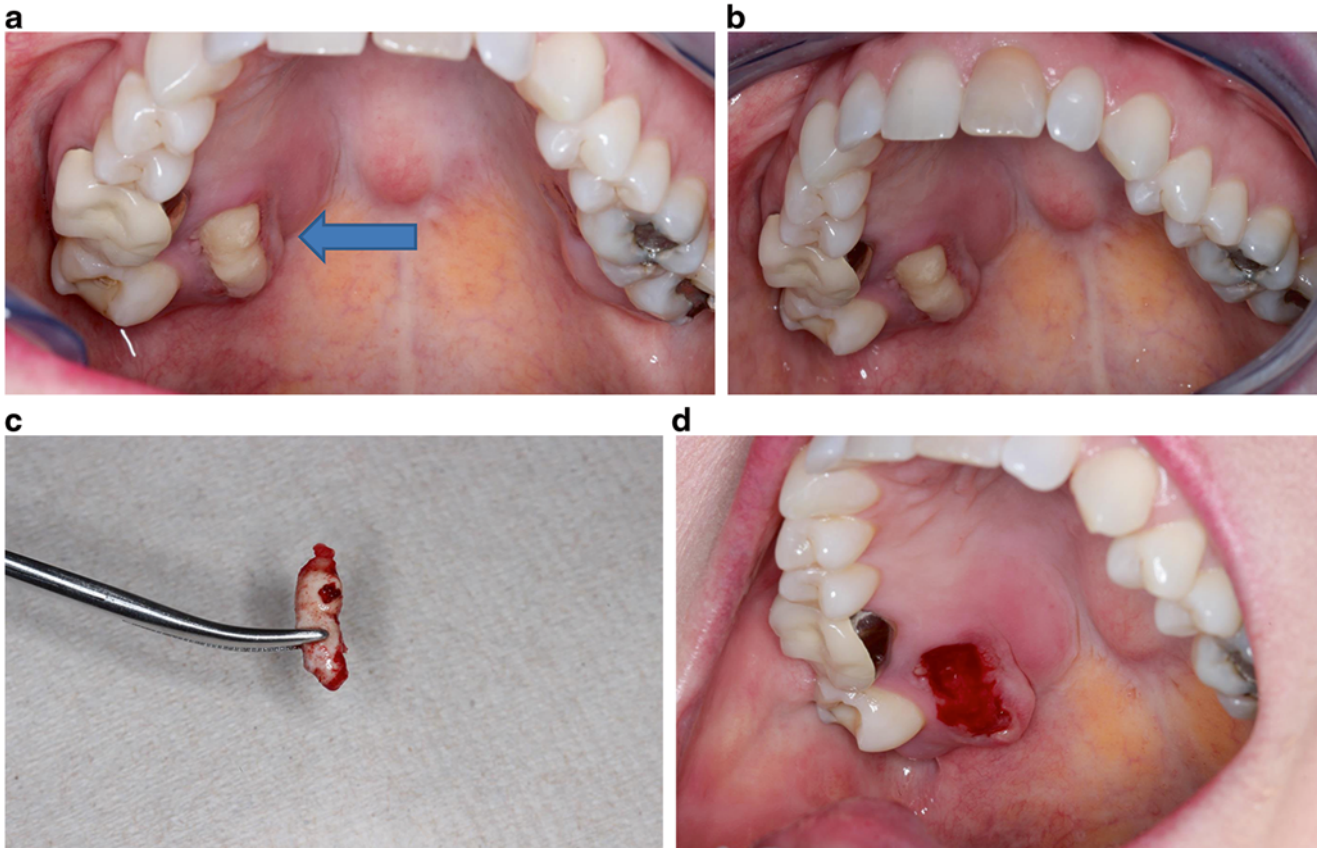

Fig. 25.15 (**a**) Patient had a history of multiple myeloma treated with bisphosphonates for 2 years. Noticed an area of exposed bone on her palate. *Arrow* shows the area. (**b**) After 4 months of careful and conservative care, the area of exposed bone was ready to be debrided. (**c**) Fragment of bone removed in clinic. (**d**) Healthy tissue found under the necrotic bone

bers of the multidisciplinary team, the oral oncology specialist can ensure quality preventive, therapeutic, and maintenance care to patients with cancer.

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Management of Nasopharyngeal Carcinoma

26

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Abstract

Nasopharyngeal carcinoma is a distinctly radiosensitive and chemosensitive tumor. Best quality radiotherapy is demanded to build up the complex concave high-dose zone for this critical location. Intensity-modulated radiotherapy (IMRT) is advocated; image guidance to ensure setup precision and adaptive re-planning if major deviations from intended dose distribution occur during the treatment course are useful improvements if resources allow. Stringent dose constraint to organs at risk should be attempted to minimize late toxicities. Addition of cisplatin-based concurrent-adjuvant chemotherapy is recommended for patients with stages III–IVB and high-risk stage IIB diseases. Contemporary series using IMRT together with extensive use of chemotherapy reported very encouraging long-term results with locoregional control in excess of 85 % at 5 years; the key remaining problems are advanced T4 disease and distant failure. Further improvement of efficacy by more potent systemic therapy and changing chemotherapy sequence to induction-concurrent is being explored.

The plasma level of Epstein–Barr Viral Deoxyribonucleic Acid is a well-established tool for non-keratinizing carcinoma for prognostication and monitoring disease progress. Integrated fluorodeoxyglucose positron emission tomography and computed tomography is useful for excluding distant metastases and posttreatment persistent/recurrent disease. Early detection of failure is critical; and aggressive treatment should be attempted as long survival could be achieved for patients with limited failure. Different salvage methods and reported results are summarized.

Keywords

Nasopharyngeal carcinoma • Radiotherapy • Chemotherapy • Salvage treatment • Late toxicity

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Nasopharyngeal carcinoma (NPC), particularly the classical non-keratinizing type, is different from other head and neck cancers for its distinctly skewed geographic and ethnic distribution, association with Epstein–Barr virus (EBV), and aggressive natural behavior with especially high predilection for distant metastases. Because of its deep-seated location and anatomical proximity to critical structures, radical surgical resection is very difficult. The role of surgery is mainly biopsy for histological confirmation and salvage of persistent or recurrent disease. This cancer is highly radiosensitive and chemosensitive, but the therapeutic margin is notoriously narrow. Thorough knowledge of its complex anatomy and natural behavior is crucial in managing this great challenge.

26.1 Epidemiology

NPC is unique in its distinct geographical and racial distribution. According to global cancer statistics from the International Agency for Research on Cancer, there were over 86,000 new cases in the year 2012; over 75 % of them came from Asia and only 6 % from Europe [1]. In fact the Guangdong province of Southern China shows the highest incidence of NPC, which accounts for its another name, the "Cantonese cancer." Majority of cases from the endemic regions (95 %) are non-keratinizing carcinoma, whereas those from non-endemic regions tend to have more patients with keratinizing carcinoma. The incidence is generally threefold higher in male than female populations, with peak incidence at 40–50 years of age.

The etiology of NPC is likely to be multifactorial. Descendants from Chinese who have migrated to Western countries show progressively lower risk, but their incidence remains higher than the indigenous populations [2]. Familial aggregation of NPC has also been reported [3]. These observations suggest inherited genetic predisposition in the pathogenesis of NPC. It has been reported that specific haplotypes in human leukocyte antigen and other genetic polymorphisms [4] could lead to increased risk of developing NPC. The almost universal association of EBV with non-keratinizing NPC supports its role in the carcinogenesis [5] and EBV Deoxyribonucleic Acid (EBV DNA) has been detected in both invasive and preinvasive lesions [6]. However, the precise mechanism is still poorly understood. The intake of preserved food, especially Chinese-style salted fish, has been one of the best studied environmental factors, while the lack of dietary fruits and vegetables intake and tobacco smoking are also potential risk factors. Interestingly, an epidemiological study from Hong Kong showed that the age-standardized incidence rate dropped by 30 % between 1980 and 1999 [7] and the same trend was also observed in Taiwan [8]. It is postulated that modernization of lifestyles in parallel with the socioeconomic development in these areas has contributed to the remarkable change in epidemiology.

26.2 Pathology and Route of Spread

26.2.1 Pathology

The latest World Health Organization Classification of Nasopharyngeal Carcinoma 2005 Edition divided NPC into three categories, namely, the non-keratinizing carcinoma, keratinizing squamous cell carcinoma, and basaloid squamous cell carcinoma [9].

The non-keratinizing subtype used to be subdivided into differentiated and undifferentiated subtypes, but such subdivision is deemed optional because of the lack of clinical and prognostical relevance [9, 10]. Microscopically tumor cells can vary in appearance from solid sheets-like tumors and clusters of tumor island to loosely cohesive cells in a background of variable number of lymphocytes and plasma cells. Tumor cells exhibit strong staining for pan-cytokeratin, p63, and Bcl-2 immunohistochemistry. EBV-encoded RNA (EBER) is almost invariably positive in in situ hybridization technique. These features are important to help differentiating NPC from reactive epithelia lesions and other malignant differentials like lymphoma, sinonasal carcinoma, and melanoma.

In keratinizing squamous cell carcinoma, typical tumor features like keratin pearls and intercellular bridges are evident, and islands of tumor are intermixed with a desmoplastic stroma. It is also immunoreactive to pan-cytokeratin markers, but EBER-ISH is less often positive than the non-keratinizing counterpart.

Basaloid squamous cell carcinoma is a rare subtype and histologically resembles other basaloid squamous cell carcinoma of other head and neck regions, but seems less aggressive clinically compared to basaloid tumors in other sites.

The frequency of the histological subtypes varies geographically. In endemic regions like Hong Kong and Singapore, the frequency of non-keratinizing carcinoma ranges from 83 to 99 %, and squamous cell carcinoma is uncommon. However, in non-endemic countries, squamous cell subtype is more often seen and can reach up to 25 % in the USA. Basaloid squamous cell carcinoma is rare and accounts for less than 0.2 %.

26.2.2 Route of Spread

Nasopharyngeal cancer typically arises in the fossa of Rosenmuller and can spread extensively to adjacent structures (Fig. 26.1). The involved local structures according to

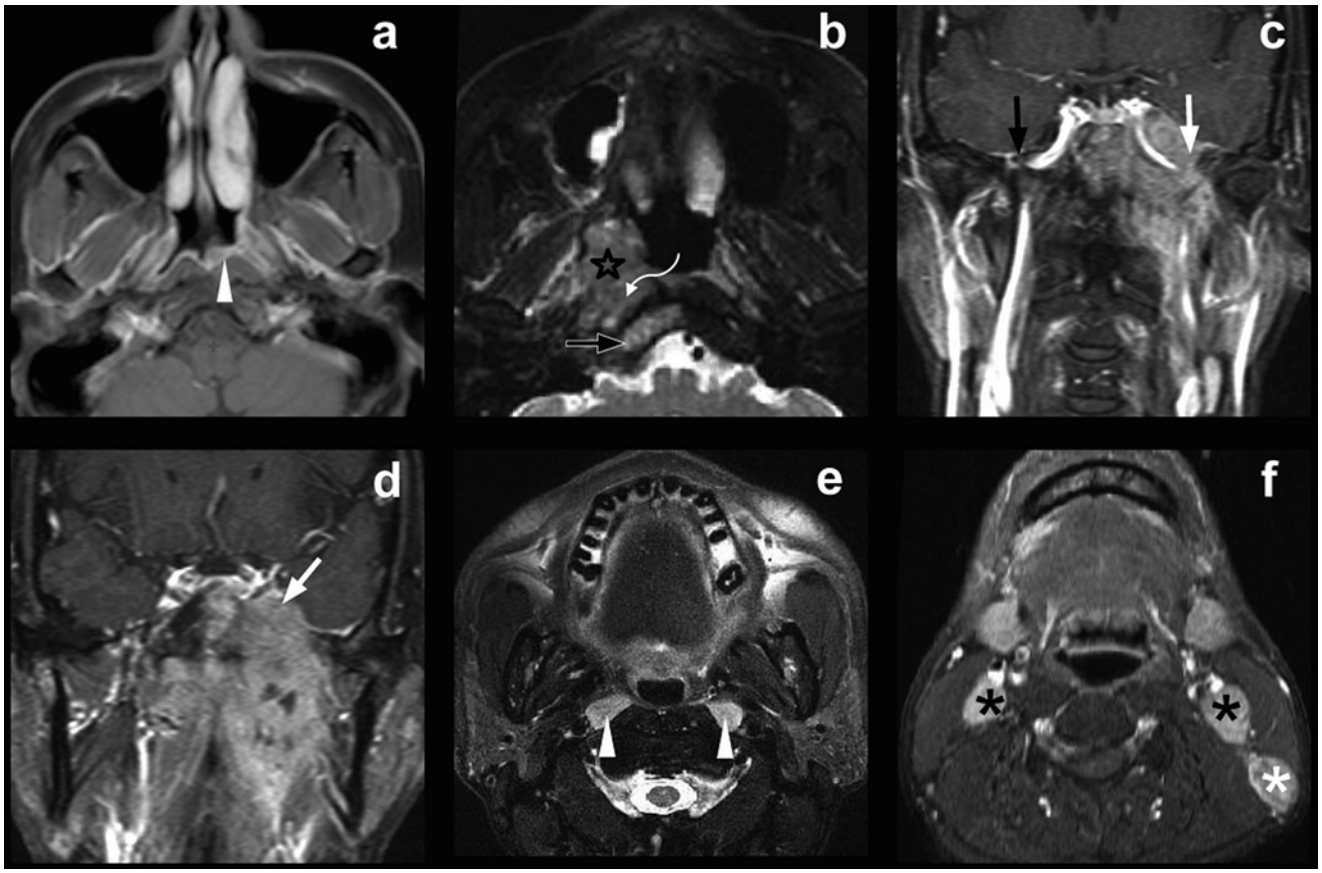

Fig. 26.1 MRI showing different patterns of local and lymphatic involvement by nasopharyngeal carcinoma: (**a**) small primary tumor (*white arrowhead*); (**b**) extension into parapharyngeal space (*star*), prevertebral muscle (*curved arrow*), and clivus (*black arrow*); (**c**) the infiltrated foramen ovale (*white arrow*) as compared to the normal opposite side (*black arrow*); (**d**) infiltration of cavernous sinus (*white arrow*) through foramen lacerum and direct skull base extension; (**e**) metastases in retropharyngeal nodes (*white arrowheads*); (**f**) metastases in Level II (*black asterisks*) and Level V cervical nodes (*white asterisk*)

the anatomic relationship to the nasopharynx and its frequency shown in magnetic resonance imaging (MRI) were tabulated in Table 26.1.

Intracranial extension is not uncommon in advanced disease. Invasion to the middle cranial fossa through foramen ovale is the most common route of spread, followed by direct skull base invasion and through foramen lacerum. The perineural spread through foramen ovale to the cavernous sinus can be appreciated in MRI but difficult in CT, and this explains how intracranial involvement can occur without skull base erosion. The 3rd to the 6th cranial nerves lie lateral to the cavernous sinus and are commonly involved in tumors with intracranial extension. The common order of involvement is cranial nerve V and VI followed by IV and III.

The nasopharynx is rich in lymphatic supply and involvement of regional lymph nodes is extremely common. Contemporary series using MRI and positron emission tomography (PET) scan as imaging modalities show that nodal involvement on initial presentation ranges from 86 to 96 % [11–13]. Level II lymph node is the most commonly involved lymph node in most series. Lymph node spread usually follows an orderly pattern, and skip metastases occurs in 7.9 % [13]. This has led to suggestion of elective nodal irradiation confined to levels II, III, and Va only, sparing the lower neck [14].

Hematogenous spread is not uncommon and is the major cause of death. Metastases occurring at initial diagnosis are around 4 % [15], but around a quarter of patients end up with distant metastases despite treatment in the era of intensity-modulated radiotherapy (IMRT) and the increasing using of chemotherapy [16]. Bone is the most common site of metastases followed by lung and liver [17, 18]. Although intracranial extension is common in advanced local disease, brain metastasis is a rare event. Around 34 % has single organ involvement and 16 % has solitary metastases at the time of diagnosis of metastases [17].

Table 26.1 Direction of local spread and the frequency of structures involved

Direction of invasion	Structures involved	Frequency (%)
Anterior	Nasal cavity	87
	Nasal septum	3
	Orbit/orbital fissure	4
	Maxillary antrum	4
Anterolateral	Pterygoid plate, pterygomaxillary fissure, pterygopalatine fossa	27
Lateral	Parapharyngeal, carotid space	68
	Pterygoid muscles	48
	Infratemporal fossa	9
Posterior	Prevertebral muscle	19
	Clivus	41
Superior	Sphenoid sinus, foramen rotundum, and ovale	38
	Petrous bone, petrooccipital fissure	19
	Jugular foramen, hypoglossal canal	4
	Pituitary fossa, pituitary gland	3
	Cavernous sinus	16
	Cerebrum, meninges	4
	Ethmoid sinus	6
Inferior	Oropharyngeal wall/soft palate	21
	hypopharynx	2

Based on data from Ref. [9]

26.3 Clinical Presentation and Screening

Symptoms of patients with NPC are related to the local disease extent and lymphatic involvement. Painless neck mass due to lymph node metastasis is present in around 75 % of the patients and is the commonest presenting symptom. Local tumor growth can cause epistaxis, nasal obstruction, and nasal discharge. Eustachian tube dysfunction secondary to obstruction of its opening by a relatively small tumor can lead to ear symptoms including hearing impairment and tinnitus. Any adult with persistent unilateral serous otitis media should have examination of the nasopharynx to rule out NPC. When the tumor invades into the skull base or extends intracranially into the cavernous sinus through the foramen ovale or foramen lacerum, the cranial nerves could be involved. The V and VI cranial nerves are most commonly affected. Lower cranial nerves IX, X, XI, and XII could also be involved as they emerge from the skull base into the parapharyngeal space. Headache or pain in the temporal or occipital regions can occur due to skull base destruction or irritation of the meningeal branch of the second division of the V nerve and its presence usually signifies locally advanced disease. Rarely, dermatomyositis can be the presenting symptom as a paraneoplastic syndrome. In endemic areas, nasoendoscopy should be included in the workup for patients with dermatomyositis. Systemic symptoms including loss of appetite and weight loss are late symptoms which may suggest distant metastases.

Unfortunately, NPC often goes totally unnoticed at early stage because of its deep-seated location. Since the survival outcome is strongly correlated with disease stage, early detection in asymptomatic patients is highly desirable. Antibodies against the antigens of EBV such as immunoglobulin (Ig) A antibody against viral capsid antigen (VCA), early antigen, and EBV nuclear antigen 1 (EBNA1) have been studied as serological markers for NPC. In a meta-analysis on the diagnostic value of IgA-VCA, very high sensitivity and specificity of 91 % and 92 %, respectively, were reported [19]. Population-based mass screening using IgA VCA has been tested in endemic regions, but the cost-effectiveness was unknown [20, 21]. Since familial aggregation is widely reported for NPC [3], Ng et al. [22] studied a screening program targeting first-degree relatives of NPC patients with annual assessment by physical examination, EBV serology (IgA-VCA and IgA EBNA1), and nasoendoscopy. Out of 929 family members, 12 cases of NPC were identified, of whom 5 (41 %) had stage I disease. Recently, incorporation of EBV DNA [23] and the use of nasopharyngeal swab/transoral brush as another means of sample collection [24, 25] have been reported. Further studies are warranted to identify a screening strategy which is the most reliable and cost-effective.

26.4 Staging Investigation

Evaluation of locoregional extent should include complete physical examination (particularly on involvement of cranial nerves and cervical nodes), endoscopy, and cross-sectional imaging. MRI is preferred over computed tomography (CT) because of its superior soft tissue contrast resolution and spatial resolution to allow accurate and exquisite delineation of tumors which is important for both staging and radiotherapy planning. A study by Liao et al. [26] on 420 patients showed that MRI was significantly superior to CT for detecting involvement of intracranial area, skull base, paranasal sinuses, oropharynx, parapharyngeal space, prevertebral muscle, and retropharyngeal node, resulting in changes of T-category in 50 %, N-category 11 %, and stage group in 39 % of patients. In addition to more accurate delineation of gross tumor volume (GTV), this affected the decision on addition of chemotherapy in 20 % of patients.

Comprehensive search for distant metastases is indicated for patients with advanced locoregional disease and those with suspicious clinical or laboratory abnormalities. Comparison of four modalities by Chua et al. [27] showed that integrated PET and CT (PET/CT) was the most sensitive and specific modality for detecting distant metastases when

compared with PEt alone, CT thorax-abdomen plus skeletal scintigraphy, and conventional workup (chest X-ray, abdominal ultrasound plus skeletal scintigraphy): the corresponding sensitivity varied from 83 to 33 %, and specificity from 97 to 90 %. Ng et al. [28] showed that the total incidence of distant metastases detected by PET/CT was up to 14 % among the newly diagnosed patients; the treatment strategy was altered in 9 % of patients (with correct modification of M-category and detection of second malignancy); PET/CT was also more accurate for detecting cervical nodes in 7 % of patients, but it was inferior to MRI for delineating local infiltration and retropharyngeal nodes [28, 29]. While PET/CT has emerged as the imaging modality of choice for detecting distant metastases, broad application is limited by the cost. Tang et al. showed that replacing conventional workup with PET/CT is more economical, and greater benefits could be obtained for the subgroup with N2-3 disease and EBV DNA≥4000 copies/mL [30].

26.5 Primary Treatment

Megavoltage photon radiation therapy (RT) has been the primary treatment modality of NPC. Therapy is tailored to disease stage (Table 26.2): stage I disease is typically managed with radiotherapy alone; stage II may be treated with radiation alone or concurrent chemotherapy; and stage III, IVA, and IVB is typically managed with concurrent chemoradiation [31, 32].

26.5.1 Radiotherapy

26.5.1.1 Dose, Time, and Fractionation

Although NPC is a radiosensitive tumor, a substantial level of dose is needed for its complete eradication. Retrospective studies show a significant dose–response relationship [33–35] and a dose of 70 Gy or more is needed even for T1–2 tumors. Change in dose fractionation does not seem to affect local control, but the risk of temporal lobe necrosis (TLN) was found to increase significantly with hypofractionation [36–38]. The general recommendation is to give around 2 Gy per fraction daily to a total dose of at least 70 Gy to the

Table 26.2 The staging system by AJCC/UICC (7th edition)

T-category			
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
T1	Tumor confined to the nasopharynx		
	Tumor extends to adjacent soft tissues: nasal cavity, oropharynx without parapharyngeal extension		
T2	Tumor extends to adjacent soft tissues: nasal cavity, oropharynx with parapharyngeal extension		
T3	Tumor involves bony structures and/or paranasal sinuses		
T4	Tumor with intracranial extension, cranial nerves, hypopharynx, orbit, infratemporal fossa or masticator space		
N-category			
N0	No regional lymph node metastasis		
N1	Cervical node(s): unilateral, ≤6 cm, above the supraclavicular fossa		
	Retropharyngeal node(s): unilateral or bilateral		
N2	Cervical node(s): bilateral, ≤6 cm,, above the supraclavicular fossa		
N3	N3a. Node(s) >6 cm		
	N3b. Extension to the supraclavicular fossa		
M-category			
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T1–T2	N1	M0
Stage III	T1–T2	N2	M0
	T3	N0–N2	M0
Stage IVA	T4	N0–N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

gross tumor, and 50–60 Gy for elective treatment of the high-risk sites.

Leung et al. [39] showed that for patients with T1–2b tumors, an additional boost by high-dose-rate (HDR) brachytherapy of 10–12 Gy in 2 weekly fractions following 66 Gy by two-dimensional (2D) RT could achieve significantly better 5-year local failure-free rate (LFFR) (96 vs. 88 %) and overall survival (OS) (91 vs. 80 %) without excessive late toxicity (14 vs. 10 %) when compared with historic controls. However, the effectiveness of boosting by brachytherapy for more advanced T stage tumor has not been demonstrated [40].

Apart from brachytherapy, boosting with stereotactic RT has been studied. A report by Hara et al. [41] on 82 patients (52 % with T3–4 tumor) showed that a single boost fraction of 7–15 Gy by stereotactic technique following the conventional 66 Gy RT, with extensive use of concurrent-adjuvant chemotherapy in advanced cases, could achieve an excellent 5-year LFFR of 98 %. However, relatively high incidences of late complications (including those of temporal lobe 12 %, retina 4 %, and carotid artery 1 %) were also observed. Similarly high incidence (8 %) of TLN had been observed in a group of 33 patients receiving moderate stereotactic boost (2 fractions of 2.5 Gy each), while no TLN was found among patients treated with RT alone [42].

In the IMRT era, dose escalation can be achieved by Simultaneous Modulated Accelerated Radiation Therapy/Simultaneous-Integrated Boost. With this strategy, different dose levels are applied to different regions simultaneously in each fraction according to the levels of risk, and the dose per fraction to GTV could range from 2.12 to 2.4 Gy. Depending on the total dose given, substantially higher biological equivalent dose can be applied to GTV. While this approach is attractive and user friendly, the close association between the risks of late neurological complications and the fractional dose prescribed to the GTV should not be overlooked. In fact, the risk of late temporal lobe complication is apparently higher when the GTV receives more than 2.15 Gy per fraction [43–45] and unacceptable rate of brain necrosis (12 %) had been reported by Bakst et al. [45] using 2.34 Gy per fraction to the GTV up to a total of 70.2 Gy. This is consistent with radiobiological observation that hypofractionation (i.e., higher dose per fraction) is particularly detrimental to neurological tissue. Clearly the risk and benefit of dose escalation or hypofractionation, irrespective of the treatment delivery technique, have to be carefully balanced.

The total radiotherapy period and fractionation scheme can affect the treatment outcome. Retrospective study showed that prolongation of treatment period significantly reduced local control [46, 47]; the risk of local failure increases by 3 % per additional day even for non-keratinizing tumor. On the other hand, some alternated fractionation schemes have been studied with randomized trials, but their benefits remain uncertain. Teo et al. [48] randomized 159 patients (38 % T3–4) to receive 20 Gy with 2.5 Gy/fraction daily (QD) followed by another 51.2 Gy using 1.6 Gy/fraction twice-daily (BID) versus a total of 60 Gy with 2.5 Gy/fraction daily (QD). There was a minor increase in 5-year LFFR (89 vs. 85 %) with the BID scheme, but excessive neurological toxicities were also incurred (49 vs. 23 %). Daoud et al. [49] randomized 154 patients (45 % T3–4) to receive 1.6 Gy/fraction BID to 70.4 Gy over 6 weeks versus 2 Gy/fraction QD to 70 Gy. Again there was a slight increase in 5-year locoregional control (LR-FFR) (81 vs. 78 %) with the BID scheme, but this time no major excessive toxicities were observed. Pan et al. [50] randomized 200 patients to receive a late course accelerated hyperfractionated radiotherapy (1.2 Gy/fraction BID to 48 Gy, followed by another 30 Gy using 1.5 Gy/fraction BID) versus standard fractionation; both the 5-year local control rate and OS rate were higher in the experimental arm (87.6 % vs. 75.9 % and 74.1 % vs. 58.0 %, respectively). These randomized studies were performed in the 2D RT era and none of the patients received chemotherapy. Inspired by the potential promising results of the Hong Kong nasopharyngeal carcinoma study group 9902 trial testing acceleration vs. conventional fractionation [51], a contemporary study was performed by Lee et al. on 706 stage III–IVB patients comparing 5 vs. 6 fractions per week at 2 Gy per fraction [52]. In this study, more than 90 % of the patients were treated with IMRT and all patients received concomitant chemoirradiation. However, no statistical improvements were observed in local control and OS in the accelerated fractionation arms.

26.5.1.2 Tumor Targets and Technique

The delineation of GTV should be based on all clinical, endoscopic, and imaging findings. The clinical target volume (CTV) covers the GTV and microscopic infiltration, including anatomical structures at risk. Fusions of diagnostic MRI and PET (if available) images with planning CT are valuable for accurate delineation of target volumes, but precise segmentation with PET can be difficult [53, 54], and it calls for close collaboration with diagnostic radiologist and nuclear medicine physician.

There is little controversy that IMRT is recommended if resources permit. Dosimetric studies have clearly shown improvement in dose conformity to complex concave target volumes and better protection of the adjacent organs [55–58].

While consensus has been reached to enhance consistency in the delineation of neck node and organs at risk (OAR), different centers have different practices with regard to the delineation of CTV, dose fractionation, priorities in target and OAR dose constraints, acceptance criteria, as well as beam arrangements. Table 26.3 shows the comparison between different RTOG protocols and our local practice.

Table 26.3 Comparison of target delineation protocols between RTOG studies and PYNEH

	RTOG 0225	RTOG 0615	NRG HN001	PYNEH
CTV1				
Margin from GTV	GTV + 5 mm	GTV + 5 mm	GTV + 3 mm	GTV_P + 5 mm
				GTV_N + 5–10 mm
				Whole NP
Minimal margin of CTV from critical OARs	1 mm from BS	1 mm from BS	0 mm from BS	1–2 mm from optic chiasm, temporal lobe, BS, and SC
Dose/fraction	2.12 Gy × 33	2.12 Gy ×33	2.12 Gy × 33	2 Gy × 35
CTV2				
Margin from GTV		GTV_P + 10 mm	GTV_P + 8 mm	
	GTV_P + 10 mm	GTV_N + 10 mm	GTV_N + 8 mm	GTV_P + 10 mm
	Whole NP	Whole NP	Whole NP	GTV_N (dubious) + 5 mm
Minimal margin of CTV from critical OARs	Not stated	Not stated	1 mm from optic apparatus, BS, and SC	2–3 mm from optic chiasm, temporal lobe, BS, and SC
Clivus	+	½-2/3 if no invasion; whole if + ve	1/3 if no invasion; whole if + ve	1/2 if no invasion; whole if + ve
Skull base	+	+ cover foramen ovale and rotundum	+ cover foramen ovale and rotundum	cover petrous tip + foramen ovale
Pterygoid fossae	+	+	+	+
Cavernous sinus		If T3–4	If T3–4 (involved side only)	If T3–4
PPS	+	+	+	Cover styloid process
Sphenoid sinus	Inferior	T1–2 — inferior;	T1–2 — inferior;	T1–2 — half;
		T3–4 — whole	T3–4 — whole	T3–4 — whole
Nasal cavity	Post 1/3	Post 1/3–1/4	Post 1/4	Post 1/3
Maxillary sinuses	Post 1/3	Post 1/3–1/4	Post 1/4	Post 1/3
Dose/fraction	1.8 Gy × 33	1.8 Gy × 33	1.8 Gy × 33	1.8 Gy × 35
CTV3				
Upper sphenoid sinus	Not stated	Not stated	Not stated	Upper ½ for T1–2
Node –ve lower neck	+	+	+	Omit if N0 or N1 based solely on RPLN involvement
Level IB	Not stated	Not stated	Optional if T1/2N0	Omit if N0
Dose/fraction	1.8 Gy × 28 using AP field	1.64 Gy × 33	1.64 Gy × 33	1.6 Gy × 35
PTVs				
Margin from CTV	5 mm (reduce to 1 mm if CTV adjacent to BS)	5 mm (reduce to 1 mm if CTV adjacent to BS)	5 mm (3 mm if IGRT) (reduce to 0 mm if CTV adjacent to BS, SC)	All IGRT
				3 mm (cranial to lower border of C1)
				5 mm (lower border of C1 to lower neck)

Abbreviations: *AP*, anteroposterior; *BS*, brain stem; *GTV_P*, GTV primary tumor; *GTV_N*, GTV neck node; *NP*, nasopharynx; *PPS*, parapharyngeal space; *RPLN*, retropharyngeal neck node; *SC*, spinal cord

26.5.1.3 Example of Planning and Treatment Practice

The current practice at the Pamela Youde Nethersole Eastern Hospital (Hong Kong) is described here as an example. The patient is set up in supine treatment position and immobilized with a customized thermoplastic mask covering the head and shoulder regions. A contrast-enhanced planning CT is acquired from skull vertex to whole lung with 3 mm slice thickness. The diagnostic MRI and PET (if available) images are co-registered with the planning CT for the delineation of target volumes and OARs. The IMRT treatment is delivered with 9–11 6-MV photon beams (mostly coplanar) using dynamic multileaf collimator technique.

Figure 26.2a, b illustrates the target volumes for a patient with T1N1 disease. A total dose of 70 Gy at 2 Gy/fraction is prescribed to CTV_1 which includes the primary tumor with a 2–5 mm margin, the whole nasopharynx, and gross lymph nodes with a 5–10 mm margin. The CTV_2 covers the high-risk structures (including the parapharyngeal spaces, the posterior third of nasal cavities and maxillary sinuses, pterygoid

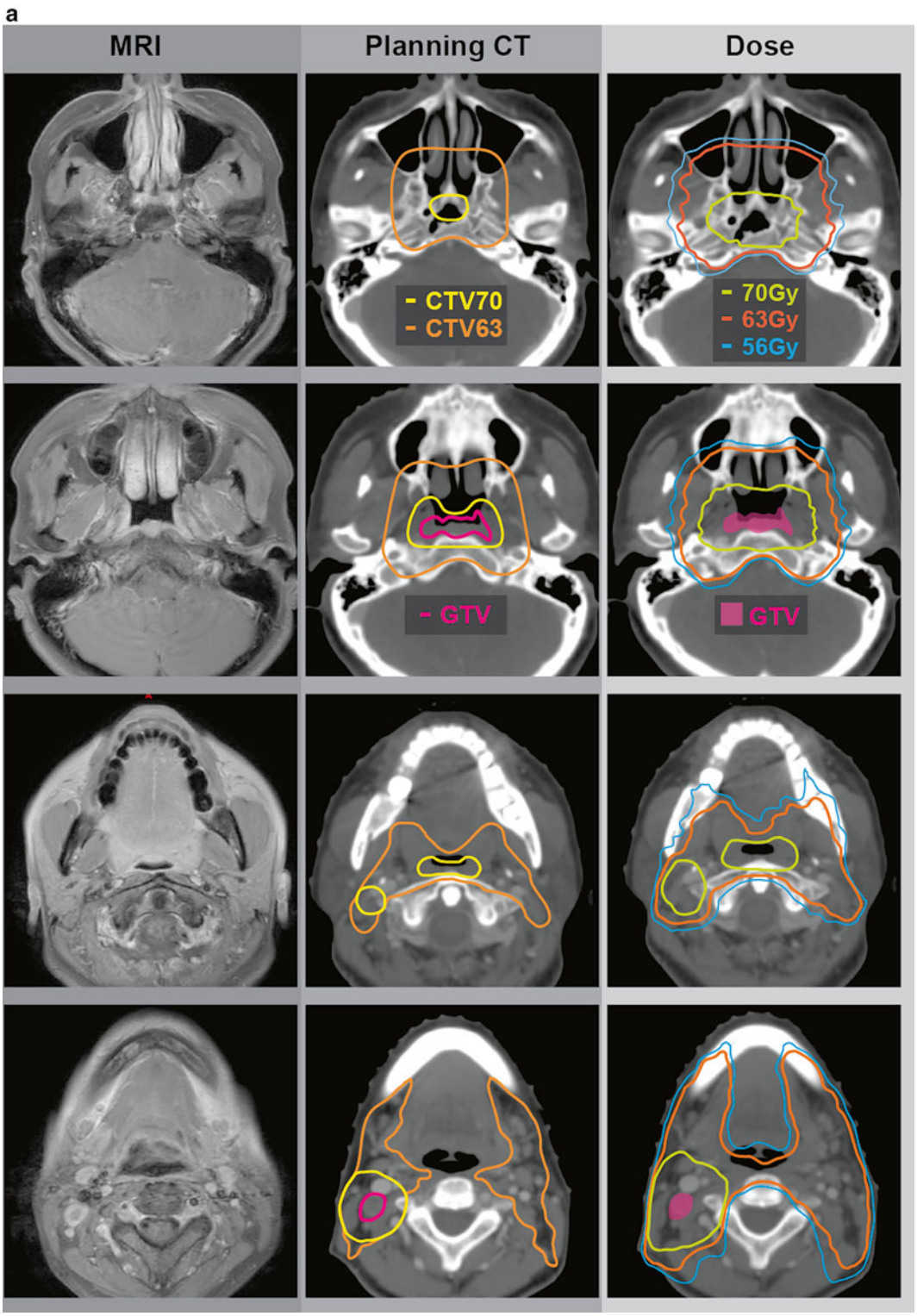

Fig. 26.2 (**a**, **b**) Delineation of tumor targets for a patient with T1N1 disease: The first column shows the MRI images. The second column shows the planning CT images: the *red line* for the gross tumor volume (GTV), the *yellow line* for the clinical target volume (CTV) aimed at 70 Gy, and the *orange line* for the CTV aimed at 63Gy. The corresponding resultant isodose curves are shown at the last column. The *yellow line*, *orange line*, and *blue line* represent the 70, 63, and 56 Gy isodose lines, respectively

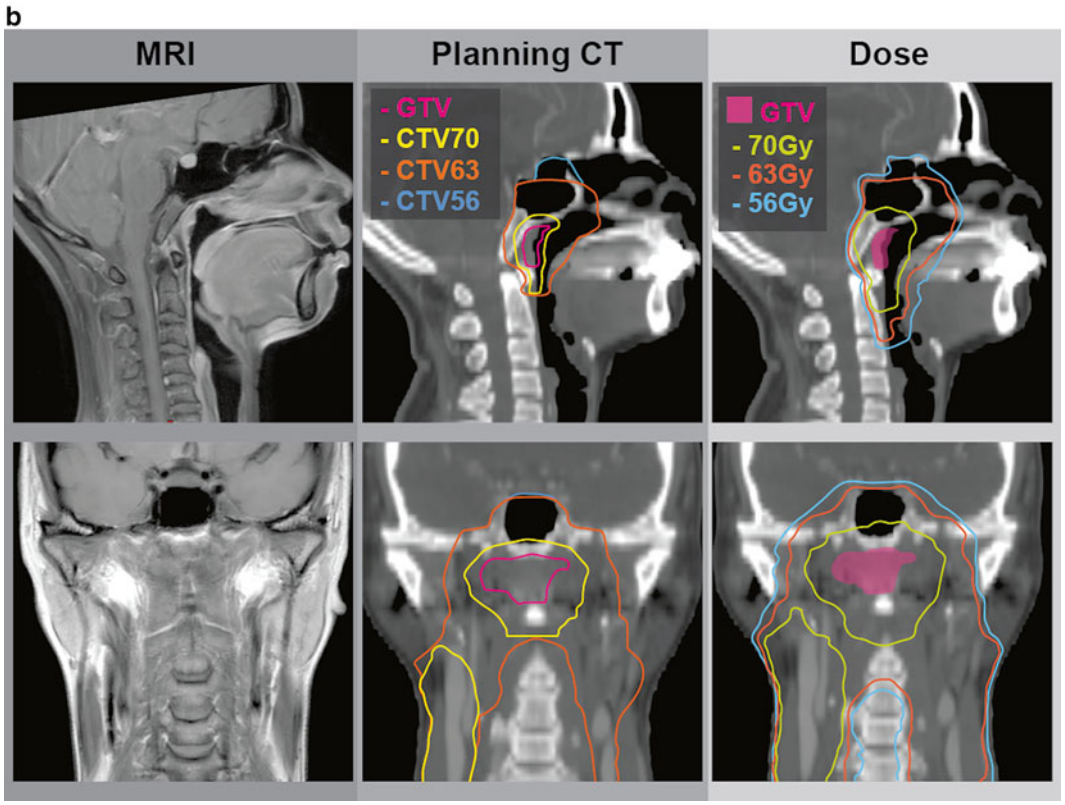

Fig. 26.2 (continued)

processes, base of skull, lower half of sphenoid sinus, anterior half of the clivus, petrous tips, bilateral retropharyngeal nodes, Levels II, III, and upper VA lymphatic regions) and receives 63 Gy at 1.8 Gy/fraction. The CTV_3 that covers low-risk structures including the remaining lymphatic Levels IV–VB and the upper half of sphenoid sinus receives 56 Gy also at 1.6 Gy/fraction. Selective sparing of level IB and lower neck [59] is considered in N0 patients. The planning target volume (PTV) is constituted by expanding the CTVs above the level of C1 by 3 mm and the CTVs below by 5 mm.

In order to achieve an optimal setup accuracy, daily orthogonal kV images are taken to verify the patient position with correction applied for deviations ≥ 2 mm. Our in-house study (unpublished data) comparing cone-beam CT and daily kV images suggested that adequate setup accuracy can be achieved with kV images when using a PTV margin of 3 mm at the nasopharyngeal region and of 5 mm below.

Table 26.4 shows the acceptance criteria for IMRT planning. Top priority is given to the critical neurological structures and GTV coverage. Optimization to achieve all the criteria is attempted as far as possible; compromise between tumor control and toxicity is discussed with individual patient if it is technically difficult to fulfill even the minimal requirement.

26.6 Treatment Outcomes with IMRT

Irrespective of how IMRT were being delivered, all series reported excellent long-term local control in excess of 85 % and an OS rate of around 80 %. Pattern of failure studies indicated that the main cause of treatment failures was distant metastasis [60]. Representative IMRT studies with 5-year results are summarized in Table 26.5. Only one randomized study has also been conducted comparing IMRT with conventional 2D RT. In the series of 616 patients by Peng et al. [61], significantly higher 5-year local control rate (91 % vs. 85 %) and OS rate (80 % vs. 67 %) were reported; patients in the IMRT arm also had significantly fewer radiation-induced toxicities than those in 2D RT group.

While the use of IMRT on patients with early-stage NPC could achieve significant sparing of parotid glands [62, 63], one should be cautioned that overenthusiasm in protecting the parotids might result in marginal miss. Furthermore, late toxicities of other OARs are closely related to the prescription practice as well as the priorities of dose constraints. This is particularly apparent for tumor with intracranial extension, and the best way to strike the balance between tumor control and risk of neurological complications has yet to be established [64].

Table 26.4 Comparison of organ at risk tolerance dose between RTOG Studies and PYNEH

	PYNEH		NRG-HN001	
Organ at risk	Per protocol	Variation acceptable	Per protocol	Variation acceptable
	Priority 1: GTV and critical OAR		Priority 1:	
			Critical normal structure (priority over coverage of the tumor)	
Brainstem	≤54 Gy	≤60 Gy (for T3–T4 only)	0.03 cc < 54Gy	0.03 cc ≤ 60Gy
Spinal cord	≤45 Gy	≤50 Gy (for T3–T4 only)	0.03 cc < 45Gy	0.03 cc ≤ 50Gy
Optic chiasm	≤54 Gy	≤60 Gy (for T3–T4 only)	0.03 cc < 54Gy	0.03 cc ≤ 56Gy
GTV-T and GTV-N	Min ≥ 68.6 Gy (98 % dose)	Min ≥ 66.5 Gy (95 % dose)	*Not stated*	
	Priority 2: Tumor targets and other important neurological OAR		Priority 2: Dose specifications	
CTV	*Not stated*		[CTV_6996] 99 % vol. > 65.1 Gy [CTV_6270] 99 % vol. > 58.6 Gy [CTV_5940] 99 % vol. > 55.2 Gy [CTV_5412] 99 % vol. > 50.2 Gy	[CTV_6996] 99 % vol. = 65.1–60 Gy [CTV_6270] 99 % vol. = 58.6–55 Gy [CTV_5940] 99 % vol. = 55.2–52 Gy [CTV_5412] 99 % vol. = 50.2–45 Gy
PTV	Min ≥ 95 % dose and <10 % vol. P70 ≥ 75 Gy	95 % vol. ≥ 100 % dose or 99 % vol. ≥ 93 % dose and <20 % vol. P70 ≥ 77 Gy	[PTV_6996/PTV_6996_Eval*] ≥95 % vol. ≥ 69.96 Gy 0.03 cc ≤ 80.5 Gy [PTV_6270/PTV_6270_Eval*] ≥95 % vol. ≥ 62.7 Gy [PTV_5940/PTV_5940_Eval*] ≥95 % vol. ≥ 59.4 Gy [PTV_5412/PTV_5412_Eval*] ≥95 % vol. ≥ 54.12 Gy	[PTV_6996/PTV_6996_Eval*] ≥95 % vol. ≥ 69.96 Gy 0.03 cc = 80.5–84 Gy [PTV_6270/PTV_6270_Eval*] ≥90 % vol. ≥ 62.7 Gy [PTV_5940/PTV_5940_Eval*] ≥90 % vol. ≥ 59.4 Gy [PTV_5412/PTV_5412_Eval*] ≥90 % vol. ≥ 54.12 Gy
			Priority 3: Other critical normal structure	
Optic nerve	≤54 Gy	≤60 Gy*	0.03 cc < 54 Gy	0.03 cc ≤ 56 Gy
Temporal lobes	1 cc vol. < 65 Gy	≤72 Gy*	0.03 cc <70 Gy	0.03 cc ≤ 72 Gy
	Priority 3: Intermediate-risk OAR			
Brachial plexus		≤1 cc vol. > 66 Gy	0.03 cc < 66 Gy	0.03 cc ≤ 70 Gy
Mandible and TM joint	≤1 cc vol. > 70 Gy	≤1 cc vol. > 75 Gy	0.03 cc <70 Gy	0.03 cc ≤ 75 Gy
Pituitary	≤60 Gy	≤65 Gy	*Not Stated*	
			Priority 4: Planning goals—salivary glands	
Parotid glands	Mean < 26 Gy (at least one gland)	V30 ≤ 50 % (at least one gland)	Mean < 26 Gy (one of the glands)	Mean 26–33 Gy (one of the glands)
			Priority 5: Planning goals—all other normal structures	
Lens	≤6 Gy	≤10 Gy	0.03 cc < 15 Gy	
Eyeballs	≤50 Gy	Mean < 35 Gy	0.03 cc < 55 Gy	
	Priority 4: Low-risk OAR			
Cochlea	Mean < 50 Gy	≤55 Gy	0.03 cc ≤ 55 Gy	
Glottic larynx		Mean < 45 Gy	Mean < 40 Gy	
Postcricoid pharynx, esophagus		Mean < 45 Gy	Mean < 50 Gy	
Oral cavity (excluding PTV)	Mean < 40 Gy	Mean < 50 Gy	Mean < 40 Gy	
Remarks		*Can be exceeded based on individual case consideration, but absolute increase is restricted to less than 5–10 % of these maximal doses (i.e., 66 Gy and 75 Gy for optic nerve and temporal lobe respectively	*The subvolume (PTV_Eval) should be used for evaluation when the volume of a critical structure overlaps with the true PTV	

Table 26.5 Treatment parameters and 5-year outcomes by intensity-modulated radiotherapy

Author	No.	T3–4 category (%)	Total dose (Gy)	Dose/fraction (Gy)	Chemo (%)	Time (years)	Local control (%)	Nodal control (%)	Distant control (%)	Overall Survival (%)
Xiao [216]	81	100	68	2.27	100	5	95	–	–	75
Lai [217]	512	52	NR	2.27	81	5	93	97	84	NR
Peng [61]	306	45[a]	70	2.12	60	5	91	92	NR	80
Lin [218]	414	65	66–70.95 (30–33fr)	NR	81	5	95	97	82	80
Wu [219]	249	86	68–72 (30–32fr)	NR	100	5	87	88	78	78
Sun [44]	868	57	68	2.27	83	5	92	96	85	NR
Ng [64]	444	68	70	2–2.12	83	5	86	92	83	80

[a]Randomized study, % is based on both treatment arms of 616 patients
Abbreviations: *NR*, not reported

26.6.1 Treatment Precision

Radiation therapy utilizing frequent 2D and 3D imaging to ensure the accuracy and precision of patient setup position throughout the course of radiotherapy is referred to as image-guided radiation therapy. Currently available electronic treatment position verification devices allow daily imaging and online correction of positional errors prior to treatment. As there is no internal motion of nasopharynx, orthogonal kV images of the skull base are good surrogates to verify the primary tumor position. Recent development of online cone-beam CT and 6D couches allows further correction on rotational error. These online corrective strategies could potentially allow using a tighter PTV margin.

Adaptive radiation therapy refers to the modification of treatment plan, usually a complete re-planning, to adapt to individual patient anatomic changes within the treatment course. A typical course of radical radiotherapy for NPC lasts for a month and a half. Studies have shown that anatomic changes due to tumor shrinkage and weight loss within the treatment course could adversely affect the ultimate doses delivered [65, 66]. In particular, the maximum dose received by the neighboring critical structures including brain stem, spinal cord, and optic chiasm would be higher than anticipated in the original treatment plan [67]. The dosimetric advantages of re-planning radiotherapy at various time points during the course of treatment have been demonstrated by some studies [68–70]. Whether such dosimetric advantages will result in better clinical outcomes or reduction in late toxicities remains unknown. Besides, this re-planning process is labor intensive and logistically difficult.

26.6.2 Technological Developments

Development of helical tomography (HT) capable of delivering fan-beam MV X-rays in a continuously rotating and translating manner opened a new opportunity for achieving highly modulated dose distribution. Dosimetric comparisons showed that HT was superior to coplanar 5-field IMRT delivered by dynamic MLC [71] and 7-field step-and-shoot IMRT [72]. For PTV coverage, 129 % improvement in conformity index and 9 % improvement in homogeneity index were reported by Lee et al. [72]. In addition, significant reduction of mean and/or maximal doses to most of the OARs could be achieved [73], but it should be noted that negative result has been observed for optic chiasm, particularly for patients with T1–2 tumor, due to less sharp dose fall-off in craniocaudal direction. However, this may be tackled with the recently introduced dynamic jaw mechanism that can improve the dose distribution at the superior and inferior ends of the target when a sharp penumbra is needed [74].

Particle beam radiotherapy with physical advantages of better spatial selectivity and/or higher biological efficacy than photons is an attractive, though expensive, technological advancement for NPC with its critical location. Some dosimetric comparisons showed that 3D spot-scanned coplanar 3-field intensity-modulated proton therapy (IMPT) was superior to coplanar 9-field step-and-shoot IMRT by photon [75] in coverage and conformity for the GTV, as well as reduction of mean dose to most OAR and medium dose volumes by a factor of 2–3. The latter improvement could be important for reducing late complications and the carcinogenic effect of ionizing radiation. Further comparative study by Widesott et al. [76] and Liu et al. [77] showed that both IMPT and IMRT could achieve similar dose coverage and

homogeneity for the PTV; the most remarkable superiority of IMPT was the reduction in total body volume receiving ≥30Gy by 15 % and reduction in brainstem/spinal cord median maximal dose for recurrent NPC, respectively.

Despite the potential dosimetric advantages of this modality, clinical experience in NPC is relatively sparse. Two abstracts by Lee et al. [78, 79] reported excellent local control even for locally advanced NPC (92 % local control for 19 T4 patients and 100 % for another 23 stage III–IB patients). The selective use of this expensive modality for extensive locoregional disease infiltrating/abutting critical OAR and re-irradiation of recurrent tumor [77, 80] is worth exploring.

26.7 Chemotherapy for Locoregionally Advanced Disease

With the high predilection for distant failure, there is little argument that addition of systemic therapy is recommended for patients presenting with locoregionally advanced NPC. Since the first report of significant survival benefits by the Intergroup-0099 Study in 1998 [81, 82], addition of cisplatin (100 mg/m^2) on days 1, 22, and 43 in concurrence with conventional-fractionated radiotherapy (RT) followed by adjuvant cisplatin and (80 mg/m^2) fluorouracil (4000 mg/m^2 in 96 h) on days 71, 99, and 127 during the post-RT phase has become a standard recommendation in the National Comprehensive Cancer Network (NCCN) practice guideline [31] for patients with stage II–IVB disease.

Subsequent evaluation of patients with stage III–IVB disease by the NPC-9901 Trial [83, 84] and the trials by Wee et al. [85, 86] and Chen et al. [87, 88] consistently confirmed that this concurrent-adjuvant regimen could significantly improve event-free survival (EFS); the latter two trials also reported significant benefit in OS. In all four trials, the improvements were confirmed both in the preliminary analyses and progress reports with 5-year results. However, the adjuvant phase is often poorly tolerated; only about 60 % of patients could tolerate all three cycles of adjuvant PF.

Trials using concurrent chemotherapy alone (vs. radiotherapy alone) were conducted, but the results showed less consistent conclusions. The trial by Chan et al. on 350 patients with stage II–IVB disease using concurrent cisplatin 40 mg/m^2 weekly showed [89] insignificant 2-year progression-free survival (PFS) for the whole series ($p=0.10$), and it was only the subgroup with T3–4 disease achieved significant improvement. Progress report [90] confirmed no significant difference in 5-year PFS ($p=0.16$). Unadjusted analyses on OS showed borderline improvement ($p=0.065$); the impact reached statistical significance only on analyses with adjustment for T stage, overall stage, and age (hazard ratio (HR)=0.71; 95 % CI, 0.5–1.0; $p=0.49$). The survival benefit was confined to the T3–4 subgroup.

Lin et al. [91] using cisplatin-fluorouracil as concurrent regimen reported significant benefit in both EFS and OS. However, subsequent re-analysis [92] with retrospective re-staging of the accrued patients into different risk groups showed that the benefit was significant for low-risk patients only. [This trial was excluded from subsequent meta-analyses due to concerns about randomization.] Kwong et al. [93] conducted a factorial study using concurrent uracil-tegafur with or without adjuvant cisplatin-based combination on 219 patients with stage II–IVB disease. The 3-year OS was 89 % by concurrent-adjuvant, 84 % by concurrent, 71 % by adjuvant chemotherapy, and 83 % by RT alone. The corresponding 3-year failure-free survival (FFS) of the four arms were 70 %, 69 %, 54 %, and 61 %, respectively. The authors concluded that the concurrent group achieved borderline improvement in OS ($p=0.06$) and no significant improvement in EFS ($p=0.14$).

The first patient data-based meta-analysis by the MAC-NPC Collaborative Group [94] was based on 1753 patients from eight valid trials reported up to 2004. The trials were grouped according to the main timing of chemotherapy: induction [95–98], adjuvant [93, 99], and concurrent chemotherapy [81, 90, 93]. The study confirmed a small but significant benefit in OS by adding chemotherapy: The absolute gain for 5-year EFS was 10 % (52 vs. 42 %) and OS was 6 % (62 vs. 56 %). The concurrent group showed a better improvement in OS (HR=0.60; 95 % CI, 0.48–0.76) than the induction group (HR=0.99; 95 % CI, 0.80–1.21) or the adjuvant group (HR=0.97; 95 % CI, 0.69–1.38). Thus, it was concluded that survival benefit was essentially observed when chemotherapy was administered concomitantly with RT. However, more detailed review of the Forrest Plot showed that among the four comparisons included in the concurrent group, only the Intergroup-0099 Study (concurrent-adjuvant vs. RT) [81] and the trial by Kwong et al. (concurrent-adjuvant vs. adjuvant) [93] reached statistical significance; both the Trials by Chan et al. [90] and Kwong et al. [93] of concurrent-alone vs. RT were insignificant.

Since the MAC-NPC emphasized the importance of concurrent chemoirradiation, this regimen (without adjuvant chemotherapy) is increasingly used in many centers. In the NCCN guideline [31], concurrent chemoradiotherapy without adjuvant chemotherapy has been included (category 2B evidence), whereas the recommendation by EHNS–ESMO–ESTRO Clinical Practice Guidelines [32] for stage III–IVB disease was concurrent chemoradiotherapy ± adjuvant chemotherapy (I, A).

The hypothesis that concurrent chemoirradiation alone is adequate for improving treatment results was supported by the preliminary analyses of a randomized trial by Chen et al. [100] comparing concurrent chemoradiotherapy with versus without adjuvant chemotherapy in 508 patients with stage III–IVB disease. All patients were given concurrent cisplatin 40 mg/m^2 weekly; those allocated to concurrent-adjuvant arm were given additional chemotherapy with cisplatin

(80 mg/m^2) and fluorouracil (4000 mg/m^2 in 120 h) during the post-RT phase. They observed no statistically significant differences in FFS at 2-year, HR = 0.74; 95 % CI, 0.49–1.10; $p = 0.13$. During the adjuvant phase, 42 % of patients experienced grade 3–4 toxicities, but there were no treatment-related deaths. The authors concluded that "such regimens should not, at present, be used outside well designed clinical trials." However, readers must be cautioned against such strong statement as follow-up was too short for definitive confirmation.

The second patient data-based meta-analysis by the MAC-NPC Collaborative Group [101], based on 4798 evaluable patients from 19 valid trials performed up to 2010, provided more information for recommending the best chemotherapy. The trials were again grouped according to the main timing of chemotherapy, but in this study, there are now separate analyses for the concurrent-alone group and the concurrent-adjuvant group. With a median follow-up of 7.7 years, the study confirmed a small but significant benefit in OS by adding chemotherapy: the absolute gain for OS was 6 % at 5 years and 8 % at 10 years (57 vs. 49 %). The concurrent-adjuvant group achieved the greatest magnitude of improvements in all endpoints (Table 26.6), while the induction and the adjuvant groups were insignificant.

All trials in the concurrent-adjuvant group used concurrent cisplatin followed by adjuvant cisplatin-fluorouracil. Robust and substantial long-term benefit was confirmed: the HR in OS by concurrent-adjuvant group was 0.65 (95 % CI, 0.56–0.76). Furthermore, 5 out of 6 comparisons were individually significant. Even the NPC-9901 Trial, which was the only trial that failed to achieve significant improvement in OS at 3 and 5 years, became significant with longer follow-up: 0.73 (95 % CI, 0.54–0.99).

The concurrent-alone group was more heterogeneous; various regimens have been used. Although the HR in OS also reached statistical significance [0.80 (95 % CI, 0.70–0.93)], it must be noted that 5/7 comparisons in the concurrent-alone group were individually insignificant. The commonly used regimen of cisplatin 40 mg/m^2 weekly [89, 90] was negative both in OS (HR = 0.81; 95 % CI, 0.61–1.07) and PFS (HR = 0.85; 95 % CI, 0.65–1.11). Significant benefit was reached only in the trial using cisplatin 30 mg/m^2 weekly for stage II–III disease [102], and the trial using oxaliplatin 70 mg/m^2 weekly in 115 patients with stage III–IVB disease [103, 104].

An exploratory study [105] based on patients treated with conventional-fractionated RT from the NPC-9901 and NPC-9902 Trials showed that while the number of concurrent cycles and the dose of cisplatin given had significant impact on locoregional control, the number of adjuvant cycles and the dose of fluorouracil given had significant impact on distant control; patients needed at least 2 cycles, but the adjuvant phase is often poorly tolerated.

Despite extensive use of chemotherapy, distant control remains a key problem, and more efficacious regimen is needed. One potential strategy is to change the chemotherapy sequence from concurrent-adjuvant to induction-concurrent. Changing to induction, with better tolerance [106] and upfront use of cytotoxic drug combination, could theoretically be more effective for eradicating potent micrometastases. In addition, this could shrink the primary tumor to give wider margin for RT, an advantage that is particularly needed for tumors infiltrating/abutting critical neurological structures. With encouraging results extensively reported from Phase II studies since the first report by Rischin et al. [107], this has been included as an option (Category 3 evidence) in NCCN guideline [31] and (II, B evidence) in European guideline [32].

There have been six randomized studies that attempted to evaluate the efficacy of induction-concurrent sequence. Five studies used concurrent-alone chemotherapy (cisplatin 40 mg/m^2 weekly) as the standard arm: two trials are still ongoing, but three reported disappointing results. The study by Hui et al. [108] on a small series of 65 patients initially showed significantly better 3-year OS by adding induction cisplatin and docetaxel; however, the impact became insignificant with longer follow-up [101]: HR = 0.64; 95 % CI, 0.39–1.39. Both the studies by Fountzilas et al. [109] by adding cisplatin, epirubicin, and paclitaxel ($n = 141$) and Tan et al. [110] by adding carboplatin, gemcitabine, and paclitaxel ($n = 172$) did not achieve OS benefit.

The NPC-0501 Trial conducted by the Hong Kong Nasopharyngeal Cancer Study Group was the only randomized controlled trial that used the Intergroup-0099 concurrent-adjuvant chemotherapy regimen with conventional-fractionated RT as the standard arm. Besides evaluating the impact of timing (induction-concurrent vs. concurrent-adjuvant), this trial attempted to evaluate two more strategies: the first strategy is to improve the current PF regimen by replacing infusional fluorouracil with capecitabine and the second strategy is to enhance the efficacy of RT by changing from conventional to accelerated fractionation. Preliminary results [52] (median follow-up 3.3 years) have been reported. Patients treated with induction-concurrent regimens had excellent tolerance in the non-concurrent phase, but decreased tolerance in the concurrent phase. Changing the sequence per se, as shown by comparison of induction using cisplatin-fluorouracil versus adjuvant cisplatin-fluorouracil, did not achieve statistically significant improvement in efficacy. But more encouraging results were achieved by changing both the sequence and the induction regimen: unadjusted comparison of induction cisplatin-capecitabine versus adjuvant cisplatin-fluorouracil showed favorable trend in PFS when given with Conventional-fractionated RT ($p = 0.045$). Multivariate analyses further showed that when adjusted for

Table 26.6 The second patient data-based meta-analysis by the MAC-NPC Collaborative Group: analyses of hazard ratio [95 % confidence interval] in 4798 evaluable patients from 19 valid trials performed up to 2010

Trial	Stage	Timing	Regimen	Overall Survival
Induction				
Chan [95]	II–IVB	Induction + Adjuvant vs. None	I: cisplatin + fluorouracil	1.30 [0.62–2.73]
			A: cisplatin + fluorouracil	
Chua [96]	II–IVB	Induction vs. None	I: cisplatin + epirubicin	0.99 [0.68–1.44]
Cvitkovic [97]	III–IVB	Induction vs. None	I: cisplatin + epirubicin + bleomycin	1.00 [0.75–1.33]
Hareyama [98]	I–IVB	Induction vs. None	I: cisplatin + fluorouracil	0.77 [0.40–1.46]
Hui [108]	III–IVB	Induction + Concurrent vs. Concurrent	I: cisplatin + docetaxel	0.64 [0.39–1.39]
			C: cisplatin	
Fountzilas [109]	II–IVB	Induction + Concurrent vs. Concurrent	I: cisplatin + epirubicin + Paclitaxel	1.00 [0.59–1.67]
			C: cisplatin	
Subtotal				0.96 [0.80–1.16]
Adjuvant				
Chi [99]	II–IVB	Adjuvant vs. None	A: cisplatin + fluorouracil + folinic acid	0.95 [0.65–1.40]
Kwong [93]	II–IVB	Adjuvant vs. None	A: cisplatin + fluorouracil	1.07 [0.66–1.88]
Kwong [93]	II–IVB	Concurrent + Adjuvant vs. Concurrent	C: uracil + tegafur	0.66 [0.36–1.19]
			A: cisplatin + fluorouracil/ vincristine + bleomycin + methotrexate	
Chen [100]	III–IVB	Concurrent + Adjuvant vs. Concurrent	C: cisplatin	0.47 [0.79–1.30]
			A: cisplatin + fluorouracil	
Subtotal				0.87 [0.68–1.12]
Concurrent-alone				
Chan [89]	II–IVB	Concurrent vs. None	C: cisplatin	0.81 [0.61–1.07]
Kwong [93]	II–IVB	Concurrent vs. None	C: uracil + tegafur	1.00[0.57–1.75]
Kwong [93]	II–IVB	Concurrent + Adjuvant vs. Adjuvant	C: uracil + tegafur	0.63 [0.34–1.15]
			A: cisplatin + fluorouracil/ vincristine + bleomycin + methotrexate	
VUMCA-95	III–IVB	Induction + Concurrent vs. Induction	I: cisplatin + epirubicin + bleomycin	0.89 [0.69–1.16]
			C: hydroxyurea	
Zhang [103]	III–IVB	Concurrent vs. None	C: oxaliplatin	0.54 [0.31–0.93]
Huang [220]	III–IVB	Induction + Concurrent vs. Induction	I: carboplatin + floxuridine	0.94 [0.69–1.30]
			C: carboplatin	
Chen [102]	II–III	Concurrent vs. None	C: cisplatin	0.34 [0.18–0.66]
Subtotal				0.80 [0.70–0.93]
Concurrent -adjuvant				
Al-Sarraf [81]	II–IVB	Concurrent + Adjuvant vs. None	C: cisplatin	0.50 [0.36–0.71]
			A: cisplatin + fluorouracil	
Wee [85]	III–IVB	Concurrent + Adjuvant vs. None	C: cisplatin	0.66 [0.48–0.96]
			A: cisplatin + fluorouracil	
Lee [83]	N2–3	Concurrent + Adjuvant vs. None	C: cisplatin	0.73 [0.54–0.99
			A: cisplatin + fluorouracil	
Lee [51] (conventional)	T3–4 N0-1	Concurrent + Adjuvant vs. None	C: cisplatin	0.97 [0.52–1.82]
			A: cisplatin + fluorouracil	
Lee [51] (accelerated)	T3–4 N0-1	Concurrent + Adjuvant vs. None	C: cisplatin	0.50 [0.28–0.90]
			A: cisplatin + fluorouracil	
Chen [87]	III–IVB	Concurrent + Adjuvant vs. None	C: cisplatin	0.69 [0.48–0.99]
			A: cisplatin + fluorouracil	
Subtotal				0.65 [0.56–0.76]
Overall				0.79 [0.73–0.86]
Overall test				<0.001
Interaction of timing				0.01
Residual heterogeneity				0.36

Abbreviations: *I*, induction; *C*, Concurrent; *A*, Adjuvant

Based on data form Ref. [101]

other significant factors and fractionation, induction cisplatin-capecitabine group had significantly lower hazard in progression ($p=0.002$) and death ($p=0.001$). Unadjusted comparison of induction cisplatin-capecitabine versus induction cisplatin-fluorouracil did not show significant difference, but adjusted analysis showed that induction cisplatin-capecitabine had lower hazard in death ($p=0.038$). In addition, this regimen incurred less neutropenia and electrolyte disturbance. Regarding the change to accelerated fractionation, the proportion of patients with 3 concurrent cycles was inevitably less with shorter overall RT time. With further lowering of tolerance by induction chemotherapy, even the proportion with ≥2 concurrent cycles was affected. In contrast to the findings in the NPC-9902 Trial, the current trial concurred with the GORTEC 99-02 trial [111] and the RTOG-0129 Study [112] on other head and neck cancers that acceleration is not beneficial for patients with concurrent chemoradiotherapy. In addition, acceleration incurred significantly higher incidence of acute mucositis and dehydration. Together with the logistic difficulty for arranging six fractions per week, acceleration is not recommended for patients treated with chemoradiotherapy, particularly those with induction-concurrent regimens. A major weakness of the NPC-0501 trial is that the design is too complex with inclusion of multiple arms and strata. Furthermore, the median follow-up for the preliminary report was 3.3 years; longer observation is needed to confirm the long-term therapeutic ratio.

It is important to note that chemotherapy does incur 2 % increase in noncancer deaths [101]. Besides exploring for more potent regimens, future studies should also explore for better patient selection to avoid overtreatment and tailoring treatment in accordance with individual risk and response.

26.8 Monitoring of Disease Progression

Early detection of treatment failure is crucial for better chance of salvage; both endoscopic and imaging examinations are needed. A systemic review of 1813 patients from published literature [113] showed that FDG-PET is the best modality for the diagnosis of persistent/recurrent locoregional disease. Both the sensitivity and specificity estimates for PET (95 and 90 %) were significantly superior to MRI and CT ($p<0.001$); the sensitivity of MRI and CT was similar (78 and 76 %, respectively), but the specificity for MRI was significantly better than CT (76 vs. 59 %, $p<0.001$).

Another useful investigation for monitoring disease is the circulating plasma EBV-DNA; patients with persistently elevated posttreatment levels had a significantly higher risk of relapse and death than those without [114–116]. Chan et al. [114] showed that the relative risk for recurrence was 11.9-fold for patients with persistently raised plasma EBV-DNA at 6–8 weeks posttreatment. Longitudinal follow-up showed that in 89 % (8/9) of patients who developed treatment failure, the EBV-DNA level started to increase 2–16 months before clinical evidence of disease progression [117].

26.9 Treatment of Persistent/Recurrent Tumors

As it takes time for tumors to regress following RT, it is difficult to decide when the residual tumors are considered as genuine persistence and proceed with salvage treatment. Kwong et al. [47] showed that the incidence of positive histology decreased spontaneously from 29 % in the first week after completion of RT to 12 % by the ninth week and then rose again. The 5-year LFFR was 82 % for patients who achieved early histological remission (<5 weeks), 77 % for those with delayed remission (5–<12 weeks), and only 54 % for those with persistent tumors at 12 weeks despite subsequent salvage treatment. The optimal time for intervention remains uncertain; avoidance of unnecessary overtreatment and excessive delay in treatment are both important, and salvage treatment decision based on findings between 8 and 12 weeks is usually considered a reasonable balance [118–120]. However, it is known that some NPC studies were based on biopsies taken between 3 and 8 weeks [121, 122]; the time of intervention of "persistent disease" has to be taken into account when interpreting the treatment results.

Because the therapeutic considerations and prognosis are different, distinction should be made between persistent disease (tumors that do not completely regress following primary treatment) and recurrent disease (tumors that reemerge after initial complete regression). Patients with persistent disease had better outcome than those with recurrent disease. Wu et al. [123] showed that the timing and the volume of tumor detected were significant independent prognostic factors; the 3-year disease-specific survival (DSS) was higher for the persistent group (patients who failed within 6 months from completion of RT) than the recurrent group (81 % vs. 46 %, $p=0.037$). Table 26.7 summarizes the recent reports on different RT methods and the outcomes for the patients with persistent disease.

Brachytherapy, using intracavitary and interstitial methods, has been widely used for superficial persistent diseases. Excellent results with 90 % or higher 5-year LFFR have been reported for patients with initial T1–2 tumors [118, 119, 121, 122]. For more bulky persistent disease, stereotactic technique is being increasingly used. Various dose prescription regimes have been employed, ranging from 7 to 35 Gy by single fraction stereotactic radiosurgery (SRS)

Table 26.7 Radiotherapy for salvage of persistent nasopharyngeal carcinoma

Author	Treatment	Treatment outcome (Actuarial rate %)		
		Year	L-FFR	Survival
Kwong [118]	Interstitial gold grain	5	T1: 87	79
Law [119]	Iridium mold	5	T1–2a: 90	65
Leung [121]	HDR-ICB	5	T1: 95 T2: 88	NR
Zheng [122]	HDR-ICB	5	T1: 100 T2: 90	NR
Yau [120]	FSRT	3	T1–4: 82	82
Wu [123]	FSRT	3	T1–4: 89	NR

L-FFR, Local failure-free rate; *HDR-ICB*, High-dose-rate intracavitary brachytherapy; *FSRT*, Fractionated stereotactic radiotherapy; *NR*, Not reported

[124, 125] to 10–24 Gy by multiple fractions stereotactic radiotherapy (SRT) [120, 123]. For the patients in Yau et al. [120] series who had positive biopsies 8 weeks after completion of primary RT (7 % of 755 consecutive patients), those treated with fractionated stereotactic RT (SRT) to a median dose of 15 Gy had a 3-year LFFR of 82 %, a result that was very close to the corresponding 86 % in the contemporary cohort with complete remission and was substantially better than the 71 % LFFR of those treated with HDR brachytherapy to a median dose of 20 Gy. Wu et al. [123] also reported a 3-year LFFR of 89 % with SRT, and they further showed that severe late toxicity rate (9 %) was substantially lower than their SRS series.

26.9.1 Surgical Salvage

For patients with local recurrence, thorough re-staging workup is warranted as 54 % of patients also have synchronous regional and/or distant failures [126].

For patients presenting with early local and/or regional persistent/recurrent tumor after previous radiotherapy, surgical salvage should be considered. Different approaches have been described for the treatment of local recurrence at the nasopharynx [127–129]. Over the years, at the Queen Mary Hospital, the maxillary swing approach has been utilized for such purpose. Using the Weber Ferguson Longmire incision and the corresponding osteotomies, the maxillary osteocutaneous complex is swung laterally. This approach allows wide exposure of the ipsilateral nasopharynx and the parapharyngeal space. If necessary, the contralateral nasopharynx can be approached by removing the posterior part of the nasal septum. Moreover, for tumors encasing the internal carotid artery and for those that eroded the skull base, the surgery can be performed with a craniotomy as a combined craniofacial approach [130]. Adequate resection of the tumor can be performed with wide margins. Upon the completion of surgery, the maxilla is returned and fixed with titanium mini-plates and screws. Nowadays, for small tumors with no parapharyngeal invasion, the transoral robotic approach can be performed, minimizing surgical trauma to the facial soft tissue and skeleton [131].

Between 1989 and 2011, nasopharyngectomy via the maxillary swing approach had been performed for 312 patients with persistent/recurrent NPC. Resection with histologically clear margins was achieved in 79.5 % of patients. The overall 5-year actuarial local tumor control was 74 %, and the overall 5-year disease-free survival was 56 % [132]. On multivariate analysis, tumor size, resection margin status, and gross tumor in the sphenoid sinus were independent prognostic factors for local tumor control. For OS, resection margin status, synchronous nodal recurrence, and cavernous sinus invasion had a negative influence [133].

To study the histological characteristics of recurrent NPC, we had performed a whole-organ histopathological study on 50 nasopharyngectomy specimens. It was found that the recurrent tumors appeared as islands of cancer cells separated by lymphoplasmacytic infiltrate and fibrosis. For tumor invading the parapharyngeal space, the removal of the pharyngobasilar fascia was essential to ensure a clear deep margin. Prominent submucosal extension of tumor was noted in the majority of patients, and a radial resection margin of 15 mm should be taken to ensure a clear resection margin [134].

After maxillary swing nasopharyngectomy, the mean hospital stay was 8.2 days. There was no hospital mortality, and all patients can resume oral feeding upon discharge from the hospital. The intra-operative blood loss and the transfusion requirement were significantly reduced by a period of controlled hypotension during osteotomy. The most common side effects of surgery included palatal fistula (3.7 %), trismus (9.2 %), and facial numbness (7.4 %) [135]. The overall quality of life after maxillary swing nasopharyngectomy has been acceptable. A study using a self-reported, health-related quality of life questionnaires showed that there was no significant change in the mean global health system scores after surgery.

Social functioning scores were the lowest of the 5 functioning scales. Surgical complications such as palatal fistula and osteoradionecrosis adversely affected the quality of life after surgery [136], demonstrating the importance of meticulous surgical techniques and ongoing modification of procedures to minimize the postsurgical morbidities for the patients.

In patients with nodal failure, the extent of involvement is often extensive; radical neck dissection should be carried out as the salvage procedure; 5-year nodal salvage of 66 % and EFS of 37 % could be achieved [137]. For those with evidence of extra-capsular invasion of tumor, radical lymph node dissection together with the application of after-loading brachytherapy to the tumor bed results in better tumor control, with a 5-year actuarial nodal control of 65 % and a 5-year disease-free survival of 44 %. In such circumstances, the simultaneous use of regional flaps (deltopectoral or pectoralis major flaps) ensures good wound healing in a previously heavily irradiated field and this is important to prevent dreaded complications of carotid exposure and blowout bleeding [138].

26.9.2 Nonsurgical Salvage

The treatment option for the majority of patients with recurrent T3–4 disease is re-irradiation with or without chemotherapy (Table 26.8). Aggressive treatment should be attempted as far as possible because long-term survival might be achieved [139]. Re-irradiation poses a therapeutic challenge and important prognostic factors should be taken into account when planning re-irradiation. These include the recurrent T stage, the degree of previous radiation-related complications, performance status, age, and any evidence of synchronous nodal recurrence [140]. Doses ≥ 60 Gy are recommended for effective salvage [141, 142], but significant morbidities are often incurred [143–145]. Nevertheless, a retrospective study by Lee et al. [146] comparing the late toxicity rate in 487 patients with two courses of external RT versus 3635 patients with one course suggested that there was partial recovery of normal tissues following the primary course: the total biological dose (BED-Σ) leading to a certain rate of toxicity was higher than that expected with a single course treatment (BED-1). Using the tumor dose as a guide, the BED-Σ that incurred 20 % overall neurological toxicity at 5 years after irradiation was 129 % that of BED-1 (using an α/β ratio of 3 Gy).

Brachytherapy has also been used for the treatment of superficial recurrent disease. Using interstitial implants with radioactive gold grains, Kwong et al. [118] reported a 5-year LFFR of 63 %; complications included headache (28 %), palatal fistula (19 %), and mucosal necrosis (16 %). Using iridium mold, Law et al. [119] achieved local control of 89 %, but the complication rate was also very high at 53 %. For more advanced recurrent tumors, 2D external RT with brachytherapy boost could achieve higher salvage rate [141, 142, 147] than brachytherapy alone.

Stereotactic technique is also being increasingly used. Local salvage rates ranging from 53 to 86 % could be achieved with SRT [124, 148–151]. Leung et al. [151] showed that the amount of total equivalent dose (TED) by fractionated SRT was a significant factor and TED ≥55 Gy was recommended. For patients with limited local failure, stereotactic radiosurgery (SRS) yielded comparable tumor control as gold grain implantation [152]. An even higher salvage rate by using SRT as a boost after external RT has been reported [149, 153, 154], and SRT appeared to achieve better local control than single fraction SRS [155]. Although most series reported a low risk of complications, torrential hemorrhage with potentially fatal outcome has been reported [149, 156, 157]; SRS should be avoided in patients with tumor encasing the carotid artery or previous high cumulative dose.

Depending on the recurrent T stage, older series using 2D technique achieved 5-year survival rates in the range of 21–41 % and the incidence of TLN ranged from 2 to 27 %. However, the degree of late complications might have been underestimated due to the lack of regular radiological assessments. New data are now available from studies employing modern techniques such as IMRT. Multivariate analysis by Zou et al. [158] showed that both IMRT and endoscopic nasopharyngectomy could achieve a higher OS rate than 2D RT in a series of 410 patients. The 5-year OS were 39 % and 21 % for IMRT and 2D RT, respectively. But the advantage was confined to patients with rT1–2 disease only and there was no difference in local relapse-free survival between these two RT techniques. A large retrospective study of 239 patients treated with IMRT was recently reported by Han et al.[145]. In this study, the mean dose to GTV was 69.94 Gy and the mean dose per fraction to GTV was 2.31 Gy; the local relapse-free survival was 85 %, but the OS rate at 5 years was only 45 %. This discrepancy between local control and survival rate was due to the substantiated radiation-related treatment death, especially massive nasopharyngeal hemorrhage (35 %). Similarly high incidence of treatment-related death was also observed in a phase II randomized trial [159] studying the effect of total dose and fraction size of IMRT; in which 38 deaths out of 117 randomized patients (32 %) were attributed to radiation injuries. Furthermore, grade 3 and 4 complications were not uncommon for the remaining treated patients in these two studies. Detailed dosimetric analyses by Liu et al. [143] revealed a 31 % risk of TLN with a short median latency period of only 15 months. Chen et al. [144] echoed similar findings in a group of 54 recurrent NPC patients treated to an average GTV dose of 69.96 Gy. While the local failure-free survival was 64 % at 2 years, the OS rate was only 44 %. Severe late adverse events occurred in 48 % of the patients including 25 % of those who died of treatment complications. Therefore, despite the potential dosimetric advantage of IMRT, the very high treatment-

Table 26.8 Efficacy and late toxicities by re-irradiation for recurrent nasopharyngeal carcinoma

Author	Patient N (% rT1)	Re-irradiation method (median dose)	Chemo (Sequence)	Year	L-FFR	Survival	Brain necrosis	Neuropathy/ myelopathy	Massive epistaxis	Death
Kwong [118]	53 (all rT1)	Interstitial gold grain (60 Gy)	8 % (S)	5	63	OS: 54	8	2 (BS)	NR	0
Law [119]	78 (all rT1–2a)	Iridium mold (55 Gy)	15 % (I)	5	89	OS: 65	5	19	NR	6
Chua [155]	24 (58 % rT1)	SRS (12.5 Gy/1 Fr)	0	3	30	OS: 52	16	NR	2	0
	24 (54 % rT1)	FSRT (48 Gy/4–6 Fr)	0	3	75	OS: 35	12	NR	4	7
Wu [123]		FSRT (48 Gy/6 Fr)	30 % (S/C)	3	75	DSS: 46	5	5 (BS)	4	4
Leung [151]	30 (47 % rT1)	FSRT (54 Gy/18 Fr)	20 % (I)	5	57	OS: 40	20	23	7	NR
Seo [156]	35 (43 % rT1)	Robotic FSRT (33 Gy/3–5 Fr)	3 % (A)	5	79	OS: 60	NR	NR	9	6
Ozyigit [157]		Robotic FSRT								
	24 (21 % rT1)	(30 Gy/5 Fr)	42 % (A)	2	82	DSS: 64	4	4	17	13
	27 (15 % rT1)	3D (57 Gy) ± ICB(HDR)	56 % (A)	2	80	DSS: 47	19	15	4	15
Low [221]	31 (all rT1–2a)	SRS (18 Gy) + ICB (HDR 18 Gy)	0	5	57	OS: 53	8	20	0	0
Chang [153]	186 (23 % rT1)	Mostly 2D (50 Gy) ± SRS (8–15 Gy)	44 %	3	NR	OS: 22	2D:14 3D: 0	NR	NR	NR
Pai [150]	36 (53 % rT1)	3D (50 Gy) + SRS (12 Gy)	0	5	NR	OS: 31	0	NR	8	NR
Lee [142]	654 (35 % rT1)	2D (46 Gy), ICB (LDR 40 Gy),	0	5	32	OS: 16	3	4	0.3	2
		Combined (2D 40 Gy +ICB 20 Gy)								
Pryzant [141]	53 (51 % rT1)	2D (57 Gy) ± B	19 % (A)	5	35	OS: 21	4	6	0	9
Chua [222]	97 (34 % rT1)	2D (60 Gy) and/or B	18 % (S)	5	NR	OS: 36	12	24	0	NR
Teo [223]	103 (22 % rT1)	2D (66 Gy) ± ICB	16 % (S)	5	15	OS: 8	20	10	5	NR
Oksuz [224]	41 (22 % rT1)	2D (50 Gy)	42 % (S/C)	5	23	OS: 28	10	0	0	NR
Leung [147]	91 (41 % rT1)	2D (50 Gy) ± ICB (HDR 15 Gy)	19 % (I)	3	38	OS: 30	27	10	2	4
Poon [161]	35 (34 % rT0–2)	Majority 2D (50–60 Gy)	All (C + A)	5	NR	OS: 26	14	31	0	NR
Zheng [225]	86 (18 % rT1)	3D (68 Gy)	22 % (I)	5	71	OS: 40	15	37	0	13
Chua [226]	31 (26 % rT1-2)	IMRT (50–60 Gy) ±SRS	68 % (I)	1	65	OS: 63	2	3	0	0
Koutcher [162]	29 (45 % rT1)	83 % IMRT (59.4 Gy) or					3	2	0	NR
		Combined (E 45 + B 20 Gy)	93 % (C ± S)	5	52	OS: 60	1	0	0	NR

Qiu [227]	70 (53 % rT1-2)	IMRT (median 70 Gy)	44 % (I), 18 % (C)	2	66	OS: 67	NR	17	6	6
Han [145]	239 (25 % rT1-2)	IMRT (mean 70 Gy)	49 %	5	86	OS: 45	68	NR	NR	83
Chen [144]	54 (20 % rT1-2)	IMRT (average 70 Gy)	52 % (C)	2	64	OS: 44	10	22	6	13
Tian [159]	117 (21 % rT1-2)	IMRT (68 Gy in 34fr or 60 Gy in 27 fr)	0 %	5	64–71	OS: 37	25	15	29	38

L-FFR, Local failure-free rate; *DSS*, Disease-specific survival; *OS*, Overall survival; *B*, Brachytherapy; *IC*, Intracavitary; *LDR*, Low-dose-rate; *HDR*, High-dose-rate; *E*, External radiotherapy; *2D*, 2-dimensional technique; *3D*, 3-dimensional conformal technique; *IMRT*, Intensity-modulated technique; *SRS*, Stereotactic radiosurgery; *FSRT*, Fractionated stereotactic radiotherapy; *C*, Combined external radiotherapy + brachytherapy; *S*, Sequential (induction or adjuvant), *I*, Induction; *A*, Adjuvant; *C*, Concurrent; *BS*, Brainstem; *NR*, Not reported

related death and complications are of serious concerns and overenthusiastic re-treatment should be viewed with great caution. Additional studies on mucosal and carotid vessel tolerances are urgently needed and quality of life should also be addressed in the future series.

Chemo-radiotherapy may also improve treatment outcome for recurrent NPC. Using CDDP/gemcitabine as induction chemotherapy followed by re-irradiation with IMRT in 20 patients (95 % rT3–4), Chua et al. [160] reported a 1-year local salvage rate of 75 %. Using concurrent CDDP followed by adjuvant chemotherapy with CDDP/FU in 35 patients (66 % rT3–4), Poon et al. [161] reported a 1-year event-free survival (ESS) of 42 %. Similar encouraging results (5y EFS 44 % and 5y OS 60 %) have also been reported by Koutcher et al. [162] using combined-modality treatment in 29 patients (83 % IMRT/93 % chemotherapy in various sequence/45 % brachytherapy boost).

At our center, in order to avoid the additional radiation-induced morbidities due to the second course of re-irradiation, the preferred treatment for rT1–2 (and rT3 with limited sphenoid floor invasion) is surgical salvage. For patients with rT3–4 diseases, 4–6 cycles of induction chemotherapy would be given to majority of them aiming to downsize the tumor, and those with good tumor shrinkage would receive re-irradiation up to 60 Gy or its equivalents. Treatment is delivered by IMRT and our preferred prescribed dose is 1.2 Gy per fraction, twice daily, at least 6 h apart to a total dose of 64.8 Gy. Considering the risk of re-irradiation and OAR partial recovery, we keep the total-dose constraint (including the dose from the first course of radiotherapy) to brainstem, optic chiasm, and temporal lobe to <130 % of their tolerance dose we use in the primary course of radiotherapy.

26.10 Treatment of Metastatic Disease

Treatment should be individualized as there is marked heterogeneity in prognosis among patients with distant metastases. Toh et al. [163] proposed a prognostic index score basing on metastasis at diagnosis or disease-free interval, performance status, and hemoglobin level. The median OS ranged from 8 for the poor to 20 months for the good prognostic group. Hui et al. [18] showed that patients with lung metastasis alone had a relatively favorable prognosis; a more aggressive approach should be considered. In addition to chemotherapy, surgical resection and/or high-dose RT may be considered in selected patients with limited metastases.

Cisplatin-based chemotherapy is the mainstay of treatment for majority of distant failures; the most common regimen CDDP/FU [164–167] achieved an overall response rate (ORR) of >66 % and median time to progression (TTP) of 8–15 months. Addition of different drugs like bleomycin,

Table 26.9 Summary of outcomes of various chemotherapy regimens in metastatic NPC

Study (year published)	Patient no.	Chemotherapy	Overall response rate (%)	CR rate (%)	Median PFS (months)	Median OS (months)
Classical platinum and 5FU regimens						
Wang [164]	25	PF	76	8	NA	NA
Au [165]	24	PF	66	13	8	11
Chi [166]	35	PF	80–100[a]	13–15[a]	NA	14–34[a]
Yeo [167]	42	JF	38	17	NA	12.1
Platinum-containing triplets or poly-drug regimens						
Siu [168]	61	CAPABLE	41–80[a]	6.8–23.5[a]	NA	14–16[a]
Hasbini [169]	44	PEMF	52	13	9	14
Leong [175]	28	GJPac → FL maintenance	86	11	8	22
Huang [228]	56	PDF	72.5	9.8	NA	NA
Second generation platinum containing doublets						
Yeo [229]	27	JPac	59	11	6	13.9
Tan [230]	32	JPac	75	3	7	12
Ngan [173]	44	GP	73	20	10.6	15
Chua [170]	19	DP	62.5	6.3	5.6	12.4
Li [171]	48	PX	62.5	6.3	7.7	13.3
Chua [172]	44	PX	53.8	2.6	7.3	28
Ma [231]	40	GOx	56.1	0	9	19.6

[a]Response rate (%) or survival (months) differs among patients with metastases and locoregional recurrences in the studies. *P*, cisplatin; *F*, fluorouracil; *J*, carboplatin; *CAPABLE*, cyclophosphamide + bleomycin + doxorubicin + cisplatin; *E*, epirubicin; *M*, mitomycin; *G*, gemcitabine; *Pac*, paclitaxel; *L*, leucovorin; *D*, docetaxel; *X*, capecitabine; *Ox*, oxaliplatin

epirubicin, mitomycin, and methotrexate to CDDP (with or without FU) failed to achieve substantial benefits, but incurred a high incidence of hematologic toxicities and even mortality [168, 169].

Table 26.9 summarizes the response and major toxicities of different regimens; cross-series comparison is impossible because of difference in patient characteristics and previous treatment. Among the modern cytotoxic drugs, studies on combination of CDDP/docetaxel [170], CDDP/capecitabine [171, 172], and CDDP/gemcitabine [173] reported ORR of 63–73 % and median TTP 6–11 months. The latter two combinations are particularly attractive because of moderate toxicity and easy administration; docetaxel should be used with caution because of very high incidence of neutropenic toxicity [170, 174]. Using a triplet combination of gemcitabine, paclitaxel, and carboplatin for 6 cycles followed by weekly FU and folinic acid for 48 weeks, Leong et al. [175] reported an ORR of 86 %, the median TTP was 8 months, and the OS was up to 22 months, but hematological toxicities occurred in >79 % of patients.

So far, the efficacy of molecular targeted therapy for NPC is disappointing. Two targets have been studied: epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF). A phase II study on combination of cetuximab (a monoclonal antibody against the extracellular domain of EGFR) with carboplatin on refractory patients only achieved an ORR of 12 % and TTP of 3 months [176]. Similarly, the results of single agent activity targeting on these pathways are rather poor [177–180]. The time to tumor progression is usually short (2.7–4.4 months) and no complete response has been reported. While treatments were usually well tolerated, one study [181] had to stop prematurely due to fatal bleeding complication. And caution with the use of anti-angiogenic agent has been raised in the setting of locally recurrent disease located close to major vessel. The use of newer anti-angiogenic agent such as pazopanib has also been reported [182]. Among 33 heavily pretreated patients, there were 2 (6.1 %) partial responses and 16 (48.5 %) stable disease, giving a clinical benefit rate of 54.5 % (95 % CI 38.0–70.2). Fifteen patients (45 %) received more than 5 cycles of treatment, 6 (18.2 %) had PR/SD that lasted at least 6 months, and one patient remains on treatment. Other targeted agents such as nimotuzumab, icotinib, axitinib, and bortezomib are currently being tested in clinical trials and their results have not been published.

26.11 Management of Late Toxicities

The close proximity of the nasopharynx to the multiple surrounding delicate structures requires a painstaking balance between local control and late toxicities occurrence. The advent of IMRT allows better sparing of these OARs, but still the mitigation and management of the late toxicities remain a major clinical challenge.

26.11.1 Hearing Impairment

Hearing loss can be sensorineural, conductive, or a mixture of both in nature. Sensorineural hearing loss (SNHL) is contributed by the loss of spiral ganglion cells, inner and outer hair cells, and stria vascularis atrophy after radiotherapy and cisplatin treatment [183]. A prospective cohort analysis indicates that high tone (≥4 k Hz) SNHL after radiotherapy concurrent with cisplatin could go up to 55 %, significantly more frequent than radiotherapy (33 %) alone . Low tone loss is much less common. Age, the mean cochlear dose and concurrent cisplatin dose are important predictors of high tone SNHL. Limiting the mean cochlea dose below 47Gy is suggested to reduce SNHL [184]. Cochlear implant can improve hearing outcomes in selected patients [185–187].

Secondary to radiotherapy, chronic suppurative otitis media, Eustachian tube dysfunction, and external auditory canal osteoradionecrosis can all lead to conductive hearing loss. A prompt referral to otorhinolaryngologists for consideration of aural toileting, antibiotics, surgery, or hearing aids fitting is required.

26.11.2 Temporal Lobe Necrosis

The incidence of TLN varies, depending on the fractional dose, cumulative dose-volume parameters, and the dosimetric prioritization [37, 188, 189]. Even a moderately hypofractionated treatment scheme can lead to unacceptably high incidence of TLN [45]. IMRT has the advantage to reduce the maximal dose of the temporal lobe dose and reduce the risk of TLN compared to conventional therapy [58].

The treatment of TLN is challenging. Asymptomatic patient with single prior treatment course and long latency period can be observed. Intravenous pulsed steroid therapy appears to be more effective than oral steroid in terms of clinical response [190]. Surgery is indicated in patients with mass effect despite medical therapy, abscess formation, or hemorrhage [189, 191–193]. Anecdotal case series have proposed the potential role of anticoagulants, antiplatelets (like pentoxifylline), high-dose vitamin (like tocopherol), and hyperbaric oxygen in the treatment of TLN, but further studies are needed to ascertain their actual treatment efficacy and safety [189]. Recently bevacizumab has also been found effective in improving the radiographical responses and neurological outcomes in patients with radiation-induced brain

necrosis [194, 195]. The preliminary encouraging results warrant further exploration.

26.11.3 Dysphagia and Aspiration

Impaired pharyngeal peristalsis, laryngeal penetration, and silent aspiration are very common and can reach up to 70–80 % [196–198]. However, patients in general pay less attention to radiotherapy-induced dysphagia and neglect the risk of aspiration [199]. In a national-wide study in Taiwan, the incidence of late-onset pneumonia was 5.5 % and thus the mortality risk should not be overlooked [200]. The use of IMRT junctioned with an anterior neck field with central shielding has been suggested to minimize the dose to pharyngeal–esophageal axis if the lower neck is free of gross disease [201]. Alternatively, excluding the medial retropharyngeal lymph node (RPLN) in CTV delineation can spare the constrictor muscles to excess radiation dose, as the risk of medial RPLN involvement is quite rare [11].

Trismus and lower cranial nerve palsy can also aggravate dysphagia and increase risk of aspiration. Hypoglossal nerve palsy is the most commonly noted neuropathy[202, 203]. Reducing the dose to tempo-mandibular joint by IMRT has led to reduction in radiation-induced trismus [204, 205].

26.11.4 Carotid Blowout Syndrome

Carotid blowout syndrome is an uncommon but fatal medical emergency. Re-irradiation and skull base osteoradionecrosis predispose carotid blowouts [206]. In a systematic review estimating the risk of re-irradiation in head and neck cancer, the overall risk is 2.6 %, and 76 % of them died. Hyperfractionated accelerated RT poses a higher risk of carotid blowout [207]. Endovascular intervention is effective in controlling intractable bleeding [208, 209].

26.11.5 Xerostomia

The degree of xerostomia has declined with the use of parotid-sparing IMRT [63], but irradiation to submandibular glands and minor salivary glands in oral cavity also attributed to xerostomia [210]. The dose to submandibular gland can be reduced safely when level IB lymph nodes were spared in carefully selected patients [211, 212]. However, overzealous sparing can lead to marginal miss [213].

Other possible late complications include endocrine dysfunction, soft tissue and bone necrosis, dental problems, and radiation-induced secondary malignancies. Clinicians should pay attention to all these potential late complications and intervene early.

26.12 Conclusion

Medical progress in the battle against NPC is one of the most gratifying successes. This peculiar cancer was invariably lethal before the advent of megavoltage RT. With improving knowledge and technology, representative series from Hong Kong showed that the 5-year DSS steadily increased from 50 % for patients treated from 1976 to 1985 [214] to 80 % for those treated in the modern era [215]. Together with decreasing incidence, our age-standardized mortality rate has steadily decreased from the peak of 14.1 in 1983 to 5.8 per 100,000 male populations in 2006.

Continuous search for more potent systemic therapies, refinement of RT technique, and precision are still demanded, especially for patients with metastatic or T4 disease. Furthermore, early detection and more accurate prognostication for personalized medicine are crucial for future improvement; concerted efforts in translational researches will—become increasingly important.

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Multidisciplinary Management of Oropharynx Carcinomas

27

Beth M. Beadle and David I. Rosenthal

Abstract

The evaluation and management of carcinomas of the oropharynx have undergone perhaps the most radical change of all of the head and neck malignancies. With the epidemic of human papillomavirus (HPV)-associated oropharynx cancers, the incidence, demographics, epidemiology, and prognosis of oropharynx cancers have changed considerably. The adoption of advanced technologies and modern therapeutics have revolutionized the treatment of these patients with a goal of providing excellent disease control and minimal morbidity. The multidisciplinary evaluation and management of these patients are crucial for optimal outcomes.

Keywords

Oropharynx cancer • Human papillomavirus (HPV) • HPV-associated cancers • Intensity-modulated radiation therapy (IMRT) for oropharynx cancer • Intensity-modulated proton therapy (IMPT) for oropharynx cancer • Transoral robotic surgery (TORS) for oropharynx cancer

27.1 Introduction

In the last two decades, the evaluation and management of carcinomas of the oropharynx have undergone perhaps the most radical change of all of the head and neck malignancies. The incidence is increasing, the patient age and gender disparities are decreasing, and the prognoses are improving as human papillomavirus (HPV) infection is recognized the major causative factor. As late as the 1990s, the standard therapy for oropharynx cancer at most institutions was open resection with postoperative radiation therapy; during this time, the majority of oropharynx carcinomas were thought to be related to tobacco use. Now, advances in radiation therapy, chemotherapy, and our understanding of a potential viral etiology of these tumors that portends a better prognosis have caused definitive radiation therapy and chemoradiation therapy to become the de facto standard of care. More recent advances in transoral robotic surgery (TORS) have now reintroduced the option of surgery to the treatment armamentarium, with a focus on "closed" or minimally invasive techniques. In addition, the integration of novel targeted therapies, including the anti-epidermal growth factor receptor (EGFR) inhibitors such as cetuximab, has been another milestone in the treatment for these patients. Overall, our understanding of the pathogenesis and methods of treatment have undergone a significant evolution, and the integration of multidisciplinary collaboration has improved outcomes and reduced treatment toxicities for patients with oropharynx carcinomas.

27.2 Anatomy and Lymphatic Drainage

The oropharynx is situated approximately in the middle of the upper aerodigestive tract. It is directly in communication with the other sites of the head and neck, superiorly

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with the nasopharynx, anteriorly with the oral cavity, and posteroinferiorly with the supraglottic larynx and hypopharynx (Fig. 27.1). Anatomically, it is bounded by the junction of the posterior extent of the hard palate superiorly, the circumvallate papillae of the tongue anteriorly, the hyoid bone inferiorly, and the pharyngeal walls in the posterolateral directions.

The oropharynx is divided into four distinct subsites for the purposes of diagnosis and treatment planning. These are (1) the base of tongue, (2) the tonsillar complex, (3) the soft palate, and (4) the oropharyngeal walls (Fig. 27.2).

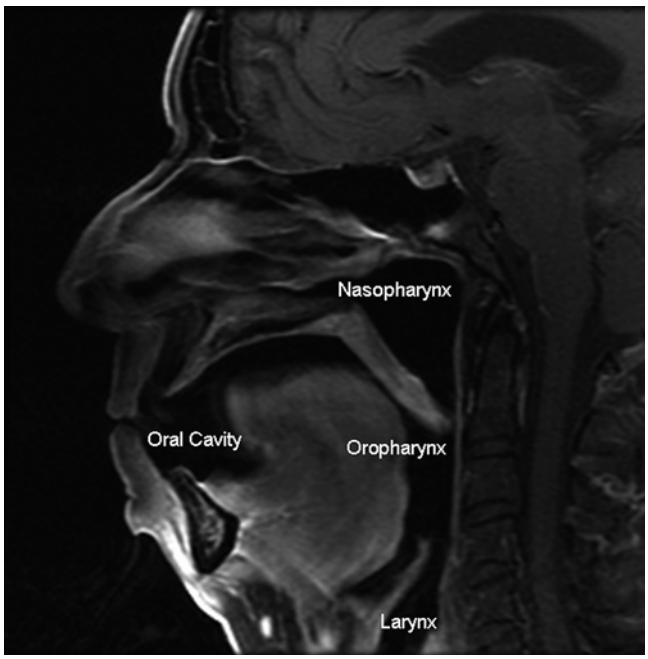

Fig. 27.1 Location of the oropharynx within the head and neck and its relationship with other sites, as shown on a sagittal MRI

27.2.1 Base of Tongue

The base of tongue is a muscular structure of the posterior tongue that is covered in squamous epithelium and contains numerous submucosal lymphoid nests; it is part of Waldeyer's ring. The base of tongue extends from the circumvallate papillae anteriorly to the base of the epiglottis inferiorly (including the valleculae) and to the glossopharyngeal sulci bilaterally. The base of tongue musculature is comprised of the genioglossus, styloglossus, palatoglossus, and hyoglossus muscles. The sensory innervation of the base of tongue is from the lingual branch of cranial nerve IX (glossopharyngeal), and the motor innervation is from cranial nerve XII (hypoglossal).

Primary tumors of the base of tongue can grow either in an infiltrative, submucosal pattern that invades the intrinsic muscles of the tongue or in an exophytic pattern across the mucosa and into the lumen of the upper aerodigestive tract. As the tumors become larger, they may go deeply through the intrinsic muscles of the tongue and affect the extrinsic musculature, inferiorly into the structures of the hypopharynx and larynx, or laterally to the glossopharyngeal sulci and tonsils; they may also cause oral tongue immobility and deviation. Tumors of the base of tongue tend to present with advanced stages since the tongue base is largely devoid of pain fibers, and lesions are frequently asymptomatic until quite large. However, due to the innervation of the base of tongue, tumors in this region can present with referred otalgia via cranial nerve IX (glossopharyngeal) as it joins the tympanic nerve (Jacobson's) and the two traverse the jugular foramen; this referred pain is typically deep in the ear canal.

Tumors of the base of tongue frequently present with nodal metastases. The base of tongue drains to levels II, III, and IV of the neck, as well as the retropharyngeal lymph

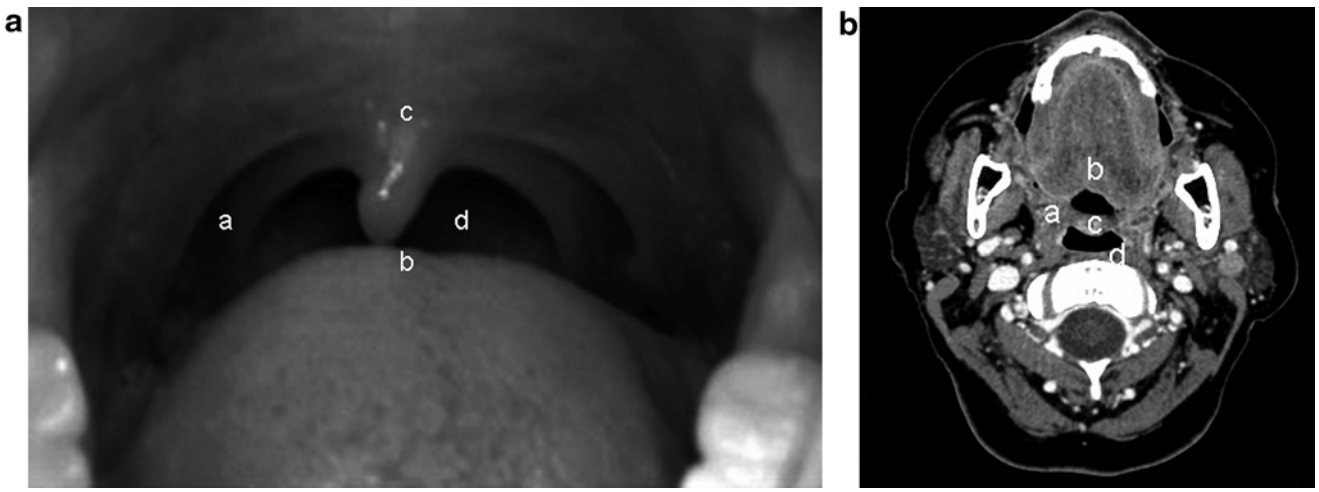

Fig. 27.2 Subsites of the oropharynx on (**a**) oral examination and (**b**) CT scan. The subsites of the oropharynx are: a—Tonsillar complex, b—Base of tongue, c—Soft palate, and d—Oropharyngeal walls

nodes. The base of tongue is a midline structure, so lymph node drainage is bilateral. Prior studies at The University of Texas MD Anderson Cancer Center have shown that approximately 70 % of patients with base of tongue tumors will present with unilateral lymph node metastases and approximately 10–20 % will present with bilateral nodal disease [1].

27.2.2 Tonsillar Complex

The tonsillar fossa is located between palatoglossus and palatopharyngeus muscles, which when covered by their mucosa make up the anterior and posterior tonsillar pillars, respectively. The tonsils are a conglomeration of largely lymphoid tissue encased in a fibrous capsule, which rest within the tonsillar fossae. The entire region is covered in a squamous epithelium that serves as the nidus for the majority of tonsillar tumors. Tonsillar anatomy involves surface involutions, such that only a minority of the total mucosal area is visible on inspection of the surface; for this reason, a tonsillectomy is necessary for the diagnosis of a potential primary tumor when no surface lesion is observed. The sensory innervation of the tonsils is branches of cranial nerve V2 (maxillary).

Primary tumors of the tonsillar fossae and tonsillar pillars can either grow as exophytic lesions along the mucosal surface, spreading onto adjacent subsites, such as the soft palate, tongue base, and pharyngeal walls, or as deeply invasive lesions into the stroma in an ulcerative or endophytic pattern. Advanced tumors are capable of significant submucosal spread, including invasion into the underlying pterygoid muscles and into adjacent regions of the head and neck, including the nasopharynx, hypopharynx, and larynx. Primary tumors may arise from the tonsillar pillars, the tonsillar fossae, or the tonsils themselves; even following a tonsillectomy, tonsil tissue typically remains that may serve as the nidus for malignancy. Lesions of the tonsillar fossae and tonsils tend to present with more advanced primary disease than do those that develop in the tonsillar pillars due to the later development of overt symptoms, including pain, odynophagia, and a globus sensation.

Tumors of the tonsillar region frequently present with nodal metastases. The tonsillar region primarily drains to level II of the neck, but lymph nodes in level I and the retropharyngeal nodes may also be involved. Tumors that arise from the tonsillar fossa are more likely to involve lymph nodes than those from the tonsillar pillars. In a study by Lindberg et al., lymph node metastases were noted in 71 % of patients with T1 tonsillar fossa tumors, 68 % of T2 lesions, 70 % of T3 lesions, and 90 % of T4 lesions [1]. Another study describing patients with tonsillar tumors treated at The University of Texas MD Anderson Cancer Center between 1968 and 1979 demonstrated 69 % of patients having lymph node metastases at presentation [2]. Since the tonsil is a lateral structure, bilateral lymphadenopathy is less common than other sites of the oropharynx. For tumors confined to the tonsillar fossa and posterior pillar, contralateral lymph node positivity is reported in up to 22 % of cases; for tumors of the anterior pillar, this is only 6 % [3].

27.2.3 Soft Palate

The soft palate is a muscular structure largely covered in stratified squamous epithelium that separates the oropharynx from the nasopharynx superiorly and the oral cavity anteriorly. The soft palate musculature includes the levator veli palatine, tensor veli palatine, uvula, palatoglossus, and palatopharyngeus muscles. Anatomically, the soft palate attaches to the hard palate anteriorly and is contiguous with the tonsillar fossae on the lateral sides. Functionally, the soft palate is crucial in speech and swallowing. The motor innervation of the muscles of the soft palate includes cranial nerve V3 (mandibular nerve) and X (vagus), which function to elevate the palate and close off the nasopharynx during swallowing and speech, preventing reflux of a food bolus superiorly and preventing breathiness and nasality of phonation, respectively, termed velopharyngeal incompetence (VPI).

Primary tumors of the soft palate typically arise from the squamous mucosa of the oral aspect of the soft palate. Lesions that arise from the nasopharyngeal portion are much less common. Typically, lesions grow along the mucosal surfaces and tend to be superficial. As the lesions increase in size, they may extend to the adjacent tonsillar fossae, pharyngeal walls, or the anterior palatoglossal arches. Compared to other sites of the oropharynx, lesions tend to be more symptomatic and present at earlier stages.

Tumors of the soft palate predominantly drain to the lymph nodes in levels II and III, as well as the retropharyngeal nodes. In a study by Lindberg et al., clinically evident lymph nodes were present in 8 % of T1 tumors, 37 % of T2 tumors, 65 % of T3 tumors, and 67 % of T4 tumors; the overall rate of nodal metastases was 40 % [1]. Given the centrality of the soft palate, bilateral lymphatic drainage is common, and bilateral nodal disease is not unusual.

27.2.4 Oropharyngeal Walls

The oropharyngeal walls are comprised of the mucosa of the lateral and posterior aspects of the upper aerodigestive tract within the confines of the oropharynx; specifically, the posterior pharyngeal wall extends from the inferior aspect of the nasopharynx to the level of the epiglottis and the lateral pharyngeal wall extends in the same longitudinal region on the right and left aspects of the oropharynx. The oropharyngeal walls consist of a squamous mucosal epithelium that overlies

the pharyngeal constrictor musculature. In turn, the pharyngeal constrictors are anterior to the retropharyngeal space, the longus capitis and colli muscles, the prevertebral fascia, and finally the vertebral bodies. The oropharyngeal walls typically are situated adjacent to the second and third cervical vertebrae, and this region is innervated by cranial nerves IX (glossopharyngeal) and X (vagus).

Primary tumors of the oropharyngeal walls typically arise from the squamous mucosa and grow toward the lumen of the aerodigestive tract and submucosally to other sites within the oropharynx. However, it is possible for lesions of the posterior pharyngeal wall to grow into the prevertebral musculature and bony involvement of the vertebral bodies, although rare, is possible. Lesions of the lateral pharyngeal wall may also grow directly into the structures of the neck and become confluent with the lymph node basins of that region. In many cases, lesions present at an advanced stage, due to the relative paucity of early symptoms until a critical size is reached.

Tumors of both the posterior and lateral pharyngeal walls primarily drain to the lymph nodes in levels II and III, as well as the retropharyngeal nodes. In a study by Lindberg et al., clinically evident lymph nodes were present in 25 % of patients with T1 tumors, 30 % of T2 tumors, 68 % of T3 tumors, and 76 % of T4 tumors [1]. An additional series, spanning 1954–1975 at The University of Texas MD Anderson Cancer Center, described on overall incidence of nodal disease of 57 % in patients with oropharyngeal wall tumors [4]. Bilateral nodal drainage, both to the retropharyngeal and cervical nodes, is common.

27.3 Epidemiology

27.3.1 Incidence and Mortality

Oropharynx cancer is one of the most common types of head and neck cancer; in contrast to other subsites of disease in the head and neck, oropharynx cancer incidence is rising [5, 6]. Globally, oropharynx cancer is estimated to affect approximately 85,000 individuals annually [7]. The diagnosis and outcomes of patients with these cancers, however, do significantly differ throughout the world. Incidence and mortality rates vary between the developed and the developing world [8, 9]. This discrepancy highlights the different propensities for disease development based on underlying lifestyle choices (for instance, tobacco and HPV), genetic dispositions, and preventive health measures, as well as the different standards of care throughout the world.

In the United States, oral cavity and oropharynx tumors are expected to affect approximately 39,500 new patients and lead to approximately 7500 deaths in 2015 [10]. As rates of head and neck squamous carcinomas related to smoking and alcohol continue to decrease, rates of oropharynx cancer, now largely linked to HPV infection, continue to rise [5]. From 1988 to 2004, overall incidence rates of oropharynx cancers increased from 2.8 to 3.6 per 100,000 [11]. Looking specifically at HPV infection, the incidence rates for HPV-positive oropharynx cancers increased from 0.8 to 2.6 per 100,000, while incidence rates for HPV-negative oropharynx cancers decreased from 3.6 to 1 per 100,000 [11]. Despite the increasing incidence, there are decreasing death rates from oropharynx cancers. In 1990, the estimated cancer death rate for oropharynx and oral cavity cancers was 5.61 per 100,000; this decreased to 3.84 in 2005 [12]. This represents an absolute decrease of 1.77 per 100,000 and a percentage decrease of 31.55 %. The underlying reasons for the reduced death rate are ultimately unknown, but may be due to improved screening and diagnosis, improved treatment of these malignancies, and improved prognosis of virally related tumors. Several studies have suggested improved outcomes for patients with HPV-associated cancers [11, 13].

In 2015, it is estimated that patients with oropharynx cancers will present with largely locoregional disease. In the era of largely HPV-associated cancers, the majority of patients present with relatively small primary tumors and more notable regional lymphadenopathy; only a very small minority (less than 10 %) present with distant metastatic disease [12, 13]. This highlights the opportunities for intervention for these patients, for whom locoregional disease is the common presentation and presents a unique opportunity for cure.

27.3.2 Changing Demographics and Risk Factors

Historically, oropharyngeal carcinoma has predominantly affected older men, with 70–80 % of patients being male and an average age at presentation of 50–70 [12]. In recent years, however, the demographics of oropharyngeal cancers have changed. Multiple studies from Western Europe and the United States have suggested less gender disparity and decreased average age of presentation, with more and more patients presenting under 45 years of age [14]. These observations prompted a variety of investigations, and even though the specific trends varied from country to country, similar changes were seen worldwide in both oral cavity [15–17] and oropharynx cancers [18–20].

Historically, one of the strongest associations in carcinogenesis is the link between the development of oropharyngeal carcinomas and the use of tobacco and alcohol products. Primary studies have suggested that smoking increases the risk of head and neck squamous cell carcinomas by 12 times in women and 5 times in men [21]. Furthermore, a synergistic effect has been seen between tobacco and alcohol use [22, 23]. A pooled analysis of 17 European and American case–control studies suggested there was a greater than multiplicative effect

between tobacco and alcohol use, with a population attributable risk for head and neck cancers of 35 % for tobacco and alcohol combined [24].

In addition to alcohol and tobacco consumption, other lifestyle factors and sexual habits have been implicated in the pathogenesis of oropharyngeal carcinomas. The use of marijuana [25–27], dietary intake of fruits and vegetables [28, 29], body mass index [30, 31], and oral hygiene [32, 33] have all been studied with relation to the development of oropharynx carcinoma. Although the data have been somewhat mixed, patients who have a low dietary intake of fruits and vegetables and poor oral hygiene seem to have higher rates of oropharynx carcinomas.

The most interesting and prognosis changing development in the field of head and neck cancers has been the link between oropharyngeal carcinomas and HPV infection, which has now been deemed an "epidemic" [34]. Although the role of HPV has been well established in the cervical cancer literature, the etiologic contribution of viral infection to oropharyngeal carcinomas is a more recent realization [35, 36]. Oropharyngeal cancers tend to be associated with high-risk HPV subtype 16 (87 %) in contrast to cancers of the uterine cervix, which tend to be associated approximately equally with subtypes 16 and 18 [37].

Recent estimates suggest that there are over 290 million carriers of HPV worldwide [38]; HPV-associated cancers are a growing public health issue throughout the world. From a global perspective, the relative HPV association of oropharynx cancers varies widely depending on the geographical area; recent data in North America indicate approximately 56 % of tumors as HPV positive compared to 39 % in Northern and Western Europe, 38 % in Eastern Europe, 17 % in Southern Europe, 45 % in Australia, 52 % in Japan, and 13 % in the rest of the world [7]. In the United States, a study performed as part of the National Health and Nutrition Examination Survey (NHANES) revealed a prevalence of oral HPV infection of 6.9 % in adults aged 14–69 [39]. In one review of 60 individual studies, the average rate of HPV-DNA positivity was 35.6 % for oropharyngeal carcinomas; this is compared to approximately 20 % in other oral cavity and larynx tumors [40]. However, this is changing, with increasing numbers of HPV-positive, and decreasing numbers of HPV-negative, oropharynx cancers [11]. Studies have shown that patients who developed oropharyngeal cancers at ages under 55 were found to have higher risk sexual behaviors and more HPV-positive tumors than those who developed cancers at a more advanced age [37]. Oral HPV infection itself, like anogenital infection, has been found to correlate with sexual behavior; the number of oral sex partners [41–43], number of lifetime sexual partners, young age at first coitus, and a history of genital warts [44] have all been shown to correlate with increased risk of oropharyngeal cancer in individual studies. Initial case–control studies did not demonstrate significant associations between sexual behavior and oropharynx cancers; however, these were likely rendered insignificant by the more traditional patients with oropharyngeal carcinomas, attributable to alcohol and tobacco, and a minority of patients with HPV-related tumors [45, 46]. In a pooled analysis of the International Head and Neck Cancer Epidemiology (INHANCE) consortium, 5462 head and neck cancer cases were matched with 6069 controls; this analysis suggested that having more lifetime sexual partners and more lifetime oral sex partners was associated with an increased risk of oropharynx cancer [43].

In addition to noting an association between HPV infection and the development of oropharynx carcinomas, patients with HPV-related tumors appear to have a better prognosis than those with non-HPV-related tumors. Fakhry and colleagues reported the outcomes of patients with HPV-related oropharynx tumors compared to non-HPV-related tumors as part of an Eastern Cooperative Oncology Group (ECOG) phase II prospective clinical trial (E2399) [47]. In this population, 40 % of patients had genomic DNA of oncogenic HPV in the nuclei of the tumor cells. Patients with HPV-positive tumors had improved response after induction chemotherapy (82 % vs. 55 %, $p=0.01$) and after chemoradiation (84 % vs. 57 %, $p=0.007$) as well as improved overall survival at 2 years (95 % vs. 62 %, $p=0.005$). An analysis of the HPV positivity in tumors of patients treated on RTOG 0129, a phase III randomized trial of chemoradiation with either standard or altered fractionation, demonstrated HPV-16 positivity in 60.6 % of oropharynx tumors [48]. In an analysis of RTOG 0129, patients with HPV-associated tumors had statistically significant improvements in overall survival at 3 years (82 % vs. 57 %; $p<0.001$) [13]. Multiple other analyses of trials for the impact of HPV have also shown statistically significant improvements in survival for those tumors that are HPV positive [49–51]. These studies have been pivotal in establishing the role of HPV positivity in both pathogenesis and prognosis for patients with oropharynx cancer.

The scientific link between oropharyngeal cancers and HPV is now well recognized, and the data suggesting improved responsiveness to both chemotherapy and radiation in HPV-positive tumors are compelling. Indeed, current clinical trials addressing treatment for these malignancies are accruing separately for patients with HPV-positive and HPV-negative tumors. The philosophical approach being developed is to intensify treatment for those patients with HPV-negative tumors, and therefore poorer prognoses, and to evaluate patterns of failure and minimize overall toxicity for those with HPV-positive tumors, and therefore better prognoses. Longer follow-up will reveal whether this is a safe and effective strategy for designing the most appropriate treatment algorithms for these two very different patient, and tumor, populations.

27.4 Pathology and Pathogenesis

The large majority of tumors that arise in the oropharynx are squamous cell carcinomas; less than 10 % of tumors are of a different histology, with minor salivary gland adenocarcinomas, lymphomas, melanomas, sarcomas, and undifferentiated cancers making up this group [52, 53]. In addition, benign conditions, including papillomas, fibromas, hemangiomas, neuromas, and cysts, may occur in the oropharynx and must be considered in the differential diagnosis. Finally, metastases to the oropharynx, although rare, have been described [54, 55]. Given the preponderance of squamous cell carcinomas, the remainder of this chapter concentrates on their diagnosis and management.

27.4.1 Role of Pathological Assessment

Tissue diagnosis and adequate pathologic assessment are crucial to the diagnosis of head and neck squamous carcinomas. Tissue can be obtained through core needle biopsies, excisional, or incisional biopsies. Conventional hematoxylin and eosin staining remains key to the diagnostic evaluation. A variety of features can be described in squamous carcinomas diagnosed through this analysis; however, the relative importance of other features of the tumor has been the subject of significant debate. Perineural invasion [56, 57], basaloid features [58], and keratinization [59] have all been investigated as potentially important prognostic features. More recently, studies suggest that basaloid features and non-keratinizing tumors may reflect HPV status and confer their improved prognosis [60].

In addition to traditional histologic appearance, the tissue from oropharynx squamous cell carcinomas also can be analyzed for characteristic molecular markers. In situ hybridization analysis for high-risk HPV subtypes is increasingly used as part of the pathologic assessment of squamous cell carcinomas of the oropharynx (Fig. 27.3a); this, however, is a technique that requires specific training and expertise. Another common method for HPV detection is the use of polymerase chain reaction (PCR) to identify the DNA of the virus. For HPV, the probes to detect the DNA are most commonly targeted to the L1 region, which is frequently conserved between the viral subtypes [61, 62]. This, however, does not provide the specific HPV subtype, which could be ascertained using HPV-subtype-specific primers. Although this is a cost-effective approach and readily available in kit form, the sensitivity of PCR is significantly decreased when fresh frozen tissue is not used. As well, there is a significant false-positive rate when paraffin-embedded tissues are the samples available [63].

A reliable and relatively inexpensive alternative to direction of HPV itself is the use of immunohistochemical analysis (IHC) for p16 overexpression. Studies begun in HPV-positive cervical cancer specimens demonstrated a correlation between HPV infection and p16 overexpression [64]. Now, viral infection with HPV is correlated with expression of p16 in carcinomas of the head and neck [13]. Studies suggest that p16 overexpression is indicative of better prognosis, similar to HPV positivity [65]; in contrast, p16 is downregulated in tobacco-related cancers. IHC analysis for p16 often demonstrates diffuse positive staining in HPV-positive tumors (Fig. 27.3b); this is a relatively inexpensive and efficient test. Given the importance of HPV association in terms of prognosis and treatment response, the accurate and inexpensive detection of HPV in tumor specimens for oropharynx cancers is of paramount concern; there are a variety of options at present to do this and make it part of standard practice in the pathologic assessment of oropharynx cancers.

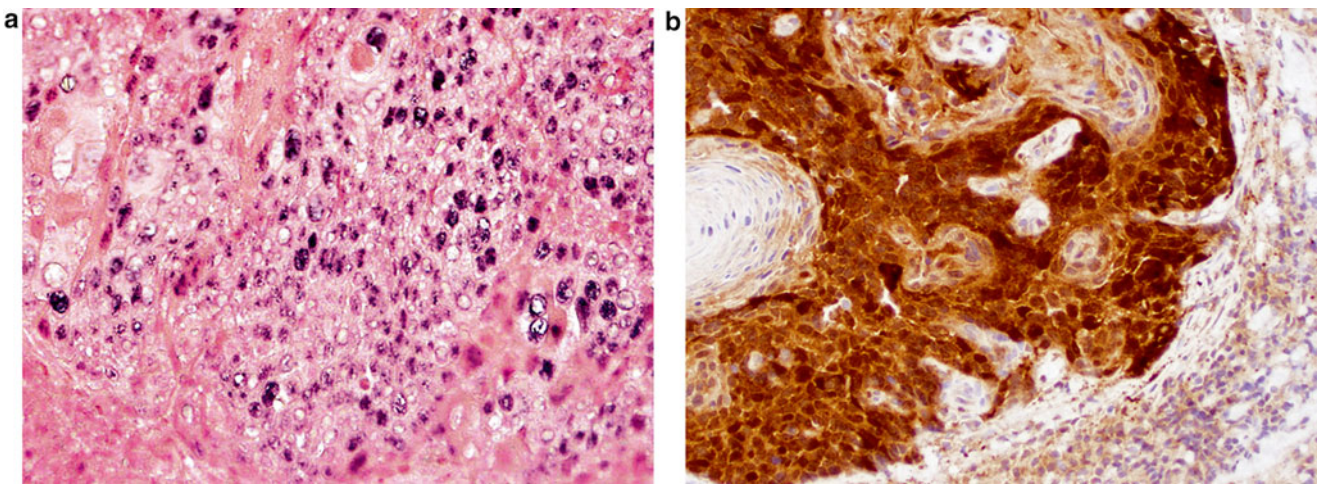

Fig. 27.3 Specialized pathologic assessment of oropharynx tumors. (**a**) HPV in situ hybridization demonstrating nuclear staining in a tonsil squamous cell carcinoma (**b**) p16 immunohistochemical analysis showing diffuse staining of a base of tongue squamous cell carcinoma

27.5 Pathogenesis of Oropharyngeal Carcinoma

Squamous cell carcinomas of the oropharynx are considered the result of multiple events at the molecular level; each of these events may reflect a change due to a genetic predisposition or an exposure to an exogenous environmental agent [66]. Multiple independent events that cause the loss or inactivation of tumor suppressor genes and activation of oncogenes appear crucial to the development of oropharyngeal carcinomas; environmental agents (including viral infection) can cause specific damage or trigger cascades that contribute to these pathways.

Elegant studies of genetic alterations in squamous cell tumor specimens from the head and neck from Califano and colleagues have suggested a model of genetic progression in these lesions (Fig. 27.4). The most common alteration is loss of chromosomal region 9p21, a region that encodes two suppressors p16 and $p14^{ARF}$; this abnormality is present in over 70 % of dysplastic lesions, suggesting that its loss is an early event in the carcinogenic pathway [66–68]. Another early genetic abnormality is loss of a region of chromosome 3p, which encodes two suppressor genes *FHIT* and *RASSFIA* [68–70]. Later genetic events appear to include loss of heterozygosity (LOH) of chromosome region 17p and p53 mutation [71]. In aggregate, these genetic events contribute to genomic instability and the development of aneuploidy; this progression has been shown to be crucial in the progression of normal mucosa to dysplasia and finally to invasive carcinoma.

Exogenous environmental factors appear to contribute to this cascade in a variety of ways. Carcinogen exposure, such as use of tobacco and alcohol, can cause direct genetic insult or act indirectly through mucosal damage. Damage of the mucosa may trigger inflammatory cascades that involve COX-2 and EGFR activation, Cyclin D1 activation, and increased proliferation; this compensatory mechanism to the acute injury increases proliferation and puts the mucosa at increased risk of mutation [72].

Viral infection with high-risk HPV subtypes exerts direct influence on the pathways of carcinogenesis in oropharyngeal carcinomas. Most HPV-related cancers carry the viral DNA integrated into the cellular chromosomes at one or more loci [73, 74]. It is believed that expression of two early genes in the viral genome, E6 and E7, is crucial to viral mediated cancer development. The E6 protein, mediated by a cellular protein called E6-associated protein (E6AP), forms a complex with the tumor suppressor p53, causing degradation of p53 via ubiquitin-mediated proteolysis [75]. The ability to inhibit the tumor suppressor activity of p53 has been shown to reduce the ability of the cell to respond to genotoxic stress [76] and genetic instability [77]. The E7 protein interferes with the activity of the protein product of the retinoblastoma gene, which is a tumor suppressor that is involved in cell cycle control and progression; in this way, the E7 protein can disrupt signals that would normally stop DNA synthesis and cell cycle progression [78–80]. The molecular effects of both E6 and E7 in HPV-associated cells are believed to contribute to the transformation of infected cells to carcinoma.

Viral infection with HPV causes distinct biomolecular features in the resultant tumors, as compared to traditional HPV-negative oropharyngeal cancers. HPV-negative tumors, most commonly associated with alcohol and tobacco, have been shown to overexpress epidermal growth factor (EGFR) and cycle D1, which correlate with poor prognosis [81–83]. The availability of the Cancer Genome Atlas (TCGA) has now allowed further identification of clusters of genetic subgroups based on mutations of multiple genes; initial analyses were performed on 279 specimens, of which only 12 % were of oropharynx origin [84]. In this analysis, HPV-associated tumors were found to be related to mutations in the oncogene PIK3CA, loss of TRAF3, and amplification of the cell cycle gene E2F1, while those that were not associated with HPV demonstrated loss-of-function TP53 mutations, CDKN2a inactivation, and frequent copy number alterations [84]. As the specimen bank grows, genomic alterations will and will likely be a part of future risk stratifications, patient counselling, and treatment algorithms.

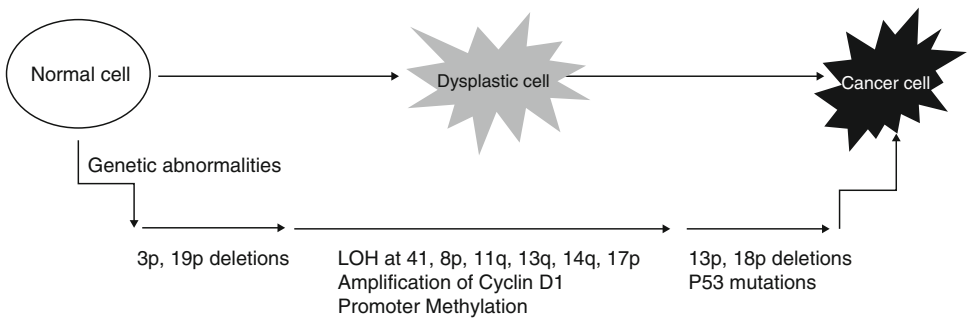

Fig. 27.4 Schematic of genetic alterations contributing to the development of squamous cell carcinoma

27.6 Multidisciplinary Initial Assessment and Staging

27.6.1 Screening for Oropharyngeal Cancer

Almost all patients with oropharynx cancer are diagnosed with nodal metastases. There is significant interest in identifying patients before they reach this stage, namely in improving screening and early detection. Given the viral association of a majority of oropharynx cancer cases in modern practice, there has been interest in creating a similar "pap-like" screening test to improve early detection of HPV-associated oropharynx cancers, similar to that for cervical cancer [85]. In one study, brush biopsies of the oropharynx abnormalities were collected from 92 patients and subsequently tested for HPV using PCR. The presence of HPV was associated with the presence of oropharynx malignancy (odds ratio (OR) = 6); however, a larger case–control study revealed no association between HPV positivity in the brush biopsies and identification of premalignant oropharyngeal lesions [85]. Hence, at the current time, there is no effective screening tool for oropharyngeal cancer.

There are no robust guidelines for screening for oropharyngeal cancers that are based on randomized data. The United States Preventive Services Task Force notes that there is insufficient evidence to recommend routine screening for oral cancer (including oropharyngeal cancer) in the adult population (Recommendation I) [86]. The American Cancer Society [87] and the American Dental Association [88] both recommend regular dental checkups that include a detailed inspection and palpation of the oral cavity and pharynx to identify worrisome lesions and aid in early detection.

27.6.2 The Role of History and Physical Examination

The primary evaluation of a patient with oropharyngeal cancer is a comprehensive history and physical examination. On history, the patient's symptoms depend highly on the location and extent of the tumor. Patients with early-stage oropharyngeal carcinomas may present with few symptoms; the tumors may have been found incidentally on scans for other indications or dental evaluations.

One common presenting symptom of oropharyngeal cancer is a painless neck mass, representing lymph node metastasis; in many cases, only after a full examination is a primary identified. When patients do develop symptoms due to local disease, pain is often the earliest to develop. This may be pain at the site of the primary or referred pain to the middle ear. The latter occurs via the pharyngeal and tonsillar branches of cranial nerve IX, which traverse the petrosal ganglion and then synapse with the tympanic nerve of Jacobson, which innervate the middle ear. As tumors progress, odynophagia, dysphagia, dysarthria, and trismus may develop and cause the patient to seek medical attention.

The physical examination is a crucial part of the evaluation for oropharyngeal cancer patients, and it highly affects treatment decisions and planning. The head and neck examination should evaluate the local extent of the primary tumor and the presence and location of lymph nodes. Inspection of the oropharynx can be performed by direct or indirect laryngoscopy or fiberoptic nasopharyngolaryngoscopy; there should be a complete evaluation of all mucosal surfaces to ensure there are no other lesions and to fully appreciate the extent of the primary tumor. In addition, digital examination is crucial to the estimate of the primary disease size. Often, there can be infiltrative processes that are underappreciated by both inspection of the mucosal surface and segmental imaging. A full evaluation of the adjacent oral cavity should be performed to understand whether the tumor invades these areas. Attempts should be made to estimate the size of the primary lesion, its limits of spread, and associated lymphadenopathy, since all of these contribute to the ultimate staging and treatment recommendations.

Depending on the subsite of the primary tumor, 45–78 % of patients may present with cervical adenopathy at the time of diagnosis [1]; assessment of the lymph nodes is crucial to an accurate understanding of the extent of disease. While level II is the most common lymph node station affected, the other cervical nodal areas, as well as the supraclavicular fossae, should be assessed. Finally, associated symptoms, such as tongue deviation, tongue fixation, trismus, and sensory impairment, should be evaluated; these suggest further extension of the tumor that will influence stage and treatment recommendations. Cranial nerves V, VII, XI, X, and XII are especially at risk for compromise due to invasion by oropharyngeal cancers, and these should be specifically assessed during the physical examination. In the case of an inadequate physical examination, the patient may require an examination under anesthesia (coupled with biopsy) to fully appreciate the extent of disease and establish a diagnosis.

Pretreatment dental evaluation is also crucial to the ultimate management of patients with oropharyngeal carcinoma. Treatment of oropharyngeal cancer with radiation has several short- and long-term effects on dentition and oral health, and an evaluation of the baseline dentition is crucial to effective management. Patients who develop xerostomia are at greater risk for dental caries and demineralization. The decrement in perfusion following radiation therapy leads to greater difficulty healing from dental procedures. A clinical dental evaluation and radiographic studies should be done to assess the status of the teeth. Prior to radiation therapy, any non-restorable teeth should be extracted. In addition, the patient will benefit from lifetime dental fluoride prophylaxis. Long-term

dental care by a dentist familiar with the effects of radiation therapy should be undertaken following treatment [89].

Finally, patients with oropharyngeal cancer should be assessed for the status of their general health, in a comprehensive manner, by the team of treating physicians; in many cases, an evaluation by an internist may be beneficial. Many of these patients have medical comorbidities, such as diabetes or hypertension, and many are at risk for secondary malignancies. In addition, patients are at risk for chemical hypothyroidism after treatment with radiation therapy to the neck; baseline thyroid function should be evaluated prior to treatment and then monitored appropriately in follow-up. A chest radiograph, complete blood count, and serum chemistry evaluation, in addition to a review of their past history, will provide a better understanding of their disease and baseline health status. Finally, lifestyle interventions, such as smoking cessation, are crucial for long-term success.

27.6.3 The Role of Imaging

Advanced imaging techniques are standard in the evaluation and staging of oropharyngeal tumors. The goal of imaging is to establish the extent and size of the primary tumor, evaluate nodal disease, and identify perineural spread and bony destruction. The optimal type of imaging for head and neck cancers depends on the site of disease and goals of the evaluation. Computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and ultrasound (US) are all complementary modalities and can be used to evaluate different aspects of the disease (Fig. 27.5).

Standard imaging evaluation for an oropharynx tumor includes CT or MR imaging of the head and neck, with intravenous contrast (unless medically contraindicated), to evaluate the primary tumor and nodal disease. CT is considered by many to be preferable to MRI for the imaging of oropharynx tumors because it is less affected by breathing and swallowing artifacts [90], although some centers prefer MRI due to their expertise with this modality. The imaging of oropharyngeal tumors on CT or MRI is quite variable, and enhancement may or may not reflect the full extent of disease. It is important to correlate the mass and enhancement observed on imaging with the clinical examination in order to fully appreciate the extent of disease. Bone invasion and destruction is well delineated on CT scan, and hence CT may indicate more extensive disease than previously appreciated. Despite the benefits of CT, it is limited by artifacts caused by metallic dental implants and fillings; angled cuts may be helpful in providing more useful images through important areas. If these maneuvers are not sufficient, MRI may be used, since it is not affected by metallic artifact.

Imaging of nodal disease can be accomplished with CT, MRI, PET, or US. Clinical evaluation and cross-sectional imaging are estimated to be negative in 15–25 % of patients with true nodal metastases from head and neck cancers [91]. However, patients with head and neck cancers often can have reactive adenopathy that does not reflect metastatic disease; hence, false positives and false negatives are clinically relevant.

With modern techniques, CT and MRI are considered equivalent in the detection of nodal disease from head and neck cancers [92]; CT is typically the primary modality used for staging of oropharynx tumors as it can effectively evaluate both the primary and nodal disease. The size criteria for suspicious nodes has been the subject of significant discussion; currently, it is accepted that level I and II nodes greater than 15 mm in longest diameter and other nodal stations greater than 10 mm should be considered suspicious [90]. In addition, the characteristics of the nodes may shed light on their metastatic burden. Regardless of size, lymph nodes with central hypodensity and peripheral enhancement as well as round nodes are concerning [90]. Finally, extranodal extension may be identified on CT as irregular nodal margins, the loss of the fat cleavage plane around the node, thickening of fascia, or frank invasion of adjacent structures [90]. Ultrasound is an

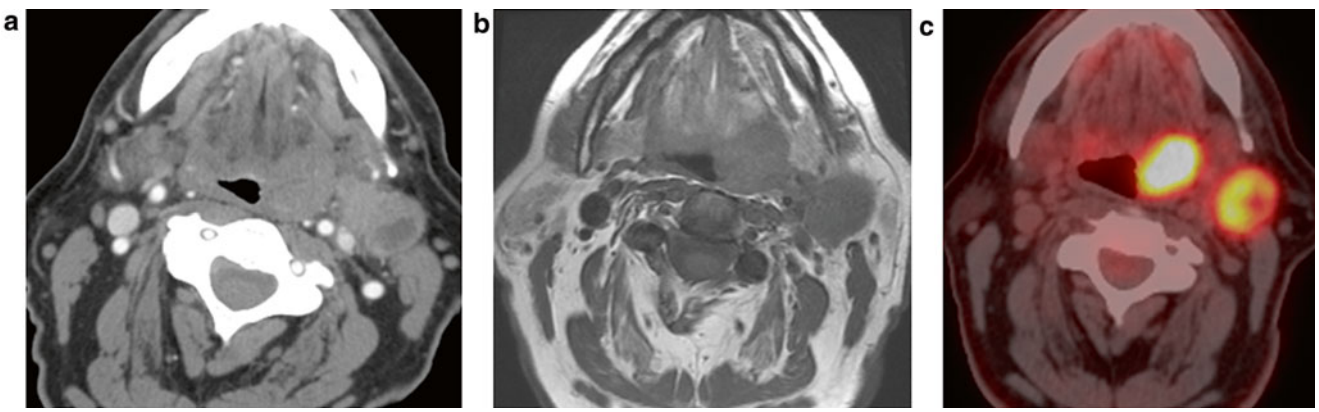

Fig. 27.5 Imaging evaluation of a T2 N2b M0 left base of tongue squamous cell carcinoma by various modalities: (**a**) CT with iodinated contrast (**b**) MRI (**c**) PET/CT

effective modality to identify and characterize lymph nodes if CT or MRI is contraindicated, and it has been especially useful when coupled with image-guided biopsy for suspicious lymph nodes for which involvement would affect a treatment plan [93]. PET is very sensitive for the identification of lymph nodes harboring metastatic disease that are at least 8 mm in size. A landmark study established a sensitivity of 90 % and specificity of 94 % for PET in the determination of histologically proven lymph node metastases, where CT and MRI had values of approximately 80 % and US of 72 % [94]. The integration of PET with CT has given even more utility to this modality, and it is now considered one of the best ways to establish the nodal status at the time of initial diagnosis.

27.6.4 Staging

The current system for staging oropharyngeal carcinomas is the American Joint Committee on Cancer (AJCC) system, which concentrates on the size and distribution of the primary, nodal disease, and metastatic disease (Table 27.1). All diagnostic modalities can be used to assess the stage, including CT, MRI, and PET imaging. In addition, clinical evaluation is crucial and may strongly affect the underlying stage. For instance, although imaging may not suggest involvement, limitations in tongue movement or tongue fixation can be assumed to indicate deep tongue muscle invasion, rendering a tumor T4. The primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010).

There is some controversy in the use of the current AJCC system, especially given the differing outcomes for patients with HPV-positive cancers. The current staging system was largely based on outcomes of patients with HPV-negative tumors; as a result, the current stage assignments have little prognostic value in modern clinical practice [95, 96]. In the HPV-era, the majority of patients present with Stage III–IVb disease, and yet they have excellent outcomes. There are multiple recommendations regarding revisions to the current staging system, including the integration of smoking history, age, and HPV status [13, 97]. It remains to be seen if the next AJCC staging system for oropharynx cancer will integrate additional factors to better predict outcomes.

Table 27.1 Staging of oropharyngeal carcinomas

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
T1	Tumor 2 cm or less in greatest dimension		
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension		
T3	Tumor more than 4 cm in greatest dimension or extension to the lingual surface of the epiglottis		
T4a	Moderately advanced local disease. Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible.		
T4b	Very advanced local disease. Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases the carotid artery.		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastases		
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension		
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension		
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension		
N2c	Metastasis in a lymph node more than 6 cm in greatest dimension		
N3	Metastasis in a lymph node more than 6 cm in greatest dimension		
Distant metastasis (M)			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping: oropharyngeal carcinoma			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage Iva	T4a	N0	M0
	T4a	N1	M0
	T1-4a	N2	M0
Stage IVb	T4b	Any	M0
	Any	N3	M0
Stage IVc	Any	Any	M1

27.7 Multidisciplinary Treatment for Locoregional Disease: Overview and by Subsite

The optimal management and outcomes of carcinomas of the oropharynx are highly dependent on the subsite of origin and extent of disease. Hence, recommendations should always account for the intricate details of the individual tumor.

27.7.1 Overview

27.7.1.1 Role of Surgery

Open surgery

Traditional open surgical resection historically was the mainstay of treatment for all head and neck cancers. However, this has largely been supplanted by transoral resection or

definitive radiation therapy. Based on past series, open surgery can be curative therapy in selected cases of oropharyngeal carcinomas in specific subsites. For early-stage lesions (T1, N0-1 disease and limited T2, N0-1 disease) of the soft palate, tonsil, base of tongue, or oropharyngeal wall, surgical resection of well-delineated lesions can be curative with relatively minimal toxicity and functional derangement. This is a reasonable approach in selected cases in which surgery can stand alone as local therapy, and the patients will not require both surgery and postoperative radiation therapy due to high-risk factors on pathologic assessment. However, since oropharyngeal tumors tend to present at more advanced stages, and there is a significant risk for lateral and retropharyngeal nodal metastases that are not readily amenable to dissection, the majority of these patients will require postoperative radiation therapy. For intermediate-stage tumors (more substantial T2 lesions, T3 lesions, or any primary tumor with N2–3 nodal disease), surgical resection is not favored due to the potential magnitude of functional debilitation resulting from a curative resection and necessary reconstruction, as well as the requirement for postoperative radiation therapy, as compared to equivalent local control and overall survival with a nonsurgical approach [98, 99]. Finally, for advanced tumors (infiltrative T3 and T4 lesions), composite surgical resection with postoperative radiation therapy was traditionally standard therapy. However, the cosmetic and functional consequences of this treatment are significant. Newer studies have investigated the use of chemotherapy and radiation as curative treatment as part of an organ-preservation approach; at this time, for patients with residual function of the oropharynx, surgical resection may not be the most favored treatment approach since equivalent local control and overall survival can be achieved with a nonsurgical approach. For these reasons, oropharynx cancer has become a primarily nonsurgical disease.

Patients with oropharyngeal cancer often present with nodal metastases, and management of the neck is often a subject of debate. The decision is based on the extent of nodal disease, primary treatment, and philosophy of the treating physician [100]. There are several approaches to treating the neck. First, the neck may be dissected as part of a definitive surgery for the primary disease; radiation therapy may be added adjuvantly, if indicated, based on pathologic risk factors. Second, the neck may be treated definitively with radiation therapy and standard neck dissection. Finally, the neck may be treated definitively with radiation therapy concurrent with primary tumor treatment with a neck dissection only in the case of persistent nodal disease. The management of the neck is somewhat controversial and dependent highly on the treatment philosophy of the institution; all have been shown to be effective strategies for management.

Transoral Robotic Surgery

While surgical resection had largely been supplanted by radiation therapy, the emergence of a minimally invasive surgical approach using TORS has reopened the discussion regarding surgery for patients with oropharynx cancers. The surgical robotic system consists of three carts: (1) a patient-side cart, from which the surgical instruments are deployed, (2) a vision cart, in which the surgical anatomy is recreated, and (3) a remote console cart, at which the surgeon sits and operates the controllers. TORS for oropharynx cancer was pioneered at the University of Pennsylvania, where en bloc resection of oropharynx tumors was first achieved in cadaveric and canine models [101]. Further study established its utility in oncologic surgeries for oropharynx cancer primaries. The FDA approved the use of the commercially available surgical robot, the daVinci Surgical System (Intuitive Surgical Inc., Sunnyvale, CA) for head and neck cancers in December 2009 [102].

In the initial feasibility trial, 45 patients were treated with TORS; 73 % had early-stage tumors, 67 % had ipsilateral neck involvement, and 18 % bilateral neck involvement [103]. En bloc resection using TORS with negative margins and ipsilateral neck dissection was performed in 69 % of cases. All patients had R0 resections, although 3 patients had piecemeal resection. In total, 17.8 % of patients received adjuvant radiation and 56 % received adjuvant chemoradiation. With an average follow-up of 1 year, the locoregional recurrence rate was 10 %. Since that time, multiple studies have been published documenting the use of TORS for oropharynx cancer with locoregional control rates of 90–100 % (Table 27.2). A recent systematic review identified 12 studies of TORS for early oropharynx cancer, comprising a total of 772 patients [104]. For patients treated with TORS, 26 % required adjuvant radiation therapy and 41 % required adjuvant chemoradiation. Two-year overall survival rates after TORS were estimated to be 82–94 %, consistent with those from the trials involving IMRT (84–96 %).

Given data suggesting equivalent outcomes, the relative toxicity of TORS (with adjuvant therapy as needed) as compared to organ-preservation strategies is of great interest. Most of the studies of TORS have evaluated toxicity, including swallowing outcomes and gastrostomy dependence. In a recent systematic review, Hutcheson and colleagues revealed 12 papers comprising 441 patients treated with TORS for oropharynx cancer [105]. Chronic gastrostomy dependence ranged from 0 to 7 %, regardless of stage. Further study is ongoing through cooperative group and single institution trials to identify the best candidates for TORS and identify the appropriate indications for adjuvant treatment.

Table 27.2 Outcomes of patients treated for oropharynx cancers with TORS: selected series

Author	Refs.	Institution	Patients (*n*)	Median FU (mo)	Local/regional control (%)	Additional Treatment	Comments
Moore	[103]	Mayo Clinic	45	12	90	18 % XRT, 56 % ChemoXRT	73 % T1/2, 76 % N0-2b
Weinstein	[211]	University of Pennsylvania	31	24	93	40 % XRT, 40 % ChemoXRT	77 % T1/2, 97 % N0-N2b
Weinstein	[136]	University of Pennsylvania	47	26	96	28 % XRT, 57 % ChemoXRT	77 % T1/2, 96 % N0-2b
Cohen	[212]	University of Pennsylvania	50	23	Not stated	24 % XRT, 54 % ChemoXRT	78 % T1/2, 74 % N0-2b
Sinclair	[213]	University of Alabama	42	17	100	45 % XRT, 30 % ChemoXRT	100 % T1/2, 100 % N0-2
Moore	[214]	Mayo Clinic	66	36	97	21 % XRT, 62 % ChemoXRT	78 % T1/2, 75 % N0-2b
Weinstein	[153]	University of Pennsylvania	30	32	97	No adjuvant therapy	83 % T1/2, 100 % N0-2
More	[215]	Kansas University	20	14	Not stated	40 % XRT, 60 % ChemoXRT	70 % T1/2, 100 % N0-2

27.7.1.2 Role of Radiation Therapy

As a single modality or with concurrent chemotherapy, radiation therapy has emerged as the standard of care for definitive treatment of oropharyngeal carcinomas [106]. The choice of technique, dose, and fractionation has been extensively studied.

Conventional Treatment

Historically, oropharynx cancers were treated with conventional radiation therapy using two-dimensional simulation to delineate standard treatment fields based on bony landmarks. Patients were typically positioned supine, with the neck extended on a fixed headrest, and immobilized with a thermoplastic mask device. The shoulders were displaced in the caudal direction, to lengthen the neck, using a pull-strap device. In cases where separation was needed in the oropharynx or to more accurately target the tumor, a bite block, intra-oral stent, or traditional cork and tongue blade was used to open the mouth in a reproducible way. After optimal positioning, orthogonal films were obtained for simulation and field delineation. Typically, the field arrangement involved a mono-isocentric technique in which two opposed lateral fields treating the upper neck were matched with a lower anterior neck AP field (the "3-field technique"), with conedown and boosts delivered to respect normal tissue tolerance (Fig. 27.6). Typically, low-energy megavoltage (4 MV or 6 MV photons) or Cobalt-60 irradiation was used to ensure adequate coverage.

For conventional treatment, targeting was based on understanding of the location of the primary tumor and neck disease with regard to bony landmarks. Care was taken to include all at-risk lymph node basins, based on the extent of disease, including the Levels II–IV lymph nodes, retropharyngeal nodes, Level IA nodes if the floor of mouth was involved, Level IB nodes if the upper jugular nodes were involved, and Level V nodes if the ipsilateral jugular nodes were involved. As mentioned above, tolerance of normal tissues, most notably the spinal cord, required field adjustments; typically, conedown fields that were off-cord were used after a dose of approximately 40–42 Gy, and posterior neck electron fields were used to treat tissues overlying the spinal cord at higher risk.

Several studies have carefully investigated the role of dose escalation and altered fractionation in the conventional treatment of oropharynx cancers. Withers and colleagues analyzed the outcomes of patients treated with different fractionation schema from a variety of centers; this study suggested that improved local control was related to total radiation dose and treatment time [107]. The EORTC investigated the clinical benefit of altered fractionation in trial EORTC 22791, which compared hyperfractionation (80.5 Gy total dose using 1.15 Gy/fraction twice daily radiation) to conventional radiation (70 Gy total dose using 1.8–2.0 Gy/fraction once daily radiation) [108]. In this study, patients treated with hyperfractionation had a significant improvement in locoregional control over conventional fractionation (59 vs. 40 %, $p=0.02$) with a trend toward improved overall survival. Based on similar findings, the RTOG began the 9003 trial, which investigated 4 different altered fractionation schemes: (1) conventional fractionation of 70 Gy total dose with 2 Gy/fraction delivered once daily, (2) split-course accelerated fractionation of 67.2 Gy total dose with 1.6 Gy/fraction delivered twice daily with a 2-week break after 38.4 Gy, (3) concomitant boost fractionation of 72 Gy total dose delivered with a once-daily 1.8 Gy/fraction treatment in the morning and a 1.5 Gy/fraction second daily fraction in

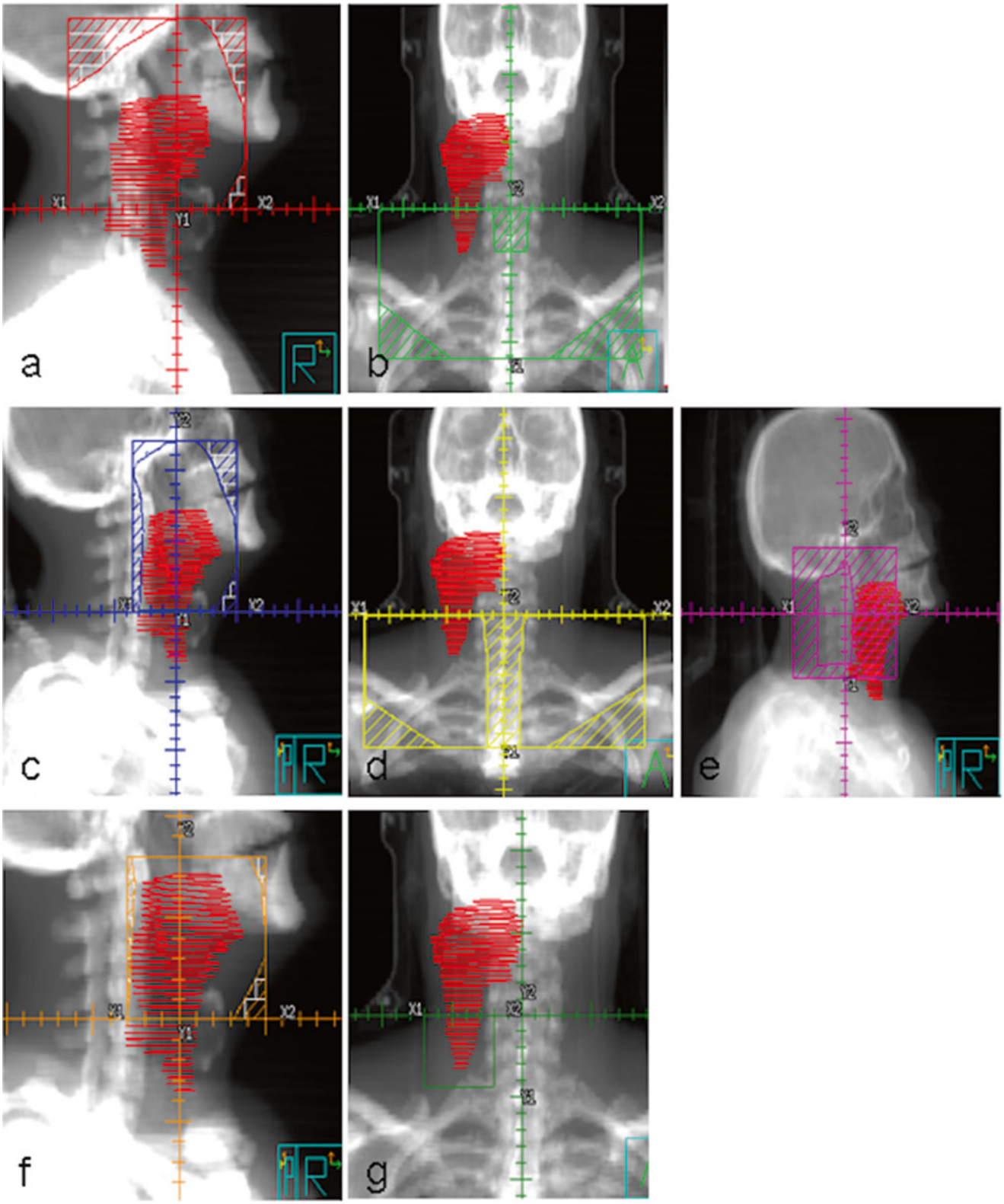

Fig. 27.6 Conventional treatment fields for a T2 N3 M0 right tonsil cancer. Initial fields are (**a**) opposed laterals and (**b**) AP:PA low neck fields to a total of 41.4 Gy. Secondary fields are (**c**) off-cord fields, (**d**) low neck fields with a midline block, and (**e**) posterior cord strip electron fields are taken to an additional 12.6 Gy (total of 54 Gy). Finally, concomitant boost fields are given as a second daily fraction during the final weeks of therapy, consisting of conedown fields to the (**f**) primary and (**g**) nodal disease for an additional 18 Gy

the afternoon during the last 12 days of treatment, and (4) hyperfractionation of 81.6 Gy total dose delivered with a twice-daily 1.2 Gy/fraction treatment [109]. Overall, 1073 patients were enrolled and 60 % had oropharynx cancers. This study suggested that patients treated with pure hyperfractionation and concomitant boost techniques had significantly better locoregional control and a trend toward improved disease-free survival compared to standard or split-course radiation. There was no difference in overall survival. In another investigation of altered fractionation, the Danish Head and Neck Cancer Study Group (DAHANCA) performed a randomized prospective trial (DAHANCA 6) comparing use of 5 (standard) vs. 6 (accelerated) fractions per week in treatment of head and neck squamous cell carcinomas to a total dose of 66–68 Gy at 2 Gy/fraction; 28 % of patients had pharyngeal tumors (76). For all patients, the overall 5-year primary tumor control rates showed a benefit to 6 fractions/week (76 % vs. 54 %; $p=0.0005$) as well as disease-specific survival (73 % vs. 66 %; $p=0.01$). There was no demonstrable benefit to 6 fractions/week in terms of neck control or overall survival. These served as the seminal trials supporting altered fractionation for improved local control of intermediate primary oropharynx cancers, while recognizing that there was little benefit for nodal or advanced primary control.

IMRT

At this time, advanced techniques with 3D planning, using CT- or MRI-based simulations, with treatment using intensity-modulated radiation therapy (IMRT) are largely considered standard treatment for oropharyngeal cancers. IMRT was developed with a goal of providing curative dose to the tumor targets while sparing normal tissues; hence, the intent was to improve toxicity.

Simulations for IMRT treatments are performed similarly to conventional treatments; patients are supine with the neck extended, shoulders displaced in the caudal direction, and immobilized with a custom-made thermoplastic mask (Fig. 27.7a). Immobilization is even more important with the use of IMRT due to the precise delineation of treatment volumes. In general, multiple fields are used (7–9 beams of 6 MV photons) to treat the primary tumor and, at least, the upper neck. The lower neck can be treated with IMRT (as a single field with the primary and upper neck) or matched to an anterior low neck field, similar to the conventional techniques. With improvements in technology, volumetric modulated arc therapy (VMAT) has also evolved to provide conformal therapy while maximizing treatment speed.

Delineation of treatment volumes and treatment planning is of paramount importance in the definitive treatment of oropharyngeal carcinoma with radiation therapy in general and especially IMRT. Understanding the full extent of disease requires integration of clinical examination and imaging findings, and the typical patterns of local and regional spread should be factored into delineated treatment volumes. For IMRT, the gross tumor volume (GTV) should encompass the primary and nodal volumes of gross tumor. If the patient received induction chemotherapy or some type of resection/biopsy, attempts should be made to recapitulate the tumor volume at the start of treatment and cover this area. The clinical target volume (CTV) for treatment planning is typically divided into three regions (Fig. 27.8). CTV1 comprises the volume of the GTV with a margin of 7–10 mm, respecting anatomic boundaries; this volume is typically taken to a dose of 66 Gy in 30 fractions (2.2 Gy/fraction) for T1–2 tumors treated with radiation alone or 69.96 Gy in 33 fractions (2.2 Gy/fraction) for T3–4 tumors if radiation is used with concurrent chemotherapy. CTV2 comprises adjacent high-risk nodal areas including a margin around CTV1 and the nodal spaces near the primary tumor; this volume is typically taken to a dose of 60 Gy in 30 fractions (2 Gy/fraction) if radiation is used alone or 63 Gy in 33 fractions (1.91 Gy/fraction) if radiation is used with concurrent chemotherapy. Finally, CTV3 comprises low-risk nodal disease, such as contralateral cervical nodal basins, and is typically taken to a dose of 54 Gy in 30 fractions (1.8 Gy/fraction) if radiation is used alone and 57 Gy in 33 fractions (1.73 Gy/fraction) if radiation is used with chemotherapy. We recommend that IMRT treatment to the primary oropharyngeal tumor and upper neck be matched with a conventional low neck field to treat the supraclavicular fossa bilaterally to a dose of 40 Gy in 20 fractions with an AP field with a larynx block followed by an additional 10 Gy in 5 fractions with a full midline block. Dosimetric analysis has shown that this technique promotes better larynx-sparing than full neck IMRT plans [110]. For patients with low nodal disease, additional boosts can be added with appositional electron fields or photon fields to augment the dose in the low neck, while respecting the accepted tolerance of the brachial plexus. Bulky lower neck nodal disease may require a planned neck dissection if the required radiation dose would exceed brachial plexus tolerance. If the use of matched fields is not supported due to technical complications, full-field IMRT or VMAT may be used. In this case, the uninvolved larynx should be contoured as an avoidance structure. Overall, this treatment algorithm is generalizable to the majority of oropharyngeal cancers, even in the setting of prior chemotherapy or surgical resection.

The outcomes and toxicity of patients with oropharyngeal cancers treated with IMRT have now been published in multiple reports. One of the first multi-institutional studies was RTOG 0022, a phase II trial to assess the use of IMRT for treatment of early-stage oropharynx cancers; it was designed to assess the feasibility of treatment delivery

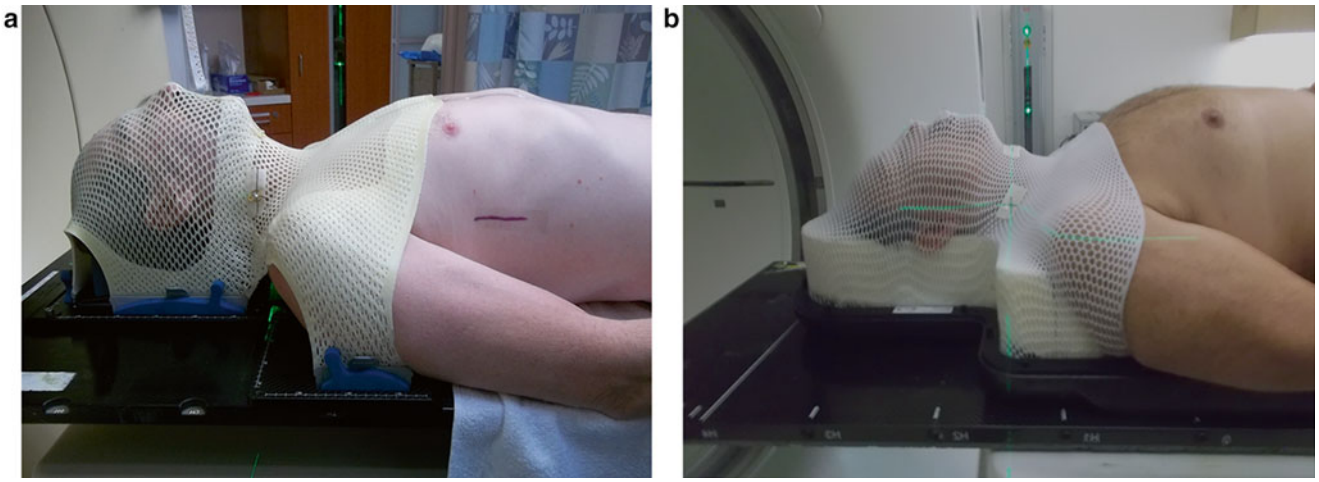

Fig. 27.7 Patient positioning for radiation therapy treatment for oropharyngeal cancer using (**a**) IMRT and (**b**) IMPT. The patient is supine with shoulders displaced in the caudal direction. For IMRT (**a**), the patient's head and neck are immobilized with a custom-made thermoplastic mask with standard headrests and carbon-fiber wedges for positioning. For IMPT (**b**), the patient's head and neck are also immobilized with a custom-made thermoplastic mask but with a custom posterior neck immobilization mold to prevent air gaps

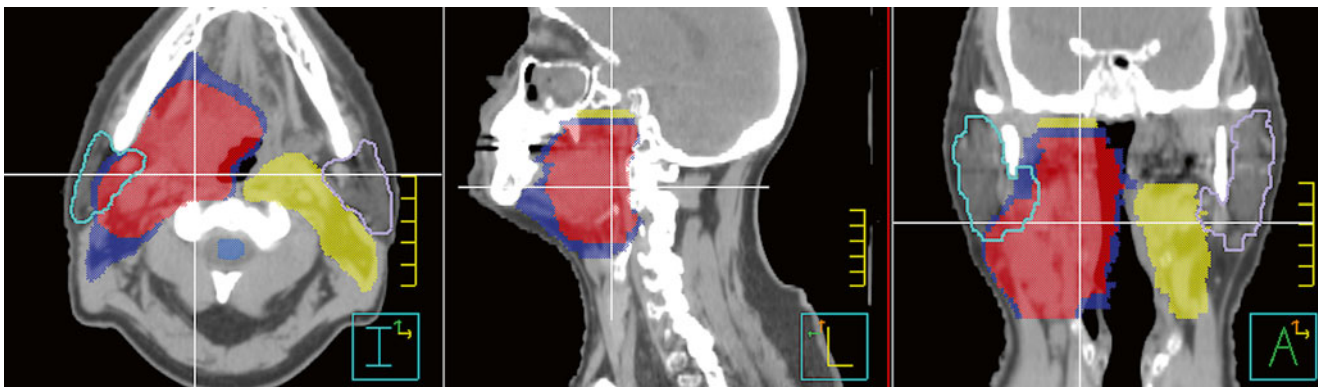

Fig. 27.8 Basic treatment volumes for IMRT for a T2 N2b M0 squamous cell carcinoma of the right tonsil, showing CTV1 (*red*), CTV2 (*blue*), and CTV3 (*yellow*)

(target coverage and parotid sparing), determine the patterns of failure, and assess early and late toxicities [111]. A total of 69 patients with clinical stage T1-2 N0-1 oropharynx cancers were treated with IMRT alone (no chemotherapy) to a dose of 66 Gy in 30 fractions. With a median follow-up of 2.8 years for living patients, the 2-year rate of locoregional failure was 9 %. The rates of grade 2 or more toxicity were 12 % skin, 24 % mucosa, 67 % salivary, 19 % esophagus, and 6 % osteoradionecrosis. The authors concluded that moderately accelerated hypofractionated IMRT was feasible with high rates of locoregional control and lesser toxicity when applied to small high-dose volumes, such as T1–2 primary tumors (compared to historical RTOG controls). Other single institution studies also indicate excellent rates of locoregional control (Table 27.3).

While the findings suggestive of excellent locoregional control are comforting, the goal of IMRT was to reduce toxicity and improve quality of life. This was tested in the Parotid-Sparing Intensity-Modulated versus Conventional Radiotherapy in Head and Neck Cancer (PARSPORT) randomized phase III trial [112]. In this study, 94 patients (85 % with oropharynx cancer) were enrolled from 2003 to 2007 and randomized between conventional radiation and IMRT, with a goal of parotid sparing. With a median follow-up of 44 months, patients treated with IMRT had statistically significant improvements in quality of life and reductions in xerostomia endpoints [112]. The randomized data supporting improved quality of life supported the adoption of IMRT as standard of care for head and neck cancers.

Proton Therapy

While IMRT is now considered standard of care for oropharynx cancers, there is emerging interest in proton therapy, especially given the proximity of critical structures in the

Table 27.3 Outcomes of patients treated for oropharynx cancers with definitive IMRT: selected series

Author	Refs.	Institution	Patients (*n*)	Median FU (mo)	Local/Regional control (%)	Additional treatment	Comments
Eisbruch	[111]	RTOG 0022	69	33	91	No chemotherapy	100 % T1/2, 100 % N0-2
Garden	[216]	MD Anderson	51	45	94	9.8 % chemotherapy	73 % T1/2, 78 % N0-2
						24 % posttreatment neck dissection	
Huang	[217]	UCSF	71	33	90	100 % chemotherapy	68 % T1/2, 96 % N0-2
						20 % posttreatment neck dissection	
Daly	[218]	Memorial Sloan-Kettering	107	29	94	87 % chemotherapy	53 % T1/2, 89 % N0-2
						9 % posttreatment neck dissection	
Lok	[219]	Memorial Sloan-Kettering	340	34	94	95 % chemotherapy	66 % T1/2, 98 % N0-2
						13 % posttreatment neck dissection	

head and neck region and opportunity to minimize normal tissue toxicity. Even with IMRT, there is toxicity in the beam path, especially notable to nontarget critical structures, such as the brainstem and uninvolved oral cavity [113, 114]. With the significant expansion in the availability of proton therapy in the United States, there is growing interest in integrating its physical properties for the treatment of oropharynx cancers.

Proton therapy can be delivered using passive scattering beams or, similar to IMRT, using spot scanning to provide differential doses by using intensity-modulated proton therapy (IMPT). Simulations are done similar to those using photon beams; however, care must be taken regarding homogeneity in the beam path, and as a result head rests and immobilizations systems must be cognizant of the need for homogeneity and to minimize air gaps (Fig. 27.7b). Initial case series have been reported in abstract form, documenting feasibility of this approach and good toxicity profiles [115, 116]. There is a particular improvement in the doses delivered to nontarget structures, such as the anterior oral cavity and normal tissue (Fig. 27.9). A randomized trial comparing IMRT and IMPT for oropharynx cancers is ongoing, with a primary endpoint of grade 3 or greater late toxicity in 2 years following radiation therapy. Further study will be needed to establish the potential benefits of proton therapy for the treatment of oropharynx cancers.

27.7.1.3 Role of Chemotherapy

The role of chemotherapy in the management of head and neck cancers has been the subject of significant debate. The Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) database has collected data from 87 randomized trials comprising more than 16,000 patients treated from 1965 to 2000, in an attempt to enumerate the added benefit of chemotherapy in the treatment of these patients [117]. The individual patient data was analyzed and patients treated with locoregional treatment alone were compared with those treated with locoregional treatment and chemotherapy (induction, concurrent, or adjuvant). Oropharynx carcinoma was the most common primary site of disease, occurring in 37 % of patients. In the latest update of the MACH-NC, the benefit of chemotherapy, specifically concurrent chemotherapy, was sizable. The hazard ratio of death was 0.88 ($p<0.0001$) with an absolute benefit of chemotherapy of 4.5 % at 5 years and a significant interaction between the timing of chemotherapy and outcome. Both head-to-head and indirect comparisons supported the finding that concurrent chemotherapy was superior to either induction or adjuvant regimens. For 50 individual trials that involved concurrent chemotherapy, the hazard ratio of death was 0.81 ($p<0.0001$) and the absolute benefit was 6.5 % at 5 years [117]. Patients treated with concurrent cisplatin, alone or in combination with other agents, had the most benefit from chemotherapy. In addition, the benefit of concomitant chemotherapy was similar regardless of the fractionation schema of the radiation therapy.

The French Head and Neck Oncology and Radiotherapy Group (GORTEC) have also investigated the use of chemotherapy in patients with oropharyngeal cancer [118]. In this trial, 222 patients with Stage III or IV oropharynx cancers were randomized to radiation alone (70 Gy in 7 weeks) or radiation with 3 cycles of concurrent carboplatin and 5-fluorouracil. There was a statistically significant

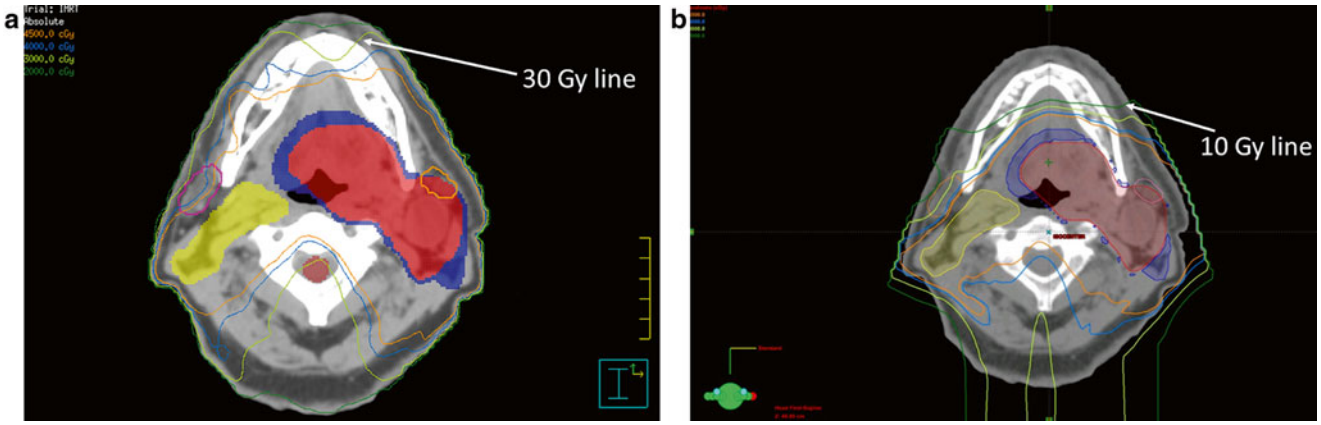

Fig. 27.9 Comparison of plans using (**a**) IMRT and (**b**) IMPT for a T2 N2b M0 left base of tongue HPV-positive squamous carcinoma. The 30 Gy line in the IMRT plan and the 10 Gy line in the IMPT plan are highlighted

improvement in locoregional control in the group that received concurrent treatment (48 % vs. 25 %; $p=0.002$), as well as an improvement in overall survival at 5 years (22 % vs. 16 %; $p=0.05$) [118]. Although it did not reach statistical significance, this improvement also resulted in increased rates of grade 3 and 4 complications at 5 years (56 % vs. 30 %; $p=0.12$). This study strongly supports the use of concurrent chemotherapy in patients with Stage III and IV oropharyngeal cancer. In fact, these data prompted an editorial in the *Journal of the National Cancer Institute* in 1999 with the historic call for combined chemoradiation to become an accepted standard of care for locally advanced oropharyngeal cancers; this data has supported a paradigm shift in the management of these patients, who were often treated surgically previously [106].

Concurrent chemoradiation has largely been accepted as standard of care for locally advanced primary tumors of the oropharynx [119, 120], but the role of induction chemotherapy has historically been controversial. Several individual trials have exhibited promising results with the use of induction chemotherapy, especially those regimens containing cisplatin [121–123]; other trials have shown promising results with the use of combined taxane induction therapy [124]. The EORTC has investigated the role of induction chemotherapy as part of the EORTC 24971/TAX323 trial comparing induction TPF (docetaxel, cisplatin, and 5-fluorouracil) with PF alone (cisplatin and 5-fluorouracil) followed by definitive radiation therapy [125]; approximately 46 % of patients on each treatment arm had oropharyngeal cancer. With a median follow-up of 32.5 months, treatment with TPF resulted in a statistically significant improvement in response to chemotherapy (68 % vs. 54 %, $p=0.006$), progression-free survival (11.0 vs. 8.2 months, $p=0.007$), and overall survival (18.8 vs. 14.5 months, $p=0.02$). In addition, the TAX 324 study compared the same induction regimens (TPF vs. PF) followed by definitive chemoradiation therapy [126]. In this trial of 501 patients, approximately 52 % were diagnosed with oropharynx cancers. With a median follow-up of 42 months, treatment with TPF resulted in improved overall survival at 3 years (62 % vs. 48 %; $p=0.006$), progression-free survival (49 % vs. 37 %, $p=0.004$), and locoregional control (38 % vs. 30 %; $p=0.04$). These studies have largely supported the use of TPF as induction therapy of choice when it is to be given prior to definitive radiation or chemoradiation therapy; however, they have not addressed whether induction therapy is beneficial as an addition to radiation or chemoradiation alone.

More recently, the benefit of induction chemotherapy followed by chemoradiation versus chemoradiation alone was addressed in two trials. The PARADIGM trial was a randomized phase III study comparing induction chemotherapy with TPF followed by chemoradiation (with either once-daily radiation and weekly carboplatin or accelerated boost radiation with weekly docetaxel, based on the response to induction) with accelerated boost chemoradiation with cisplatin [127]. The primary endpoint of the trial was overall survival. The study was halted early due to slow accrual; however, 145 patients (55 % with oropharynx cancers) were accrued in total. With a median follow-up of 49 months, there was no difference in overall survival or progression-free survival between those patients treated with induction followed by chemoradiation and those treated with chemoradiation alone [127]. The DeCIDE trial was a randomized phase III study comparing induction chemotherapy with TPF followed by chemoradiation (with hyperfractionated twice-daily radiation with docetaxel, 5-FU, and hydroxyurea) versus chemoradiation alone (same regimen) [128]. The primary endpoint was overall survival. The study was initially designed to accrue 400 patients, but it was revised with a goal of 280 patients. The trial was completed with the revised accrual target, with 280 patients enrolled (55 % with oropharynx

cancers). With a minimum follow-up of 24 months, there was no statistically significant difference in overall survival or recurrence-free survival [128]. Despite negative results in both trials, the issue of induction chemotherapy remains controversial. Critics of these trials suggest that they were not powered sufficiently to demonstrate the benefit of induction, and ended early; however, in many circles, these trials have been used to largely justify the abandonment of induction chemotherapy in favor of definitive chemoradiation.

27.7.1.4 Role of Molecularly Targeted Agents

The explosion of genomic and proteomic analyses in head and neck cancers has provided an exciting opportunity for the development and integration of molecularly targeted agents in the treatment of oropharyngeal cancers.

Cetuximab, an anti-EGFR receptor antibody, is the most well-studied and successful molecularly targeted agent to be integrated into the treatment of head and neck cancers. In the initial report of a phase III study, Bonner and coworkers investigated the outcomes of patients treated with radiation alone compared to those treated with radiation and concurrent cetuximab [129]. A total of 434 patients were enrolled, and 60 % of these patients had oropharynx cancers. For all patients, the addition of concurrent cetuximab provided a statistically significant improvement in 3-year overall survival (55 % vs. 45 %; $p=0.05$) with a hazard ratio for locoregional progression or death of 0.68 (95 % confidence interval, 0.52–0.89, $p=0.005$). The patients in the experimental arm suffered no increase in high-grade mucositis or dysphagia requiring feeding tube placement, which is common with concurrent chemotherapy, as compared to those patients treated with radiation alone. However, patients treated with concurrent cetuximab did have a higher incidence of drug-related maculopapular skin reaction, which largely resolved when the drug was completed and a 2–3 % incidence of high-grade infusion reactions. In an update of this trial, published in 2010, the authors demonstrated a continued survival benefit to concurrent cetuximab at 5 years (45.6 % vs. 36.4 %; $p=0.018$) [130].

Based on these findings, there was interest in combining the proven benefit of cetuximab over radiation therapy alone and chemotherapy over radiation therapy alone. In the randomized phase III trial RTOG 0522, patients were randomized between radiation with cisplatin with or without cetuximab [131]. The primary endpoint was progression-free survival. A total of 891 patients were analyzed (70 % with oropharynx cancer). With a median follow-up time of 3.8 years, there were no statistically significant differences in progression-free survival, overall survival, distant metastasis, or locoregional failure [131]. As a result of this trial, the interest in combining cetuximab with cisplatin for concurrent therapy has largely ended. Patients requiring concurrent therapy are typically treated with either cytotoxic therapy, most commonly cisplatin, or cetuximab, based on comorbidities and tolerance.

In the era of HPV-positive tumors, and the improved outcomes with standard therapy, there is increasing interest in de-escalating treatment. The goal is to maintain excellent rates of locoregional control and overall survival while reducing the toxicity, especially in light of the long life spans expected in this healthy population. One area of interest is the use of cetuximab, in place of cisplatin, to de-escalate therapy. The RTOG conducted a randomized phase III trial, RTOG 1016, for patients with p16-positive oropharynx cancers; this trial treated patients with definitive radiation (70 Gy in 6 weeks) and randomized them between definitive cisplatin and cetuximab. Accrual is now complete, and further follow-up will reveal the outcome of this trial.

27.7.2 Base of Tongue Cancer

Tumors of the base of tongue tend to be locoregionally aggressive, with the majority being poorly differentiated and showing a propensity for local, regional, and distant spread. As a result, initial staging is crucial to determining the best definitive management, as the risk of metastatic disease is higher than other subsites of the oropharynx. There is some controversy in the optimal management of tumors of the base of tongue; institutional biases are significant, and the data reflect varying penchants for treating these tumors.

27.7.2.1 Role of Surgery

Previously, open surgical resection was used often as definitive treatment of tumors of the base of tongue, but management decisions depend significantly on the stage of disease. Although resection had been standard for very small and very large primary lesions, open surgery has become less common in recent years. The emergence of TORS has reenergized interest in primary surgery for carefully selected patients.

For early-stage tumors, there is published data on the efficacy of open surgical resection alone. Foote et al. reported the outcomes of 55 patients treated with open surgery alone, typically a partial glossectomy and in some cases a subtotal or total laryngectomy (11 patients) [132]. The crude rates of local control were 77 % for T1, 83 % for T2, and 75 % for T3 tumors with a disease control rate of 49 %. In this population, 16 patients required surgery to manage surgical complications, and 5 patients required permanent feeding tubes. Currently, surgical resection may be considered for small, especially exophytic lesions, in which a limited surgery may be performed with a minimum of morbidity, adhere to principles of oncologic resection, and avoid the need for postoperative radiation therapy. However, more infiltrative lesions do have the potential to require more extensive resections,

which result in more functional debilitation and may have inferior outcomes compared to nonsurgical approaches.

Historically, advanced primary tumors, such as T4 lesions, have been treated with open surgical resection followed by postoperative radiation therapy. The surgery of choice for these lesions is typically laryngectomy since a large resection of the tongue base will result in severe dysphagia and put the patient at risk for aspiration. Zelefsky and colleagues reported on a series of patients with advanced base of tongue and tonsil cancers treated with surgical resection and postoperative radiation therapy [133]. Overall, there was an 81 % 7-year local control rate for patients with base of tongue tumors with 94 % for T3 and 75 % for T4 tumors. In another study, de los Santos and colleagues reported on 51 patients treated with advanced base of tongue tumors treated with open surgery and postoperative radiation therapy at The University of Texas MD Anderson Cancer Center; 90 % of patients had T3 or T4 primary tumors [134]. The 5-year locoregional control rate was 74 %. Although toxicity was not reported explicitly, 21 patients were reported to have swallowing dysfunction.

With the emergence of TORS in the past 5 years, there is increasing interest in resection of base of tongue cancers using this approach. Many of the initial reports of TORS include patients with base of tongue cancers [135, 136] and have documented excellent local control with this method. However, the large majority of these cases have also been treated with adjuvant radiation or chemoradiation as well.

Although surgical resection may be performed with adequate local control in early-stage tumors as well as late-stage tumors (when combined with postoperative radiation), approaches using definitive radiation therapy, with or without chemotherapy, have been widely accepted due to the reduced toxicity of treatment with equivalent outcomes [106, 118]. With the emergence of minimally invasive surgical methods, like TORS, further study is needed to establish the best candidates for one approach versus the other.

27.7.2.2 Role of Definitive Radiation Therapy: Radiation Therapy Alone or with Chemotherapy or Molecularly Targeted Therapy

Radiation therapy, alone or in combination with systemic therapy, has emerged as the standard of care for the majority of tumors of the base of tongue. The use of a nonsurgical approach, even for small lesions, has improved outcomes and minimized toxicity for these patients. At this time, definitive radiation therapy using IMRT is typically the treatment of choice for T1 and T2 primary tumors. For T3 lesions, concurrent chemoradiation is often the optimal treatment. For T4 tumors, surgery with postoperative radiation has historically been the treatment of choice; however, a nonsurgical approach with concurrent chemoradiation has now emerged as standard treatment for these lesions. Due to the midline nature of the base of tongue, all patients should have lymph nodes treated bilaterally. In selected cases, boosts to the primary tumor directly or via a submental approach may be performed with brachytherapy; however, the use of dose escalation, with 3D conformal techniques or IMRT, has largely supplanted brachytherapy.

External beam radiation has been used for definitive treatment of base of tongue cancer with excellent results. Historically, these studies have used conventional planning for treatment with daily fractions of 2 Gy, although current practice largely employs IMRT. Primary radiation therapy has an excellent local control rate for T1 and T2 tumors, typically in the range of 80–90+% across various institutions and treatment algorithms (Table 27.4). The reported outcomes for T3 lesions are more variable, likely due to the heterogeneity in this stage. Complications from definitive radiation alone have been well documented. Rates of bone and soft tissue necrosis have reached 5–7 % in multiple studies [132, 137].

The use of brachytherapy in conjunction with external beam radiation has been widely studied. Harrison and colleagues reported on a group of patients treated with 50–54 Gy external beam radiation followed by a boost of

Table 27.4 Outcomes of patients treated for tumors of the base of tongue with radiation therapy

Author	Refs.	Institution	Patients (*n*)	Median FU (mo)	Local control (%)				Comments
					T1	T2	T3	T4	
Spanos	[137]	MD Anderson	174	100 (extrapolated)	91	71	78	52	Once-daily fx
Foote	[132]	University of Florida	84	96	89	88	77	36	Once-daily fx
Weber	[220]	MD Anderson	173	22	100	86	59	44	8 % with interstitial boost; once-daily fx
Mak	[221]	MD Anderson	54	41	100	98	76	9	Concomitant boost
Mendenhall	[99]	University of Florida	217	(All over 48 mo)	96	91	81	38	69 % hyperfractionated
Harrison	[138]	Memorial Sloan-Kettering	68	36	87	93	82	100	EBRT ± brachy

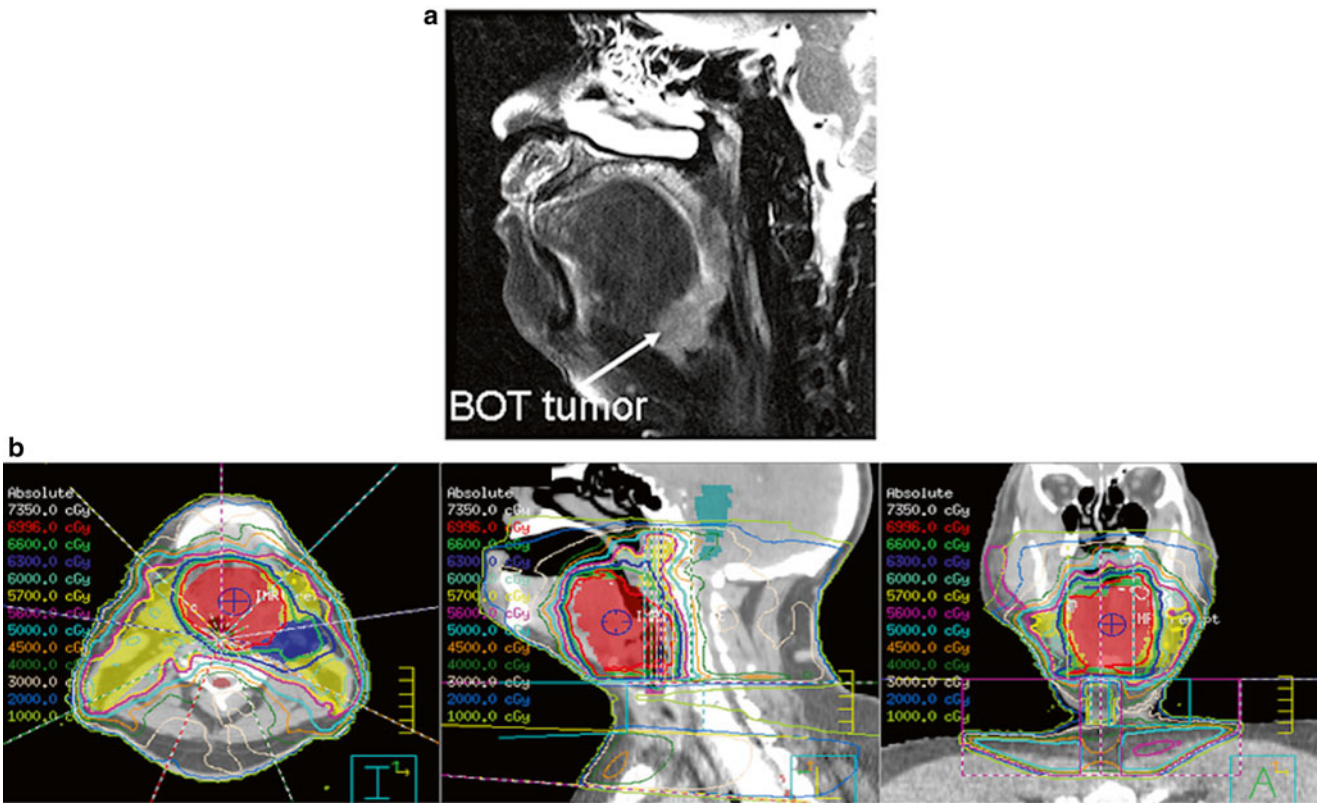

Fig. 27.10 Base of tongue tumor. (**a**) Initial T2-weighted MRI appearance of a T3 N1 M0 base of tongue squamous cell carcinoma. (**b**) IMRT treatment plan for definitive chemoradiation of this lesion to a dose of 70 Gy in 33 fractions

20–30Gy with an Iridium-192 implant [138]. The 5-year actuarial local control rate was 87 % for T1, 93 % for T2, and 82 % for T3 lesions. The rates of soft tissue or bone necrosis, bleeding, or ulceration were 19 %. Similar outcomes have been reported on the combination of external beam radiation and brachytherapy at other institutions (Table 27.4). Although the combination of external beam and brachytherapy has proven effective, it has largely fallen out of favor due to the emergence of altered fractionation, chemoradiation, and IMRT in standard practice; these methods of treatment intensification provide at least equivalent outcomes using solely external techniques.

At this time, standard practice in treatment of base of tongue carcinomas employs definitive radiation therapy with or without systemic therapy (Fig. 27.10). Using the same principles outlined for general treatment of oropharynx cancers, small primary tumors are typically treated with radiation alone and those that are locally advanced (T3 or T4) are typically managed with altered fractionation or concurrent chemoradiation. For patients with positive nodes, extensive neck disease may be managed with concurrent chemoradiation.

27.7.3 Tonsillar Cancer

Tumors of the tonsillar complex are the most common of the oropharyngeal tumors, comprising 70–80 % of the total cases. Like tumors of the base of tongue, these lesions commonly metastasize to the cervical lymph nodes, with greater than 50 % of patients presenting with nodal metastases; however, contralateral nodal disease is more limited. Consideration can be made for unilateral treatment, unlike the majority of oropharynx cancers; however, this decision must be made carefully. For lesions that cross the midline, involve a midline structure (such as the base of tongue), or have advanced neck disease, bilateral treatment is warranted.

There is excellent data documenting the outcomes of patients treated with surgery and with radiation therapy for tonsillar cancers. The management philosophies employed with tonsil cancer are often extrapolated to other sites.

27.7.3.1 Role of Surgery

Surgical resection has been shown to be effective treatment for certain tonsillar cancers at the very early and late stages of disease. For early-stage disease confined to the tonsillar fossa, single modality therapy has provided excellent results.

Open surgery alone has provided excellent local control rates, in the range of 80–90 % [139]. However, for tumors with extension to the lateral pharyngeal wall or base of tongue, local control drops precipitously [140, 141]. New surgical techniques, including transoral robotic surgery (TORS) and transoral laser microsurgery (TLM), are now being utilized in early-stage tonsillar cancers with promising results [142–144]. These studies show that resections using these methods can provide excellent local control with acceptable morbidity, although VPI remains a potential problem. Regardless of the technique used for primary treatment, due to the potential for nodal metastases in patients with tonsil cancer, the neck must be addressed.

For locally advanced tonsil cancers, management has evolved from surgery with postoperative radiation, which was historically the standard treatment for advanced lesions, to nonsurgical approaches. In order to achieve negative margins, a complete resection adhering to oncologic principles required large volume composite resections and flap reconstructions; often, multiple positive lymph nodes were found. The use of adjuvant radiation therapy in these cases improved outcomes for patients with advanced disease. Foote and colleagues reviewed the results of patients with advanced tonsil cancers with surgery with or without adjuvant radiation [139]. In this series, 39 % of patients treated with surgery alone had locoregional failure, compared to 31 % undergoing surgery and radiotherapy; the latter group had more advanced neck disease than the former. For patients with Stage III disease, the 5-year overall survival was 100 % for those treated with surgery and radiation, compared to 56 % for those treated with surgery. For patients with Stage IV disease, the 5-year overall survival rates were 78 % for those treated with surgery and radiation and 43 % (Stage IVA) and 50 % (Stage IVB) for those treated with surgery alone.

Zelefsky and colleagues reported the results of patients with advanced oropharyngeal cancers treated with surgery and postoperative radiation; 20 of these patients had tonsil cancer [133]. For this subset, the 7-year actuarial local control rate was 83 %. For patients who had close or positive margins and received a postoperative radiation dose of 60 Gy or more, the long-term control rate was 93 %.

Overall, there is data to support the use of robotic or laser surgery alone in early-stage cancers, when it can be used as a single modality and lead to acceptable functional outcomes (for instance, without the development of VPI or the need for an obturator). There are no randomized studies that have compared the outcomes of surgery and radiation therapy; comparisons between individual non-randomized studies have shown no compelling differences in their results. For advanced-stage therapy, the use of surgery and postoperative radiation is effective; however, the improved outcomes of chemoradiation have led to similar rates of locoregional control in a population that would require major resections, reconstructions, and postoperative radiation therapy regardless.

27.7.3.2 Role of Definitive Radiation Therapy: Radiation Therapy Alone or with Chemotherapy or Molecularly Targeted Therapy

External beam radiation has been an effective modality for the treatment of tumors of the tonsil (Table 27.5). For early-stage disease, several individual institutions have reported their results. Mendenhall and colleagues reviewed the experience of the University of Florida using definitive radiation treatment for tonsil cancer as an institutional policy [145]. In this series of 503 patients treated with either continuous conventional or hyperfractionated radiation therapy, the 5-year rates of local control were 88 % for T1 tumors, 84 % for T2 tumors, 78 % for T3 tumors, and 61 % for T4 tumors. In this population, 57 patients received chemotherapy and 198 patients underwent planned neck dissection. Overall, there were no severe acute radiation complications; however, 9 % of patients developed long-term sequelae of radiation, including osteonecrosis requiring surgery, dysphagia requiring feeding tube, bone exposure, fistula, and fatal aspiration. Another series documented the experience of 465 patients treated with radiation therapy for early tonsillar cancers at the Institut Curie [146]. In this series, the local control rates were 89 % for T1, 84 % for T2, 63 % for T3, and 43 % for T4 tumors. The authors further noted that patients with tumors confined to the tonsillar fossa had higher local control rates than those from other sites.

Table 27.5 Outcomes of patients treated for tonsillar tumors with radiation therapy

Author	Refs.	Institution	Patients (*n*)	Median FU (mo)	Local control (%)				Comments
					T1	T2	T3	T4	
Mendenhall	[145]	University of Florida	503	(All over 48)	88	84	78	61	3 % contralateral failure in pts treated unilateral
Bataini	[146]	Institut Curie	465	60	89	84	63	43	
Mazeron	[151]	Henry Mondor Hospital	165	60	100	94	–	–	

The ipsilateral treatment of tonsillar cancers has been an area of active investigation, with the intention of sparing normal tissue toxicity for patients with well-lateralized tumors. O'Sullivan and colleagues documented the experience at Princess Margaret Hospital, in which they treated 228 patients with largely T1 or T2 N0 tonsillar cancers [147]. Overall, 191 patients had T1/2 tumors, 30 patients had T3 tumors, and 7 patients had T4 tumors with 133 patients having N0 disease, 35 patients having N1 disease, and 27 patients having N2/3 disease. Radiation was delivered using wedged-pair Cobalt-60 treatment matched to an ipsilateral low neck field. The 3-year local control rate for all patients was 77 %, regional control was 80 %, and cause-specific survival 76 %. For the subset of patients with T1 or N0 disease, there was 100 % control of the contralateral neck; for all patients, there was 97 % control of the contralateral neck. The authors identified a group of patients with greater than 10 % risk of contralateral neck failure; this included patients with T3 lesions, lesions involving the medial third of the soft palate, lesions involving the middle third of the base of tongue, and patients with N1 disease. The latter, counterintuitive, association of N1 disease with an increased risk of contralateral neck failure was explained by the fact that those patients with N1 disease had a high proportion of advanced T-stage; of the 64 patients with T2-4, node-positive disease, 73 % were N1. In another series, the University of Florida review of patients treated with definitive radiation for tonsillar cancer included 58 patients treated with ipsilateral primary and neck radiation therapy; of these, only 2 patients (3 %) developed failure in the contralateral neck [145]. Another review by Jackson and colleagues documented the experience of 178 patients treated with ipsilateral definitive radiation therapy for tonsil cancers [148]. In this series, locoregional control was 91 % for Stage I, 74 % for Stage II, 51 % for Stage III, and 53 % for Stage IV disease. The contralateral nodal failure rates were less than 4 % for all stages. Overall, the rate of local control was 84 % for T1/2 tumors. In a series published by Chronowski and colleagues, the MD Anderson Cancer Center experience was reported [149]. A cohort of 102 patients was treated with unilateral radiation for tonsillar cancer. With a median follow-up of 38 months, there were no local or ipsilateral neck failures. There were contralateral neck failures in 2 % of patients. These data suggest that ipsilateral treatment is appropriate for selected cases of well-lateralized tonsillar tumors, especially T1–2 with no invasion of central structures.

There is a well-documented prior experience in the use of external beam radiation with an interstitial brachytherapy boost for tonsillar cancer. Pernot and colleagues documented their experience treating 343 patients with this approach [150]. Local control rates were 89 % for T1, 85 % for T2, and 67 % for T3 tumors. Mazeron and colleagues also described a similar experience using external beam radiation to a dose of 45 Gy with a 30 Gy interstitial boost; only 2 out of 69 patients experienced locoregional recurrence at a median follow-up of 5 years [151]. Although it has been shown effective, the use of interstitial brachytherapy as a boost for tonsillar cancers has largely been supplanted by the ability to deliver high doses using conformal methods of external beam therapy, including IMRT, or treatment intensification with concurrent chemotherapy.

External beam radiation therapy with IMRT has emerged as an effective technique for treatment of tonsillar cancers of all stages. As with other oropharynx subsites, understanding the full extent of the disease at the onset of treatment is crucial to determine appropriate volumes (Fig. 27.11). For lesions that extend onto midline structures, including the soft palate or base of tongue, bilateral treatment is warranted. For well-lateralized T1/2N0 tumors with no invasion of midline structures (including the palate or base of tongue), ipsilateral treatment can be entertained.

27.7.4 Soft Palate Cancer

Soft palate carcinomas are relatively rare compared to other tumors of the oropharynx; however, they tend to present at earlier stages due to early symptom development and easy inspection and palpation of this region. Despite these features, these tumors are often highly infiltrative with indistinct margins and, as a result, are often more extensive than initially anticipated [53].

Since the soft palate is a midline structure, with no anatomic barriers either medially or laterally, tumors often extend to the tonsillar region or cross midline. Imaging is often helpful at delineating the submucosal extent of these lesions; however, careful consideration for broad coverage is necessary for definitive treatment by any modality. Soft palate carcinomas often present with ipsilateral lymph node metastases, but bilateral disease reaches 50 % in some series of T3 and T4 primary tumors [3].

27.7.4.1 Role of Surgery

Surgical resection of soft palate carcinomas presents challenges due to the infiltrative nature of these lesions. In addition, open surgical excision of the soft palate, except in the most limited of cases, leads to the development of VPI. These effects may be amenable to correction with prosthetic devices. More recent advances in laser surgery, new prosthetic technology, and microvascular free flap reconstruction may offer improved outcomes in patients with surgical resection of these tumors [152]. In addition, the ability to use minimally invasive approaches with TORS has led for some discussion of surgery in well-delineated soft palate cancers.

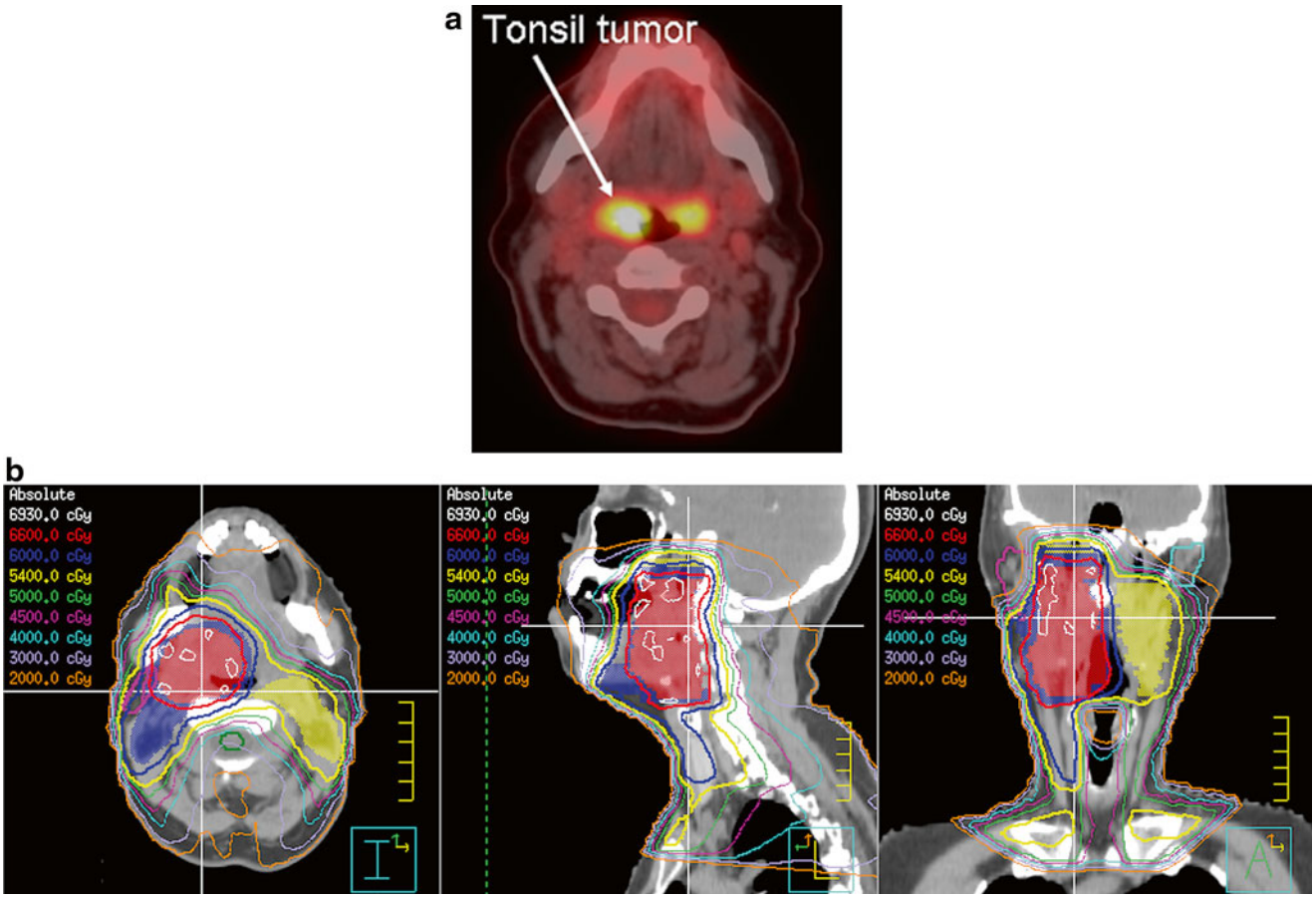

Fig. 27.11 Tonsillar tumor. (**a**) Initial PET/CT appearance of a T2 N2b M0 right tonsil squamous cell carcinoma. (**b**) IMRT treatment plan for definitive radiation of this lesion to a dose of 66 Gy in 30 fractions with concurrent cetuximab

There are some soft palate lesions (approximately 10 %) included in the TORS studies [153]; further study is needed to understand the best practice with regard to surgical resection of these lesions.

27.7.4.2 Role of Definitive Radiation Therapy: Radiation Therapy Alone or with Chemotherapy or Molecularly Targeted Therapy

External beam radiation therapy alone, or in combination with brachytherapy, has been established as a highly effective treatment of carcinoma of the soft palate (Table 27.6). Lindberg and colleagues described a series of patients treated with definitive external beam radiation therapy and noted local control rates of 100 % for T1, 88 % for T2, 77 % for T3, and 83 % for T4 tumors [154]. A study from the Netherlands noted a local control rate of 93 % for T1, 67 % for T2, 58 % for T3, and 37 % for T4 lesions treated with external beam radiation [155]. In the latter study, the mean total dose was 68 Gy. Patients who received a boost with an intra-oral cone (29 % of the patients included in the study) had fewer complications than those that received high dose as a result of external beam delivery alone.

The use of brachytherapy for the treatment of soft palate carcinomas is also the subject of extensive experience. Pioneered largely in France, excellent local control has been achieved with brachytherapy, often following external beam radiation. Esche and collaborators reported a series of 43 patients who were treated with 50 Gy of external beam radiation therapy to the oropharynx and bilateral necks followed by 20–35 Gy with an Iridium-192 low-dose-rate brachytherapy implant [156]. This regimen yielded a local control rate of 92 % and cause-specific survival at 3 years of 81 %. In a similar analysis, Mazeron and colleagues reported on a subset of patients who received external beam radiation to a dose of 45 Gy followed by a 30 Gy boost with Iridium-192 brachytherapy [157, 158]. Local control was reported to be 85 % for soft palate tumors. These reports suggest decreased toxicity, namely xerostomia, with the use of a low-dose-rate implant, presumably due to less scattered dose to the parotid glands. Small series have also reported excellent local control rates with combinations of external beam radiation and

Table 27.6 Outcomes of patients treated for tumors of the soft palate with radiation therapy

Author	Refs.	Institution	Patients (*n*)	Median FU (mo)	Local control (%)				Comments
					T1	T2	T3	T4	
Keus	[155]	Netherlands Cancer Institute	235	60	92	67	58	37	
Lindberg	[154]	MD Anderson	Not given	48	100	88	77	83	Once-daily fx
Fein	[222]	University of Florida	45	48	81	65	50	25	Once-daily fx
Fein	[222]	University of Florida	24	48	100	100	60	0	Twice-daily fx
Mazeron	[158]	Henry Mondor Hospital	59	48	93	87	–	–	± EBRT ± brachy

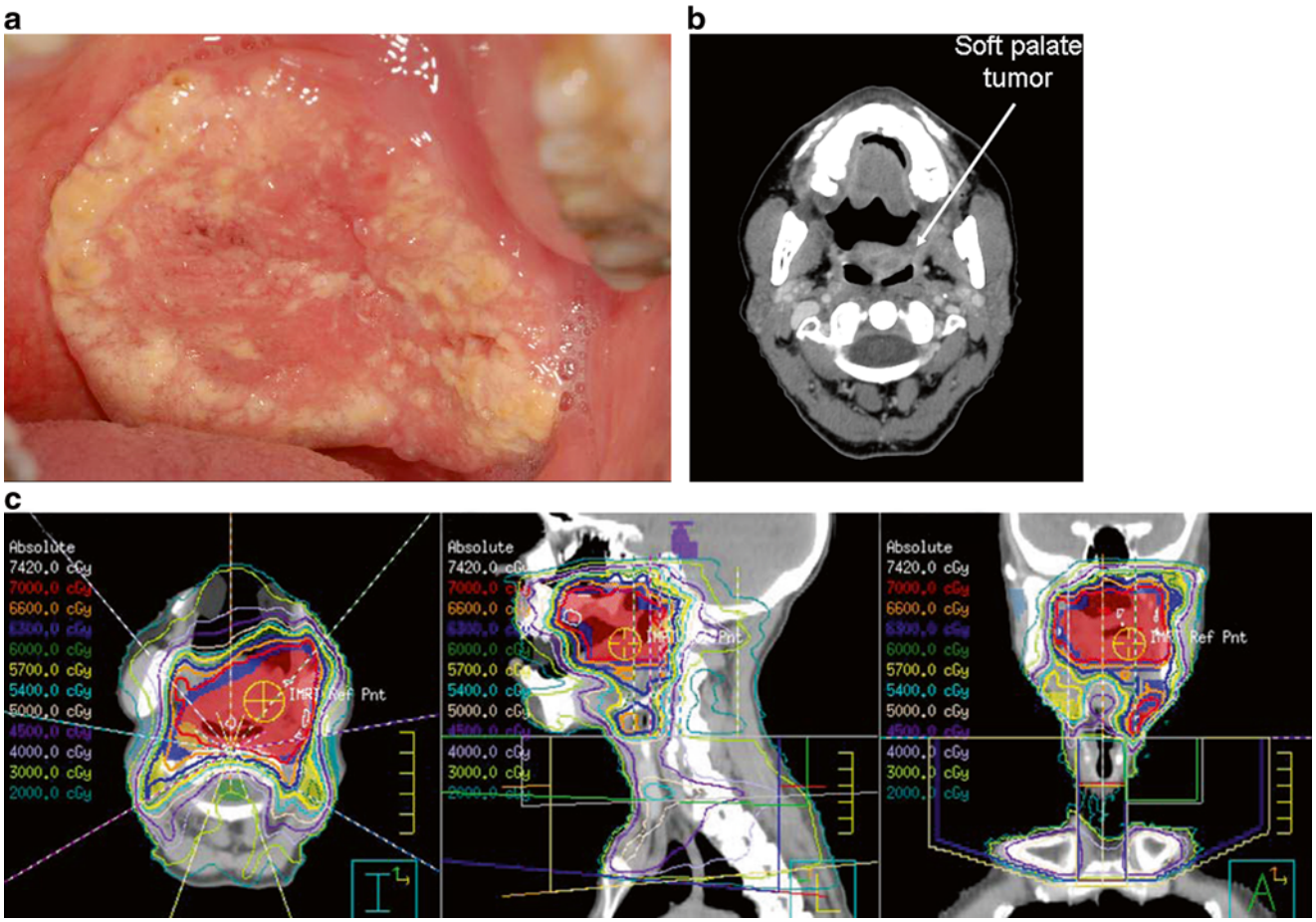

Fig. 27.12 Soft palate tumor. (**a**) Initial clinical presentation of a T4 N1 M0 squamous cell carcinoma of the soft palate. (**b**) Initial contrast-enhanced CT appearance of the same T4 N1 M0 squamous cell carcinoma of the soft palate on (**c**) IMRT treatment plan for definitive chemoradiation of this lesion to a dose of 70 Gy in 33 fractions

both high-dose-rate and pulse-dose-rate brachytherapy; however, these have yet to be well established in routine practice [159]. Indeed, newer techniques, like chemoradiation and IMRT, have allowed a sufficient increase in treatment intensity with reduced dose to normal tissues, thereby making brachytherapy less popular.

External beam radiation therapy with IMRT has emerged as an effective technique for treatment of soft palate carcinomas. As with other oropharynx subsites, understanding the full extent of the disease at the onset of treatment is crucial to determine appropriate volumes (Fig. 27.12). Since the soft palate is a midline structure, the bilateral necks should be treated in all cases.

27.7.5 Oropharyngeal Wall Cancer

Tumors of the oropharyngeal wall are a rare subtype of oropharyngeal carcinomas. Because of the few early symptoms and the considerable amount of potential space in the posterior pharynx, these lesions are often not identified until they are quite large. As a result, the majority of patients present at advanced stages. Historically, the prognosis for tumors of the oropharyngeal wall was less favorable than other subsites of the oropharynx [154].

The pharyngeal wall is a midline structure with no anatomic boundaries to tumor spread. These lesions tend to invade the retropharyngeal and prevertebral spaces and only rarely spread in the lateral direction. Initial imaging with MRI is often helpful at delineating the full extent of the primary tumor and elucidating the extent of any vertebral extension [3]. Due to the midline nature of the pharyngeal wall, these lesions can metastasize to lymph nodes bilaterally.

27.7.5.1 Role of Surgery

The posterior pharyngeal wall is in close proximity to the prevertebral musculature and fascia, and lesions in this area often invade these structures. In selected cases of very small, superficial lesions, surgery is an appropriate therapy. In these cases, resections may be performed with negative margins and little functional debilitation. However, the majority of cases present at advanced stages. For these cases of technically resectable, locally advanced tumors, the postoperative morbidity is often significant and reconstructive options are often limited. In addition, for lesions that cannot be resected without compromising clear margins, postoperative radiation therapy may be indicated, thereby adding to the potential toxicity of definitive treatment. Finally, locally advanced tumors often are accompanied by early invasion of prevertebral musculature, rendering these tumors unresectable.

Small series have reported outcomes for definitive surgical resection for selected cases of oropharyngeal wall carcinoma. Guillamondegui and colleagues reported the outcomes of 94 patients with pharyngeal wall tumors following surgery; 67 of these patients had primary tumors in the oropharynx and 27 in the hypopharynx [160]. For the entire group, they noted a 28 % locoregional recurrence rate after resection. Salvage treatment with radiation or surgery was successful in less than 30 % of patients.

27.7.5.2 Role of Definitive Radiation Therapy: Radiation Therapy Alone or with Chemotherapy or Molecularly Targeted Therapy

In recent years, radiation therapy has become widely used as definitive therapy for carcinomas of the oropharyngeal wall. Historically, the definitive treatment of oropharyngeal wall tumors with radiation therapy was a technical challenge; the curvature of the mucosa around the vertebral body was in close proximity to the typical spinal cord block in conventional radiation treatment fields. In an attempt to deliver curative dose and respect the tolerance of the adjacent spinal cord, oblique fields and other special techniques were utilized; however, it is widely believed that these techniques resulted in geographic misses of the tumor in some cases. The development of IMRT has been crucial to the curative treatment of oropharyngeal carcinomas with radiation therapy; the ability to deliver curative dose to the curved target, while respecting the tolerance of the spinal cord, has revolutionized treatment of this disease.

The radiation treatment of patients with oropharyngeal wall carcinomas has been the subject of several small studies due to the relative rarity of the tumors; however, oropharyngeal wall tumors are often included as small subsets in larger head and neck trials. In a dedicated pharyngeal wall series by Hull and colleagues, 148 patients were treated for carcinoma of the pharyngeal wall; tumors were in the oropharynx in 63 % of patients and hypopharynx for 37 % [161]. The majority of patients were treated with hyperfractionation to a total dose of 76.8 Gy; local control rates were 93 % for T1, 82 % for T2, 59 % for T3, and 50 % for T4 lesions. On multivariate analysis, locoregional control rates were superior for those patients treated with hyperfractionation ($p = 0.0009$). The use of concomitant boost therapy has also been successful for tumors of the oropharyngeal wall. Data from The University of Texas MD Anderson Cancer Center suggest local control rates of 93 % for T2 tumors and 82 % for T3 tumors using this fractionation schedule [162].

Similar to other subsites, external beam radiation therapy with IMRT has largely emerged as a standard of care for carcinomas of the oropharyngeal wall. The full extent of disease, including involvement or invasion of the vertebral region, must be delineated and used to design treatment volumes (Fig. 27.13). Given the midline nature of the oropharyngeal wall, the bilateral neck should be treated in all cases.

27.8 Multidisciplinary Follow-Up and Surveillance

Surveillance following definitive treatment of oropharyngeal carcinomas with either surgery or radiation therapy is complex. As a result, complementary modalities of expert physical examination and imaging are helpful for surveillance. Treatment-related toxicities are also important metrics to assess, with an emphasis on quality of life and opportunities for improvement. Finally, patients require careful screening for second primary tumors, due to the high rate of second malignancies in this patient population.

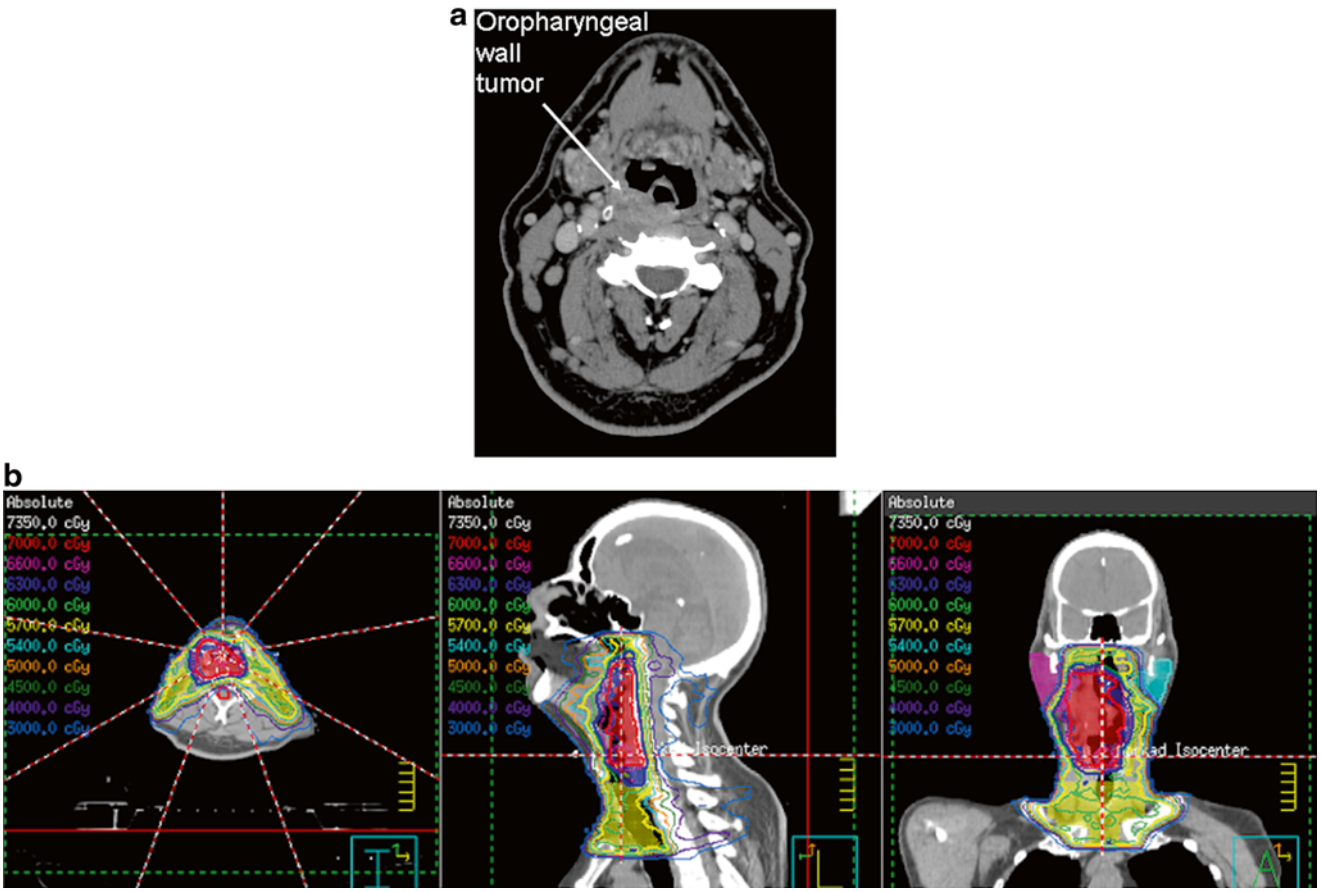

Fig. 27.13 Oropharyngeal wall tumor. (**a**) Initial contrast-enhanced CT appearance of a T3 N1 squamous cell carcinoma of the right oropharyngeal wall. (**b**) IMRT treatment plan for definitive chemoradiation of this lesion to a dose of 70 Gy in 33 fractions

27.8.1 Role of Clinical Evaluation

A history and physical examination are considered the mainstay of surveillance for patients with oropharyngeal cancer. Symptoms such as non-healing ulcers, pain, trismus, nerve deficits, or swelling should be fully evaluated as potential recurrence or treatment-related toxicity. Patients with head and neck cancers are at high risk for second primary tumors, so the evaluations should be comprehensive. Recurrence and treatment effects can be subtle, and stability over time and correlation with imaging is crucial.

In addition to second primary head and neck cancers, patients with oropharyngeal carcinoma are at increased risk for the development of other second primaries [163]. Patients with diseases linked to alcohol and tobacco use are at risk for second primaries of the lung and esophagus, among others. Patients with diseases linked to HPV may also be at risk for other HPV-associated primary tumors [164]. Comprehensive follow-up protocols should include screening for these tumors, as well as attempts to prevent development of these lesions through education and screening, as well as continued support for cessation programs.

Patients treated for oropharyngeal cancers are at risk for hypothyroidism if radiation was used to treat the low neck [165]. Physicians should be attuned to the signs and symptoms of hypothyroidism, and patients should be evaluated with a blood test for thyroid-stimulating hormone (TSH) at appropriate intervals.

Finally, patients with oropharyngeal carcinomas treated with radiation are at high risk for dental disease. A full dental evaluation should be performed prior to the onset of radiation; in addition, comprehensive follow-up with a dental specialist skilled in the evaluation and treatment of patients who have had head and neck radiation therapy is crucial for long-term oral health. The use of fluoride application trays is important, and a skilled dentist should evaluate the patient at regular intervals to assess dental health and any necessary interventions [166, 167].

27.8.2 Role of Imaging

Imaging studies in patients treated with radiation therapy and surgery for oropharyngeal carcinomas are often challenging to interpret. Baseline posttreatment studies are necessary to

establish the new normal anatomy and judge subsequent changes; these are typically performed between 6 weeks and 6 months following the conclusion of definitive therapy. Both CT scans with contrast and MRI scans provide key information to differentiate posttreatment changes from recurrent disease, especially when used in conjunction with physical examination. In addition, PET has been shown to have a sensitivity over 88 % and specificity over 75 % in the detection of residual or recurrent tumor [168, 169].

Complete resolution of a lesion on CT or MRI studies often correlates with control at the primary site. Tumors that shrink by more than 50 %, but less than fully resolve, require serial examination to distinguish the development of scar tissue from persistent disease; consideration may be given for biopsy of these areas for further investigation. For patients evaluated with PET scan, an FDG-avid lesion in the follow-up period should be evaluated with a biopsy. Even patients with a negative biopsy may benefit from rigorous surveillance with short interval physical examination and repeat imaging.

27.8.3 Optimal Follow-Up Schedule

It is recommended that comprehensive head and neck physical examinations be completed every 1–3 months for the first year, every 2–4 months for the second year, and every 4–6 months for years 3–5; at that time, follow-up examinations can be spaced annually. In addition, posttreatment imaging is recommended to provide a baseline within 6 months of the completion of treatment; this should be deferred until at least 6 weeks following therapy, however, to ensure resolution of the acute effects of either surgery or radiation. Reimaging is recommended if indicated through changes in the physical examination.

27.9 Multidisciplinary Treatment for Recurrent Disease

The treatment of recurrent disease in the oropharynx is complex. An analysis from the National Cancer Database noted that, from 1985 to 2001, rates of definitive chemoradiation increased from 15 to 30 % [170]; these rates have increased even more since 2001. Although our outcomes have improved significantly, locoregional recurrence [171] and secondary cancers [172] remain a challenge. Given that many patients are now treated with definitive chemoradiation, optimal management of persistent/recurrent disease, either in the treated field or marginal to it, is difficult secondary to the prior administration of high doses of radiation to adjacent critical structures. This has been the subject of extensive debate [173]. The management of these cases is highly individualized, based on the details of the initial treatment, extent and timing of the recurrence, and baseline performance status of the patient.

27.9.1 Role of Surgery

Open surgical resection is a standard therapy for post-radiation recurrent or persistent disease in the oropharynx [174]. However, even in the best cases, salvage rates are relatively low; the failure to eradicate disease with chemoradiation portends a poor prognosis [175–178]. Many patients with recurrent disease are not candidates for surgical resection due to the extent of their disease at the time of presentation.

Surgical salvage may be performed through a transoral, transmandibular, or cervical approach. However, operating in a previously irradiated field does pose significant challenges. Postoperative complications following salvage surgery, after radiotherapy, have been reported as high as 42 % [179, 180]. The use of reconstructions with vascularized regional pedicled myocutaneous and microvascular free flaps may improve the healing of these patients by providing fresh tissues and blood supply, as well as allowing larger resections [181].

There are several small series of reports documenting the outcomes of patients treated with open surgical salvage for recurrent oropharyngeal carcinoma. Agra et al. noted that patients with Stage I and II disease at recurrence had a 5-year overall survival rate of 43.6 % compared to 24.1 % for those with Stage III and IV disease at recurrence ($p=0.027$); the authors also noted that patients with a disease-free interval of greater than 1 year prior to recurrence had a significantly better 5-year survival than those with recurrence in less time (26.7 % vs. 42.1 %; $p=0.023$) [180]. Kim et al. also noted that patients with T1 or T2 tumors at the time of recurrence had a statistically significant improvement in outcomes with surgical salvage and microvascular flap reconstruction than did those with T3 and T4 tumors and those patients who continued to smoke after diagnosis [181].

In addition to primary management, TORS has been integrated into the arsenal for treatment of recurrent disease. In a retrospective multi-institutional case–control study, patients with recurrent oropharyngeal cancer treated with salvage surgery with TORS ($n=64$ patients) were compared to matched controls who underwent open surgery ($n=64$ patients) [182]. Patients treated with TORS had lower incidence of tracheostomy, feeding tubes, and positive margins; in addition, patients treated with TORS had higher rates of 2-year recurrence-free survival. This suggests that TORS may be a promising tool for surgical salvage in well-selected patients with recurrent oropharynx cancer; further study is warranted.

Overall, salvage surgery is considered the primary therapy for patients with recurrent oropharyngeal cancer after definitive chemoradiation. However, the extent of disease at the time of recurrence considerably impacts whether the patient is a candidate for resection and the outcome if resection is possible. Hence, early detection of recurrent disease with careful surveillance is crucial.

27.9.2 Role of Radiation Therapy

In recent years, re-irradiation has become more common as an acceptable, although high-risk, means of attempted salvage for selected patients with recurrent oropharyngeal carcinoma or second primary tumors. For patients who present with recurrent disease that is not amenable to surgical resection, optimal therapy is left to radiation and chemotherapy. Re-irradiation does pose a significant risk for severe life-threatening complications, and it should only be used judiciously in selected patients with recurrent disease.

One of the longest experiences of re-irradiation in head and neck cancer is from the University of Chicago, in which a regimen of concomitant chemotherapy and re-irradiation has been used as salvage therapy for almost 20 years [183, 184]. The regimen utilized in these studies employs a combination of 5-fluorouracil, hydroxyurea, and week-on/week-off radiation therapy. Further reports utilizing similar regimens from the Institute Gustave Roussy and University of Alabama-Birmingham have reported similar results [185–187]. Although the median survival for these patients remains limited, these series have demonstrated a durable disease response and survival in a subset of patients (approximately 15–25 %).

Collaborative group trials have also explored the implementation of re-irradiation in the setting of recurrent disease. The RTOG tested a similar regimen of chemotherapy and re-irradiation in a phase II multi-institutional trial (RTOG 96-10) [188, 189]. Eighty-six patients were treated with 60 Gy of radiation to the volume of recurrent disease in a week-on/week-off regimen with 5-fluorouracil and hydroxyurea; 34 % of patients had primary disease in the oropharynx. The radiation was delivered with conventional techniques with twice-daily fractionation (1.5 Gy per fraction twice daily for 5 days, followed by 9 days off, repeated for 4 cycles). The overall survival rate at 2 years was 15.2 % and 5 years was 3.8 % [188, 189]. Although toxicity was considered "acceptable," there was 17.7 % grade 4 and 7.6 % grade 5 toxicities reported [189]. A follow-up phase II trial replaced the prior chemotherapy regimen with cisplatin and paclitaxel while employing a similar radiation schema (RTOG 99-11) [190]. This study enrolled 105 patients, with 40 % having primary tumors in the oropharynx. The 2-year overall survival rate was 50.2 %, which compared favorably to the prior study. The toxicity, however, remained relatively high; 8 % of patients suffered grade 5 toxicities and 28 % with grade 4 or 5. A subsequent phase III RTOG trial was designed to test the use of chemotherapy alone with the chemotherapy re-irradiation regimen of protocol RTOG 99-11; however, this trial closed prematurely due to inadequate accrual. In aggregate, these studies have been interpreted as promising, with a subset of patients achieving significant long-term locoregional control and survival with re-irradiation; this is tempered, however, by a subset of patients who experience severe toxicity, including death.

Additional series are now being published that document similarly promising results in selected patients treated with re-irradiation (Table 27.7). There are emerging reports of using IMRT for re-irradiation. Lee and colleagues reported on the outcomes of 69 patients treated for unresectable recurrent disease with 60 Gy (median dose); 70 % of these patients were treated with IMRT [191]. The 2-year overall survival rate was 12 %. Looking at the entire cohort, which did include patients who also received surgical resection as well as re-irradiation, there was an improvement in locoregional progression-free survival in those patients treated with IMRT. In addition, for the entire cohort, there were acute grade 3 and 4 complications in 23 % of patients and late in 15 % of patients. Sulman and colleagues reported on the outcomes of a series of 54 patients all of whom were treated with IMRT for unresectable recurrent disease [192]. The 2-year overall survival was noted to be 58 % with a locoregional control of 54 %. In this series, 32 % of patients experienced grade 3 and 4 toxicities; there were no deaths. In total, these experiences suggest a 2-year overall survival rate of 35–58 % with significant rates of grade 3–5 toxicity. McDonald and colleagues published a literature review on the risk of carotid blowout following re-irradiation to the head and neck [193]. From 27 published reports, a cohort of 1554 patients was assembled; there were 41 carotid blowouts, to give a rate of 2.6 %. Of these, 76 % of the carotid blowouts were fatal. This study highlights that fatal complications of re-irradiation are rare, but they do occur.

Overall, the reports on re-irradiation for recurrent or second primary tumors suggest that it is a feasible approach in highly selected patients; it is imperative for the patients to understand, however, the risks of potential toxicity, including the very real risk for major edema, tissue necrosis, stroke, and death. Patient selection is crucial to the judicious use of re-irradiation; patients who require re-irradiation more than 2 years following definitive treatment for their first primary tumor, and those who have a second primary (rather than recurrent disease), do tend to have improved outcomes. In terms of treatment, the targets in recurrent disease are limited to the tumor or tumor bed with a small margin. Doses in the range of 60–66 Gy at 2 Gy daily fractionation or 1.5 Gy twice daily with or without chemotherapy appear to provide a sustained benefit in those patients who respond; patients

Table 27.7 Summary of selected clinical reports of the treatment of unresectable disease with re-irradiation

Author	Refs.	# patients	% Oropharynx[b]	% Chemo	% IMRT	MS	2 year OS	2 year LRC	Grade 4+ toxicity
De Crevoisier	[186]	169	60 %	84 %	0 %	10 mo	21 %	11 % (PFS)	13 % acute, 12 % chronic, 3 % carotid hemorrhage
Dawson	[223]	40	10 %	35 %	0 %	12.5 mo	32.6 %	19.5 %	10 % acute, 20 % chronic, 3 % carotid hemorrhage
Spencer	[224]	52	21 %	100 %	0 %	9.4 mo	15 %	Not reported	2 % acute, 8 % chronic
Kramer	[225]	38	11 %	100 %	0 %	12.4 mo	35 %	37 %	16 % acute, 29 % chronic, 5 % carotid hemorrhage
Salama	[226]	66	27 %	100 %	0 %	11 mo[a]	11 %	36 %	13 % chronic[a] 5 % carotid hemorrhage[a]
Lee	[191]	69	15 %[c]	71 %	70 %	15 mo[a]	12 %	19 %	4 % chronic[a]
Sulman	[192]	54	41 %	66 %	100 %	25.3 mo	54 %	58 %	32 % grade 4 0 % grade 5
RTOG 96-10	[189]	81	34 %	100 %	0 %	8.2 mo	16.2 %	Not reported	23 % grade 4 7 % grade 5
RTOG 99-11	[190]	99	40 %	100 %	0 %	12.1 mo	25.9 %	Not reported	28 % acute 9 % grade 5 2 % carotid hemorrhage

MS median survival, *OS* overall survival, *LRC* locoregional control
[a]Describes full series of patients, including those who received surgery
[b]Percentage of patients with oropharyngeal primary at the time of initial diagnosis
[c]Percentage of patients with oropharyngeal primary at the time of recurrence; initial diagnosis was not reported

treated with chemoradiation historically have better overall survival in this setting. Highly conformal techniques, such as IMRT, appear to be beneficial, presumably by sparing more normal tissues previously treated with radiation; however, the data on this are limited. One advantage to IMRT is the ability to limit the dose to the carotid arteries in patients in which the disease is located in a discrete location. Further studies are necessary to elucidate the optimal selection and management of these patients; however, re-irradiation is a viable option in selected cases of recurrent disease.

27.9.3 Role of Chemotherapy

If recurrent oropharyngeal cancer is not amenable to treatment with surgical salvage or re-irradiation, chemotherapy is often used for palliation. Systemic chemotherapy has been shown to have only a modest impact on overall survival in patients with recurrent disease; median survival in phase III trials has been 6–9 months [194–199].

Multiple studies have established platinum-based chemotherapy as the standard treatment for recurrent oropharyngeal carcinomas. Higher response rates have been observed in combination regimens, including platinum/5-fluorouracil [196, 197] and platinum/cetuximab [198]; however, survival was not improved with these regimens over platinum alone. Vermorken and colleagues reported a survival benefit to the use of platinum, 5-fluorouracil, and cetuximab compared to platinum and 5-fluorouracil alone with a median survival of 10.1 vs. 7.4 months ($p=0.0362$) for patients with newly diagnosed recurrent or metastatic oropharyngeal carcinoma [200]. This is the first study to demonstrate improved survival over platinum-based chemotherapy alone.

Multiple clinical trials have investigated new regimens for treatment of recurrent oropharynx cancer. In the phase III randomized SPECTRUM trial, patients with recurrent or metastatic head and neck cancer (37 % with oropharynx cancer) were randomized to receive platinum-based chemotherapy with or without panitumumab, a monoclonal antibody to EGFR [201]. A total of 657 patients were enrolled. The addition of panitumumab did not improve overall survival in this population; however, it did improve progression-free survival. In a subset analysis, the addition of panitumumab did appear to improve overall survival for p16-negative patients; however, this was not observed in the p16-positive group. Further study is warranted for the use of panitumumab base

on p16 status. In the GORTEC 2008-03 trial, patients with recurrent head and neck squamous carcinoma (22 % with oropharynx cancer) were treated with cisplatin, docetaxel, and cetuximab. Presented in abstract form at the 2012 ESMO meeting, the objective response rate for this regimen was 87 % with an overall survival of more than 13 months [202]. Overall, there is continued interest in testing molecularly targeted agents in combination with chemotherapy for first-line treatment of metastatic or recurrent disease.

For patients with recurrent disease that have failed platinum-based regimens, second-line agents are much less successful, and median survival falls dramatically to approximately 3.5 months [203]. For patients with good performance status, active therapies such as taxane- and vinorelbine-containing regimens may be utilized [204–206]. More recently, cetuximab has been employed in patients who have progressed on first-line therapy with some promising results. In a pooled analysis of three prospective studies investigating the use of cetuximab (with or without platinum) in the second-line setting, overall response rates from 10 to 13 % and disease control rates from 46 to 56 % were observed along with a median survival of approximately 6 months [207].

Overall, chemotherapy is the mainstay of treatment for patients with recurrent oropharyngeal carcinoma who are not candidates for surgical resection or re-irradiation. Although overall survival is limited, palliation is achieved for some duration of time. Following the exhaustion of active regimens, best supportive care is the recommendation for treatment for these patients.

27.10 Multidisciplinary Treatment for Metastatic Disease

Although many patients present with Stage IV disease, this is typically due to advanced locoregional disease (Stages IVa and b) and rarely due to the concomitant diagnosis of distant metastases (Stage IVc). In fact, metastatic disease has historically been uncommon as a first site of relapse for cancers of the oropharynx, but it may be more of a problem for patients with small primaries and more advanced nodal disease. Lindberg and colleagues found that distant metastasis was the first site of relapse for oropharyngeal carcinoma in only 7.7 % of patients treated definitively with radiation therapy from 1960 to 1974 [208]. In a more recent review of patients with Stage III and IV oropharyngeal carcinomas treated with definitive radiation therapy with or without chemotherapy at The University of Texas MD Anderson Cancer Center, the 5-year actuarial distant failure rate was 11 % for patients with N1/2a disease and 28 % for patients with more advanced nodal disease (N2b/N2c/N3) ($p<0.001$). For patients with locoregional control, the rate of distant failure at 5 years was 17 % [209].

In the HPV era, there is a small subset of patients who develop aggressive and unusual metastatic disease. In the pre-HPV-era, distant metastases from head and neck cancer typically occurred in the lungs; in the HPV era, other metastatic sites are more common. Huang and colleagues described a subset of patients with p16-positive tumors that recurred at multiple distant sites, and sites that were unusual as compared to historic locations [210]. In this series, p16-positive cancers that developed metastatic disease were found in lung, but also the duodenum, liver, brain, and skin. Other centers have observed similar unusual behavior, and there is ongoing interest in identifying underlying biological bases for this behavior.

Despite the relative rarity of distant metastases in oropharyngeal carcinoma, its management does pose complex treatment questions. Largely, metastatic disease is managed with systemic treatment, as used in the recurrent setting (see the above section for a detailed review). Systemic chemotherapy has had a modest impact on overall survival in patients with metastatic disease; median survival is typically 6–9 months [194–199]. Like the treatment of locoregionally recurrent disease, platinum-based chemotherapy is typically considered first-line therapy in the metastatic setting.

Radiation therapy and surgical resection are typically employed in the metastatic setting for rare cases of solitary metastases with long-term control goals, but more generally for palliation of impending neurologic or musculoskeletal compromise. Radiation therapy can be used palliatively for sites of painful lesions, impending spinal cord compression, or for brain metastases. Surgical resection of isolated lesions may be beneficial in the setting of no other detectable disease. Overall, patients with metastatic oropharyngeal carcinoma are best managed in a multidisciplinary forum with consideration of systemic control, palliation, and end of life issues.

27.11 Future Directions

Although enormous strides have been made in the treatment of oropharyngeal carcinomas, further advances are needed to optimize the outcomes for these patients. Multidisciplinary management has improved the survival and local control for these patients, while minimizing toxicity and improving functionality, but patients do still fail, both locally and distantly, and they do suffer long-term toxicities from their definitive therapy.

The field is growing rapidly, and there are exciting developments in multidisciplinary management of these patients. Advances in imaging technologies have provided important new understanding of the extent of oropharyngeal disease and the ability to tailor treatment and monitor for recurrence accordingly. Advances in robotic surgery continue to optimize outcomes and minimize toxicities in patients treated with resection, and these techniques provide more patient

options for surgical treatment. There are ongoing clinical trials looking at the integration of TORS in the multidisciplinary management of patients with both HPV-negative and HPV-positive oropharynx cancers. New basic science investigations into the molecular mechanisms of pathogenesis in oropharyngeal cancers provide exciting areas for further research and development of novel treatments, including targeted agents. Finally, the optimal integration of chemotherapy, biologically targeted therapy, radiation, and surgery is still an area of vigorous investigation. The development of new chemotherapy combinations and utilization of biologically targeted agents has promise for the prevention of metastatic disease and intensification of radiation therapy. Improvements in conformality and dose delivery with IMRT have reduced toxicity in patients treated with definitive or postoperative radiation therapy. The ongoing investigations of proton therapy will help to determine the most effective and least toxic radiation modality for these patients, who have fewer comorbidities and longer life spans than ever before. Understanding the natural history of individual tumors, based on their location, stage, and molecular features, may allow us to further adjust treatment recommendations.

Overall, oropharyngeal cancer is a complex disease that requires the integration of almost every medical field. Attempts to improve outcomes, while minimizing toxicity, are active areas of research, and the field continues to evolve at an impressive pace.

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Multidisciplinary Management of Hypopharyngeal Carcinoma

28

Marc Hamoir, Jean-Pascal Machiels, Sandra Schmitz, and Vincent Grégoire

Abstract

Despite advances in treatment modalities, the management of hypopharyngeal squamous cell carcinoma (SCC) remains difficult. Most patients have advanced locoregional disease at the time of diagnosis.

Treatment selection favors laryngeal preservation approaches either surgically or non-surgically to improve the quality of life without compromising locoregional control and survival. For patients with early disease, conservation surgery and primary radiotherapy are equally effective therapeutic options. For patient with advanced locoregional disease, a conservative treatment combining chemotherapy and radiotherapy should be favored. Total laryngopharyngectomy (TLP) remains indicated in tumors not suitable for conservative nonsurgical approaches and for salvage. Despite a good locoregional control rate, most patients succumb to distant metastases, intercurrent diseases, or second primaries.

Future developments should be connected with treatments with a better toxicity profile than chemotherapy aimed to decrease the rate of late distant recurrences and the occurrence of second primaries. Targeted agents could be nicely incorporated into the standard regimen to either improve efficacy and/or decrease treatment toxicity. Ongoing studies investigating the combination of targeted agent administration during or after induction chemotherapy or with concomitant chemoradiation regimens will help to better define the respective role of chemotherapy and targeted agents in the multimodal treatment of this disease. In addition, efforts to identify predictive biomarkers that could help to better select the patients who will benefit of a specific treatment modality are of crucial importance.

Keywords

Hypopharyngeal cancer • Head and neck squamous cell carcinoma • Conservation • Laryngopharyngectomy • Intensity-modulated radiation therapy • Laryngeal preservation • Lymph node metastases • Neck dissection

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28.1 Epidemiology, Etiology, and Molecular Biology

Hypopharyngeal cancer represents approximately 7–9 % of all cancers of the upper aerodigestive tract. The estimated incidence in the USA is 2500 cases per year [1]. In Belgium (11 million inhabitants), 214 new patients with hypopharyngeal cancers (9 %) were diagnosed in 2010. Most of them (75 %) are localized in the pyriform sinus, whereas the remaining 25 % occurred in another hypopharyngeal site (posterior pharyngeal wall: 20 %, postcricoid: 5 %) [2, 3].

The male/female (M/F) ratio is 3 in the USA for 5 in Belgium [1, 2]. Excessive alcohol and tobacco use remain the primary risk factors. Patients are typically 55–70-year-old men, heavy smokers, and drinkers. Although earlier reports from northern Europe indicated a link between Plummer–Vinson syndrome and other nutritional deficiencies inducing postcricoid cancers in women, hypopharyngeal cancer in women is currently more likely to be associated with alcohol and tobacco abuse than with deficiency diseases [4–6]. Most hypopharyngeal cancers are diagnosed in people older than 40 years. The mean age at presentation is 65 years. Human papillomavirus (HPV) seems to be implicated in the physiopathology of hypopharynx cancers, but at a lower extent than in oropharynx and oral cancers.

The occurrence of multiple tumors is not uncommon and the risk of second primary tumor is estimated at 25 % [7]. Many studies focused on molecular and genetic alterations do not make any distinction between different locations of head and neck squamous cell carcinoma (HNSCC). These genetic alterations are thoroughly described in Chap. 5. Briefly, the Epidermal Growth Factor Receptor (EGFR) is a transmembrane tyrosine kinase receptor belonging to the HER/erbB family and is overexpressed in up to 90 % of HNSCC [8]. Overexpression of EGFR, as well as high *EGFR* gene copy number, is associated with poor prognosis and radioresistance [9, 10]. Recently, deep sequencing technology has allowed a better characterization of the implicated genes [11, 12]. Somatic mutations in *TP53 (47–72 %), NOTCH1 (14–19 %), CDKN2A (9–22 %), PIK3CA (6–21 %), FBXW7 (5 %), HRAS (4–8 %), FAT1* (23 %), and *CASP8* (8 %) have been reported. Besides these mutations, some genes or their related proteins have been found to be altered by other mechanisms (amplification, deletion, epigenetic). In hypopharynx SCC specifically, 11q13 amplification (encodes, i.e., for cyclin D1) was reported in 78 % and loss of p53 heterozygosity in 70 % [13]. Recently, it was prospectively demonstrated that TP53 mutations, and particularly disruptive mutations of TP53, were associated with reduced survival. Mutations of TP53 were more frequent in hypopharynx SCC (75 %) than in other sites [14].

28.2 Anatomy and Pathways of Spread

28.2.1 Primary Site

The pharynx is a continuous structure, extending from the base of the skull to the upper esophagus, divided into three segments: nasopharynx, oropharynx, and hypopharynx according to anatomic landmarks (Fig. 28.1). The hypopharynx is roughly a triangular space, wide superiorly, extending from the oropharynx above (at the tip of the epiglottis or the level of the hyoid bone) to the upper esophagus below (at the lower end of the cricoid cartilage). Although it is closely connected with the posterior part of the larynx, the hypopharynx must be considered as a separate structure embryologically and anatomically. The hypopharynx is divided into three sites: the pyriform sinuses (right and left), the posterior hypopharyngeal wall, and the postcricoid region (Figs. 28.1 and 28.2).

The pyriform sinuses, so named for their pear shape, are paired and created by the invagination of the larynx into the hypopharynx. The medial wall is in close continuity with the lateral face of the larynx, and superiorly, it becomes the

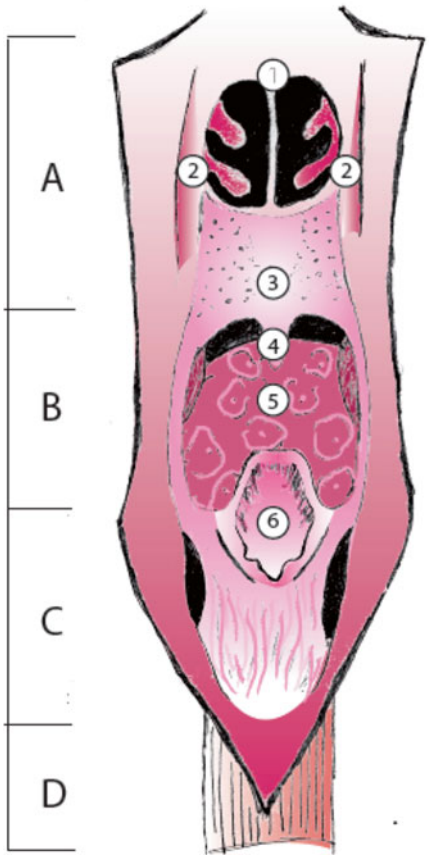

Fig. 28.1 Schematic view of the pharynx. *1* nasal septum, *2* pharyngeal opening of Eustachian tube, *3* soft palate, *4* uvula, *5* base of tongue, *6* epiglottis. (A) nasopharynx, (B) oropharynx, (C) hypopharynx, (D) esophagus

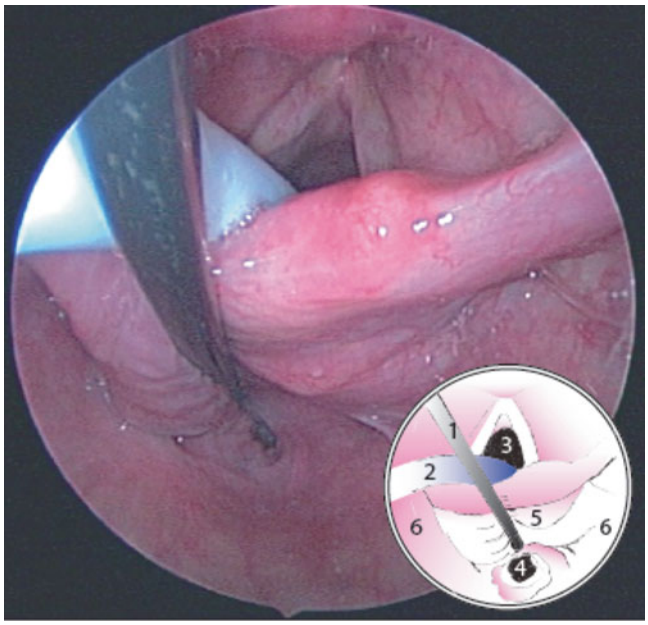

Fig. 28.2 Endoscopic view of the larynx and the hypopharynx. *1* suction tube, *2* endotracheal tube, *3* larynx, *4* upper esophagus, *5* postcricoid area, *6* piriform sinus

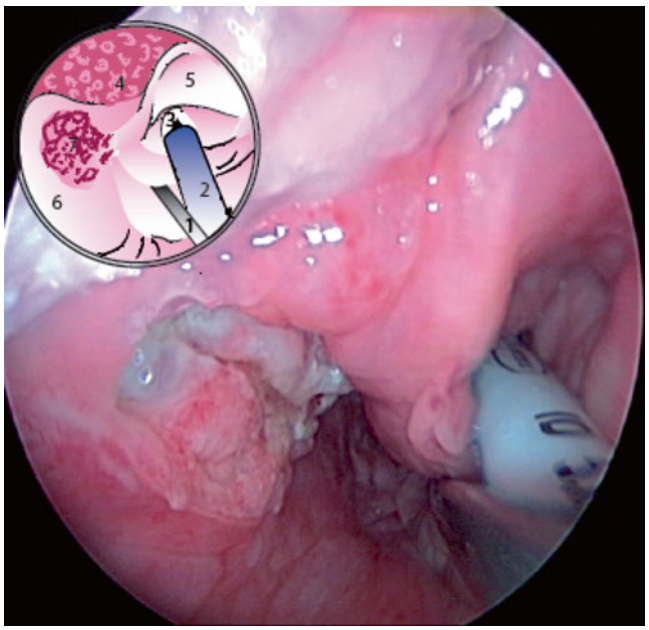

Fig. 28.3 Endoscopic view of a left piriform sinus tumor. *1* suction tube, *2* endotracheal tube, *3* larynx, *4* base of tongue, *5* epiglottis, *6* piriform sinus, *7* tumor

aryepiglottic fold. The lateral wall is a prolongation of the lateral wall of the oropharynx. The anterior wall is the region where the medial and lateral walls converge. The apex is the most inferior extent where the three walls merge, below the level of the vocal cords. The superior extent is bordered by the pharyngoepiglottic fold that extends from the lateral pharyngeal wall to the epiglottis. The posterior hypopharyngeal wall is in continuation with the posterior pharyngeal wall. Arbitrarily, the boundary between the oro- and hypopharyngeal walls is the level of the hyoid bone. It extends down to the upper esophageal sphincter. The posterior hypopharyngeal wall is formed by the constrictor muscles and is in direct contact with the prevertebral fascia posteriorly. The postcricoid region is the posterior surface of the larynx, extending from the arytenoids to the inferior edge of the cricoid cartilage and the upper esophagus. The pyriform sinus forms the posterior wall of the paraglottic space [15]. This close proximity to the posterior paraglottic space makes this a potential route for spread into the endolarynx, resulting often in fixation of the hemilarynx. Tumors of the medial wall of the pyriform sinus have a behavior very similar to supraglottic tumors arising from the aryepiglottic fold and it is often difficult to identify the origin of some of these lesions. Posteriorly, there is no barrier to stand in the way of tumor extension to the postcricoid area or crossing from the ipsilateral arytenoid to the contralateral arytenoids (Fig. 28.3). Tumors of the lateral wall have also few barriers to growth. They can extend medially to involve the posterior hypopharyngeal wall or anteromedially to involve the anterior and medial walls. They can easily invade the apex inferiorly and extend frequently submucosally to involve the thyroid cartilage and cricoid cartilage or directly the thyroid gland or soft tissue into the neck (Fig. 28.4a, b). Besides, they can extend down to the cervical esophagus through submucosal spread, making an accurate delineation of tumor extension very difficult. Their behavior may be similar to esophageal tumors with extensive spread along lymphatic spaces and skip lesions. Posterior hypopharyngeal wall tumors are infrequently diagnosed at early stage. They spread frequently along the mucosa to involve either the posterior or lateral oropharyngeal walls. At advanced stage, they can invade deeply the prevertebral tissue or even bone of the cervical spine (Fig. 28.5).

28.2.2 Regional Lymphatic Drainage

The head and neck region has a rich network of lymphatic vessels draining from the base of the skull through the jugular nodes, the spinal accessory nodes, and the transverse cervical nodes to the venous jugulo-subclavian confluent or the thoracic duct on the left side and the lymphatic duct on the right side [16, 17]. The whole lymphatic system of the neck is contained in the celluloadipose tissue delineated by aponeurosis enveloping the muscles, the vessels, and the nerves. Typically, the lymphatic drainage of the hypopharynx is bilateral; however, the lateral wall of the pyriform sinus only drains to the ipsilateral neck. Except level Ia (submental nodes), all node levels are at risk of harboring

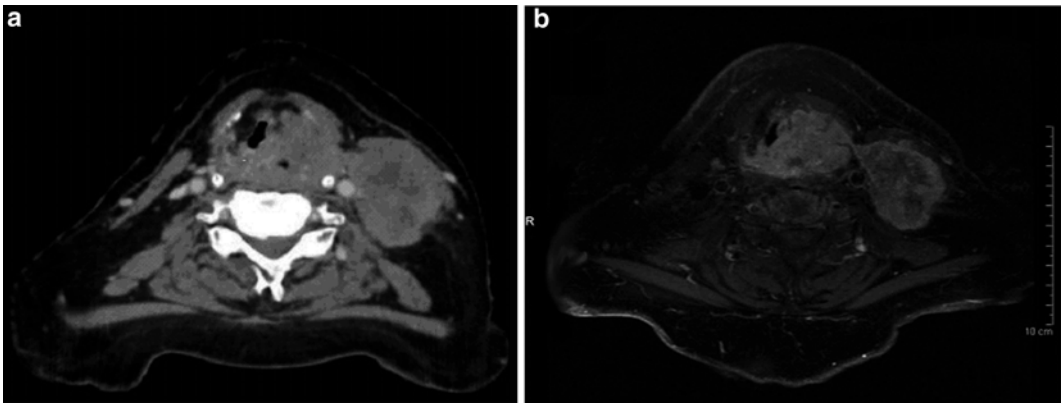

Fig. 28.4 Computed tomography (**a**) and magnetic resonance (T2-weighted) (**b**) images of an advanced pyriform sinus cancer invading the thyroid cartilage and directly extending to the soft tissues of the neck (T4a) with large lymph node metastasis (N3)

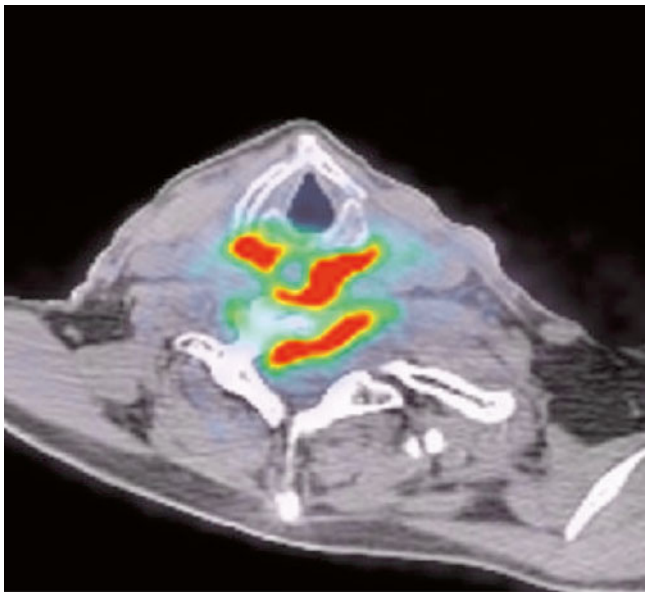

Fig. 28.5 PET-CT image of a posterior pharyngeal wall cancer with invasion of the prevertebral fascia and bone of the cervical spine

cells disseminating from hypopharyngeal primaries, but the highest incidence of nodal metastasis is observed in levels III and IV. In case of infiltration of the apex of the pyriform sinus and/or the pharyngo-esophageal junction, level VI is also at risk of nodal infiltration.

28.2.3 Distant Metastases

Patients with advanced hypopharynx cancer have a high incidence of distant metastases (60 %) [18]. Among patients locoregionally controlled, the incidence of distant failure was reported as 23 % [19, 20]. The lung is the most common site of distant metastases in 60–80 % of patients, followed by bones, liver, and mediastinal lymph nodes [18].

28.3 Clinical Manifestation, Work-Up, Staging Evaluation

28.3.1 Clinical Manifestations

The time between initial symptoms and diagnosis is typically longer than that for other HNSCC. When symptomatic, most hypopharyngeal tumors are already advanced. The most common symptom is chronic sore throat. Typically, pain is unilateral and well localized with or without referred otalgia. Other symptoms include varying degree of dysphagia, from foreign body sensation in the throat to inability to swallow solid or even liquid food. Aspiration is occasionally seen. A unilateral asymptomatic mass in the neck is often the initial symptom. Typically, metastatic lymph node is located in level II or III. The incidence of clinically positive lymph nodes upon initial clinical examination is very high, even in early tumors: 63–68 % for T1–T2 and 73–79 % for T3–T4 [21, 22]. Other symptoms, reported in more advanced lesions, include weight loss, hemoptysis, and hoarseness induced by direct extension into the larynx or recurrent nerve involvement. Dyspnea is present in very advanced tumors growing into the larynx. Because many patients are diagnosed at advanced stage, weight loss and malnutrition are common at presentation.

28.3.2 Work-Up

28.3.2.1 Clinical Examination

Clinical evaluation includes complete history of the disease and physical examination including weight and weight loss. Performance status (Karnofsky, ECOG-WHO) should be carefully assessed. Flexible fiberoptic endoscopy is the examination of choice, allowing assessment of the tumor size and extension to adjacent structures. Visualization of the pyriform sinuses may be optimized with the Valsalva

maneuver. All the upper aerodigestive tract must be meticulously assessed looking for synchronous second primaries. Lesions located in the apex of the pyriform sinus or postcricoid region are not always easy to see but may be suspected by either pooling of saliva or arytenoid edema [23]. Assessment of vocal cord mobility is paramount in medial wall tumors particularly. Neck palpation is required not only to detect enlarged lymph node but also for tumor evaluation. In advanced tumors, it is not infrequent to palpate the tumor by direct extension. A rigid endoscopy under general anesthesia remains a major step in the diagnosis. Tumor extension can be accurately delineated and biopsies of the tumor or any other suspicion of second primary can be performed. When required, teeth extraction is done simultaneously. In very advanced tumors with airway obstruction, tracheotomy can be also performed during the same procedure. The neck should be examined in a systematic fashion. Any lymph nodes should be assessed with regard to size, location, and mobility. On neck examination, loss of the grating sensation (laryngeal crepitus) of the laryngeal cartilages over the prevertebral tissues may indicate deep pharyngeal wall involvement.

28.3.2.2 Imaging for Locoregional Disease Evaluation

CT scan and/or MRI are essential to assess the primary tumor and regional lymph nodes. Imaging work-up can provide information about submucous tumor extension and cartilage involvement, leading to upstaging in a significant number of cases. The contrast-enhanced CT scan is typically used as the initial imaging modality and is generally considered as more useful for staging hypopharyngeal cancers. MRI tends to be superior to CT in predicting tumor invasion and is particularly indicated in the selection of patients suitable for conservation surgery [24]. Recently, criteria for diagnosis of invasion of laryngeal cartilage were reassessed and MRI was found as more accurate than CT [25]. CT and MRI are considered as of comparable value in the radiological evaluation of the neck relative to clinical exam [26]. Diffusion-weighted MRI (DW-MRI) was reported as a better tool for regional staging of HNSCC [27, 28] and data suggest that DW-MRI should be used routinely in the initial imaging work-up of HNSCC [28].

The role of 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) is emerging in the initial assessment of HNSCC. Integrated PET-CT overcomes poor anatomic localization of PET together with the morphologic data revealed by CT. In a meta-analysis totaling 1236 patients, it was however demonstrated that the accuracy of FDG-PET was only marginally superior to that of CT or MRI, thus questioning the routine value of FDG-PET for nodal staging [29]. A lot of work has been conducted on the use of PET for radiation treatment planning of HNSCC [30, 31], and it is likely that somehow metabolic imaging will affect the gross tumor volume (GTV) and hence the clinical (CTV) and planned target volumes (PTV).

28.3.2.3 Metastatic and Second Primary Evaluation

Despite a high specificity (94 %), chest X-ray has a low sensitivity (50 %) for the detection of pulmonary metastases [32]. Spiral chest CT is now routinely performed in the initial work. The sensitivity for the detection of distant metastases as well as for the detection of second primary in the lung is high. Use of FDG-PET was reported as detecting more distant metastases than conventional CT staging [33–35]. The results of a large prospective study have demonstrated that FDG-PET significantly improves the staging of HNSCC. The greater impact is due to the detection of metastatic or additional disease [36].

The incidence of second primary tumors of the upper aerodigestive tract varies from 3 to 15 %. The majority is detected within 2 years following diagnosis of the initial tumor [37]. Second primary cancers are common in patients with hypopharyngeal carcinoma. A high rate is reported for patients undergoing routine panendoscopy [37]. Routine esophagogastroscopy in the initial work-up is justified, based not only on the detection of second primary but also because many patients have gastroesophageal reflux leading to more or less severe esophagitis requiring medical treatment. On the other hand, routine bronchoscopy is no longer necessary. Second primary tumors in the lung or distant metastases are now better ruled out using spiral chest CT or FDG-PET-CT.

28.3.2.4 Patient Evaluation

A full dental evaluation is required before the beginning of radiotherapy. This step is critical because of xerostomia caused by radiotherapy potentially leading to dental decay and osteoradionecrosis. In case of significant denutrition defined as weight loss more than 10 % during the 6 months before diagnosis, nutritional improvement via enteral and hyperalimentary routes through a feeding tube is highly recommended before starting the treatment. Percutaneous gastrostomy is generally preferred to nasogastric feeding tube for long-term enteral support.

A complete blood count is routinely asked. Hepatic enzymes assess the liver function. Many patients have an underlying hepatic disease due to alcohol abuse. Serum creatinine is asked to assess renal function for general tolerance to therapy. If the serum creatinine concentration is elevated and platin-based chemotherapy (CH) is under consideration, 24-h creatinine clearance must be measured. Serum albumin and prealbumin are good indicators of the nutritional status. Baseline TSH level should be routinely asked [38].

28.3.2.5 Staging Evaluation

T staging for hypopharynx carcinoma is based on size, sites of involvement, and vocal cord mobility (as an indirect way to measure tumor extension). In 2002, the TNM staging system had subdivided T4 into resectable tumor, T4a, and unresectable tumor, T4b [39]. However, in the last edition of the TNM staging system, the concept of resectability disappears and T4a is further defined as a moderately advanced local disease and T4b as a very advanced local disease [40]. Typically, T4a hypopharyngeal cancer can invade thyroid or cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment, while T4b invades prevertebral fascia, encases carotid artery, or involves mediastinal structures. This change of definitions is probably proposed because there is confusion in the literature between "unresectable tumor" and "unresected" tumor. Some publications report results on medical treatments combining chemo- and radiotherapy in the so-called unresectable disease including tumors staged from T1 to T4 [41, 42]. Unresectable tumor means that the tumor is not resectable from an oncological point of view. This definition should not be amalgamated with an unresected tumor, which means that the tumor is theoretically resectable with free margins, but the multidisciplinary team, typically for functional reasons, decided to select a nonsurgical approach.

Regional staging (N) is uniform for all HN cancer sites with the exception of the nasopharynx. No changes were made in the seventh edition. Table 26.1 summarizes the details of T, N, and M stages for hypopharyngeal cancers.

Table 28.1 TNM classification of hypopharyngeal cancer

T staging
TX: The primary tumor cannot be assessed.
T0: No evidence of primary tumor is present.
TIS: The tumor is carcinoma in situ.
T1: The tumor is limited to one subsite of the hypopharynx and is 2 cm or less at its greatest dimension.
T2: The tumor involves more than one subsite of the hypopharynx or an adjacent site or is larger than 2 cm but not larger than 4 cm at its greatest diameter without fixation of the hemilarynx.
T3: The tumor is larger than 4 cm at its greatest dimension or involves fixation of the hemilarynx.
T4a: Moderately advanced local disease. The tumor invades the thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment, soft tissues, including prelaryngeal strap muscles and subcutaneous fat.
T4b: Very advanced local disease. The tumor invades the prevertebral fascia, encases the carotid artery, or involves mediastinal structures.
N staging
NX: The regional lymph nodes cannot be assessed.
N0: No regional lymph node metastasis is present.
N1: Metastasis is found in a single ipsilateral node (3 cm or less at its greatest dimension)
N2: Metastasis is found in a single ipsilateral lymph node (>3 cm but <6 cm in greatest dimension) or in multiple ipsilateral lymph nodes (none >6 cm at greatest dimension).
N2a: Metastasis in a single ipsilateral lymph node (>3 cm but <6 cm at its greatest dimension)
N2b : Metastasis in multiple ipsilateral lymph nodes (none >6 cm at greatest dimension)
N2c : Metastasis in bilateral or contralateral lymph nodes (none >6 cm at greatest dimension)
N3: Metastasis is found in a lymph node larger than 6 cm at its greatest dimension.
M staging
M0: No distant metastasis is present.
M1: Distant metastasis (e.g., lung, mediastinal lymph nodes, skeletal, hepatic) is present.
Stage grouping
Stage 0: TisN0M0
Stage I: T1N0M0
Stage II: T2N0M0
Stage III: T3N0M0, T1N1M0, T2N1M0, T3N1M0
Stage IV A T4aN0M0, T4aN1M0, T1N2M0, T2N2M0, T3N2M0, T4aN2MO
Stage IV B T4b any N M0, any T N3 M0 any T N3 M0
Stage IV C any T any N M1

Based on data from American Joint Committee on Cancer Staging [40]

28.4 Primary Therapy

28.4.1 Factors Affecting the Choice of Treatment

The management of hypopharyngeal cancer requires consideration of the tumor's localization and extension, the patient's age, performance status and patient's preference, the presence and extent of lymph node metastasis, and the anticipated functional outcome and long-term toxicity (Table 28.1).

28.4.1.1 Age

In general, advanced age is not a contraindication to treatment. Survival rates for patients over 75 years of age are comparable to other age groups [43]. However, in hypopharyngeal cancer, 5-year site-specific survival for patients older than 75 years is not more than 10 % with many patients eliminated from treatment consideration due to associated medical conditions [44]. In view of this poor prognosis, a palliative approach without surgery is often recommended in many of these patients [43].

28.4.1.2 Medical Status

When surgery is planned, medical contraindication is based on the preoperative assessment of anesthetic risk. Patients with a poor pulmonary function are clearly not good candidates for conservation surgery because these patients are at greater risk of aspiration and recurrent pneumonia.

Conservation surgery is indicated for early stage in patients who can tolerate some degree of chronic aspiration. Patients who are candidates for organ-preservation protocols combining CH and radiotherapy (RT) should have an adequate performance status and good hematological, hepatic, renal, and cardiovascular functions.

Prior RT in the head and neck for cancer located in another site requires a careful consideration of the dose and the volumes irradiated. In general, those patients are poor candidates for a full second dose of irradiation. Treatment combining surgery, concurrent CH, and reirradiation offers potential for long-term survival. Owing to the substantial toxicity and lack of an optimal regimen, reirradiation of recurrent head and neck cancer should be limited to clinical trials [45].

28.4.1.3 Lymph Node Status

In patients clinically N0, the volume that needs to be treated by neck dissection (ND) or RT should include levels II, III, and IV bilaterally, due to the high incidence of bilateral neck metastases [46].

Only patients with very early tumor of the lateral wall of the pyriform sinus are suitable for a unilateral treatment of the neck. In patients with advanced regional lymph node involvement, ND will be invariably followed by postoperative radiotherapy (PORT) or CH-RT with cumulated morbidity. For this reason, primary nonsurgical treatment seems preferable for those patients, with ND performed only for residual disease in the neck at completion of (CH) RT. Prior dissection or irradiation of the neck modified clearly the classic distribution of neck metastasis (levels II–IV). This concept must be kept in mind in patients with prior history of HN cancer.

28.4.1.4 Functional Outcome and Long-Term Morbidity

The functional deficit expected to result from a treatment is a useful parameter helping to the final decision when one or more options are supposed to produce equivalent locoregional control. For instance, either surgery or RT can be expected to control early lesions equally well. Surgery for an easy resectable lesion resulting in minimal functional deficit may be preferred over RT. Conversely, when surgery requires sacrifice such as larynx, due consideration must be given to organ-sparing nonsurgical approaches.

28.4.1.5 Patient's Preference

Finally, the patient's preference, his ability and willingness to cope with the treatment, and its functional consequences may also influence the decision. Logistic concerns and social factors must also be considered and the input of the social worker and the family is invaluable.

28.4.2 Treatment Modalities

28.4.2.1 Surgery

The emergence of organ-preservation strategies has dramatically limited the role of primary surgery in this setting. The surgeon is more frequently faced with failures of primary nonsurgical therapies. Besides the surgeon expertise, accurate selection of the patients suitable for surgery who require combination of large resection and well-vascularized flap reconstruction is key in salvage surgery. Advances in microrevascularized free flaps have considerably expanded the possibilities of reconstruction following resection of advanced tumors.

Partial Laryngopharyngectomy

Conservation surgery is rarely considered to be suitable because of either oncologic reasons or patient factors such as postoperative swallowing disorders [47, 48]. Early T1–T2 tumors show similar outcomes with RT or surgery. Operability needs to be determined by the possibility to perform voice-sparing surgery with clear margins and acceptable morbidity. Pathologic studies have shown that assessment of the extent of the disease based on endoscopic findings only was inaccurate [49]. Therefore, conservation surgery risks a high incidence of positive margins. Small lesions often discovered incidentally during a systematic work-up for a unilateral asymptomatic mass in the neck may be amenable to conservation surgery. Lesions that do not extend into the apex of the pyriform fossa, the posterior wall, or the postcricoid area may be resected while preserving the larynx. Tumors limited to the lateral wall of the pyriform fossa may be treated with a partial pharyngectomy (PP). Extension to the medial wall of the pyriform fossa without vocal cord fixation may be managed with a partial pharyngolaryngectomy (PPL). Superficial well-localized tumors of the posterior hypopharyngeal may present an opportunity for wide excision through pharyngotomy or laser resection. On the other hand, submucosal spread and fixation to prevertebral structures complicate resection.

Conservation surgery may be precluded in favor of RT in individuals with poor underlying pulmonary function or poor overall functional status, which prevents them from tolerating minor aspiration in the postoperative period. The absence of functional outcome data comparing conservation surgery with nonsurgical approaches complicates the treatment decision.

Transoral CO_2 laser resection: This approach involves specialized transoral endoscopes with an operating microscope coupled to a CO_2 laser. Proponents of this approach claim that it can be used to resect any tumor suitable for open conservation surgery, provided that adequate transoral exposure can be obtained [50, 51]. Transoral laser surgery holds the theoretical advantages of not violating other normal anatomic structures

of the anterior neck, as is required for the described open approaches and avoiding tracheotomy; thus, better functional outcome is suggested. Although an 87 % local control rate has been described using laser procedures in a series of 129 pyriform sinus cancers [50], these techniques have not been widely adopted, in part because of their technical difficulty and absence of data that fully substantiate functional outcomes that are superior to those of open procedures or nonsurgical therapy. These tumors require wide mucosal and muscular margins not always easily achieved using this transoral approach. An open approach is still necessary to perform ND. Moreover, many patients are treated with adjuvant PORT.

Partial lateral pharyngectomy: Small tumors confined to the lateral wall of the pyriform sinus or posterolateral wall of the hypopharynx are amenable to conservative PP [52]. Only T1 of the posterior or posterolateral wall of the hypopharynx extending from above the level of the cricopharyngeal muscle to the level of the tip of the epiglottis is suitable for the procedure. Technique of PP requires resection of the posterior third of the thyroid cartilage and the hyoid bone, the lateral wall of the pyriform sinus, and as much of the posterior hypopharyngeal wall as required for an adequate resection margin. If the defect is too large for primary closure, closure with a myocutaneous flap or free flap is preferred [53, 54]. In recent series, the 3-year local control rate using this approach was 88.5 %, but most of the patients had PORT [55]. Functional results are generally good with no aspiration or long-term dysphagia.

Partial pharyngolaryngectomy: This procedure is essentially an extension of the traditional supraglottic laryngectomy to include the medial wall of the pyriform sinus [56]. A few decades back, PPL had been proposed for early stage pyriform sinus cancer with favorable oncologic results [57, 58]. More recently, high local control rates have been reported [59]. Selected patients with a tumor located in the medial wall of the pyriform sinus may be treated with this procedure. The ipsilateral arytenoid cartilage and the vocal cord must be mobile and free of tumor. Involvement of the apex of the pyriform sinus and extensive submucosal spread are contraindications for this procedure.

More extensive pyriform lesions are resectable sparing the larynx provided that reconstruction was achieved using free flaps. PPL associated with an extended pharyngectomy may be indicated for tumors of the medial wall extending to the lateral wall of the pyriform sinus with possible extension to the posterior hypopharyngeal wall, preserving laryngeal function (Fig. 28.6) [60]. In cases of hemilaryngeal fixation, or invasion of the apex, a technique of wide vertical hemilaryngopharyngectomy (HLP), including the hemicricoid and hemithyroid cartilages and resection of the ipsilateral thyroid lobe, has been described. A free graft of costal cartilage was employed to restore laryngeal infrastructure in addition to the rest of the reconstruction [61]. In our experience of 34 cases with a majority of stage III and IV lesions, the 5-year local control rate was 86 % and 65 % of the patients remained disease free up to 5 years at 5 years [53]. Recently, we reported the outcomes of 13 patients who underwent conservative extended PPL with reconstruction achieved by using free flaps. At 12 months, no patient was gastrostomy dependent. At 3 and 5 years, the locoregional control was 100 % and 83 %, overall survival was 46.3 % and 30.8 %, and disease-specific survival was 54.5 % and 36.4 %, respectively. These results suggest that in selected patients, extended conservative surgery is an organ-preservation surgical procedure that may challenge organ-preservation approaches combining CT and RT [62].

Supracricoid hemilaryngopharyngectomy: supracricoid HLP can be performed for lesions involving the aryepiglottic fold and medial, anterior, and lateral wall of the pyriform sinus [63]. The procedure includes resection of the ipsilateral half of the hypopharynx, the entire hemithyroid ala, including the hemilarynx, the pre-epiglottic space, and one

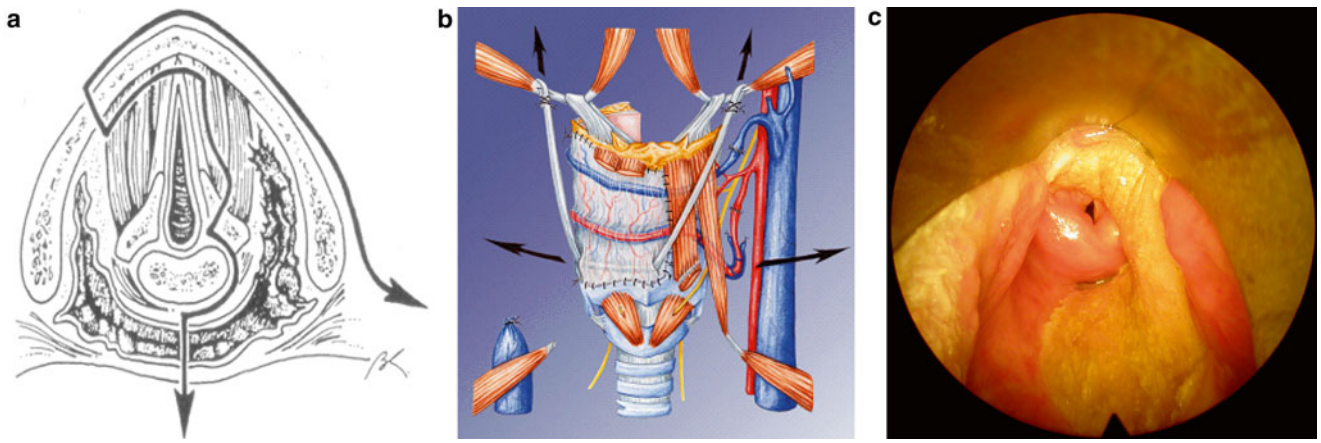

Fig. 28.6 Extended partial laryngopharyngectomy. Reconstruction using a stretched radial forearm free flap (**a**, **b**, **c**). (**a**) Reprinted from Hamoir et al. [60]. With permission from John Wiley & Sons. (**b**): Adapted from Hamoir et al. [62]. With permission from John Wiley & Sons

arytenoid. Contraindications are invasion of the apex or postcricoid region, invasion of the posterior hypopharyngeal wall, and fixation of the ipsilateral vocal cord. Early decannulation is usually possible, and rates of local control and laryngeal preservation of more than 90 % have been recently reported in a series where almost all patients had induction CH and 50 % of them had PORT [64]. Although the postoperative course is often marked by a gradual recovery of swallowing ability, more than 90 % of patients no longer depended on gastrostomy tube at 1 year after surgery, in the largest published series [65].

Posterior partial pharyngectomy: Occasionally, limited midline posterior pharyngeal wall tumors are amenable to this approach, which involves creating a unilateral or bilateral lateral pharyngotomy opening up to the level of the lateral wall of the pyriform sinus. This approach may be combined with an anterior opening of the vallecula, above the hyoid bone. This allows direct exposure and resection of the posterior wall, typically to the depth of the prevertebral fascia.

Reconstruction requires use of a thin flap. Radial forearm flap or split jejunal transfer is used to reconstruct the pharyngeal wall [66].

Near-total laryngopharyngectomy: The procedure proposed by Pearson preserves one uninvolved arytenoid with a portion of the thyroid cartilage, recurrent laryngeal nerve, and a thyroarytenoid muscle to allow creation of a permanent tracheoesophageal shunt allowing lung-powered speech. However, the patients remain dependent on a permanent tracheostomy [67]. Near-total laryngopharyngectomy (NTLP) can be considered in patients with T2 and T3 lesions of the pyriform sinus in whom total laryngectomy is contemplated. Vocal cord fixation is not a contraindication. The resected specimen includes the entire hemilarynx from the base of the tongue to the trachea, the pyriform sinus, and part of the posterior pharyngeal wall, if indicated. The remaining contralateral posterior glottic tissues are reconstructed to form a semirigid tracheoesophageal shunt to allow phonation and effective swallowing. Reconstruction of the pharyngeal defect with a skin graft or myocutaneous flap is usually necessary to prevent pharyngeal stenosis [68].

NTLP has been used successfully by a limited number of surgeons with good locoregional control and minimal aspiration. In the Mayo Clinic experience, local control was reported as similar to that expected with TLP and conversational voice was achieved in 85 % of patients [68]. This procedure is not recommended for salvage after radiation failure, postcricoid or interarytenoid tumors, bilateral vocal cord fixation, and tumors approaching the posterior midline.

Preoperative Details

Prior to treatment, the risks and benefits of treatment options should be frankly discussed with the patient. This should specifically address possible severe swallowing and speech dysfunction. Before treatment, a thorough speech therapy evaluation is necessary.

Total Laryngopharyngectomy ± Esophagectomy

Many patients are not suitable for conservation surgery and require total laryngectomy in combination with partial or total pharyngectomy and cervical esophagectomy. Total esophagectomy can be performed in combination with TLP if the tumor is extended below the cervical esophagus or in case of second primary [69].

Primary surgical procedures that do not spare the larynx are typically reserved for T4a tumors, as well as for some smaller tumors in which laryngeal function after primary CH-RT is expected to be poor. In contrast, T2–T3 lesions that involve the pyriform sinus apex or postcricoid region may require TLP for surgical cure and are thus deemed better candidates for organ-preservation protocols.

Total Laryngopharyngectomy: Some hypopharyngeal cancers can be resected by total laryngectomy with partial pharyngectomy. The pharyngeal defect is usually closed by primary closure. Because submucosal spread of hypopharyngeal tumors mandates wide margins, primary closure is sometimes not possible. If the pharyngeal defect is more extended or in a salvage situation after radiation failure, pedicled flap or free-tissue transfer is often required. Use of a pectoralis major myocutaneous flap usually allows a single-stage closure [70, 71]. Most advanced tumors operated by TLP, including the cervical esophagus, invariably require pedicled or free-tissue transfer for restoration of swallowing function.

Reconstruction of the hypopharynx and cervical esophagus is largely determined by the size of the defect, the availability of microvascular expertise, and the medical conditions of the patient. These defects can be reconstructed either by various tubular fasciocutaneous free flaps or pedicled myocutaneous flaps, but the preferred method of reconstruction is a free jejunal interposition [72, 73]. Free jejunal transfer has the advantages of fewer mucosal sutures, to be naturally tubular, and to be harvested endoscopically. Longer segments of jejunum can be harvested for defects extending to the nasopharynx. Radial forearm flap has the advantages of ease of harvest and avoidance of intra-abdominal surgery. However, in salvage situation or in patients with poor general status, use of a tubular pectoralis major myocutaneous flap has the cumulated advantages of a rapid reconstruction and the transfer of a large amount of well-vascularized muscle into the neck to protect the great vessels [74]. A salivary bypass is usually placed between the oropharynx and the esophagus to prevent stenosis and postoperative fistula. Typically, the bypass is removed endoscopically a few weeks following surgery.

Surgery with curative intent is contraindicated in T4b patients with prevertebral musculature or cervical spine involvement, massive mediastinal nodal enlargement, and carotid artery involvement.

Total Laryngopharyngectomy with Total Esophagectomy: TLP with esophagectomy includes the resection of the larynx, circumferential hypopharynx, and varying lengths of the esophagus. When the lesion involves the esophagus, usually a total esophagectomy is recommended. Gastric transposition or gastric "pull-up" is indicated when total esophagectomy is necessary. Gastric transposition for esophageal replacement after laryngopharyngectomy was first reported in 1960 [75]. Elimination of the thoracotomy lessened the morbidity and mortality of the procedure and produced great improvements in results [76]. Further modifications and improvements were subsequently reported [77, 78]. Gastric transposition remains the most satisfactory one-stage method of reconstruction. However, the patient must be sufficiently healthy to withstand this extensive operation successfully. If the stomach is not suitable for use, the posterior mediastinal route can be used for left colon interposition [77, 79].

Neck Dissection: Indications and Types

Hypopharyngeal tumors have a high propensity for neck node metastases. At the time of diagnosis, 70 % of patients have clinically lymph node involvement [21, 22]. In addition, the incidence of patients with occult metastases is ranged between 17 and 56 % [80–82]. This is most likely in pyriform sinus and posterior pharyngeal wall tumors and least likely in postcricoid tumors [80].

Consequently, for patients with SCC of the hypopharynx clinically N0, selective treatment of the neck is appropriate. Typically, levels II–IV should be treated. For tumors with invasion of the apex of the pyriform sinus or with esophageal extension, level VI nodes should also be included.

Similar guidelines could also be recommended for N1 patients without radiological evidence of extracapsular spread (ECS) [83]. For patients with multiple nodes (N2b), available data suggest that adequate treatment should include levels I–V. As for N0 patients, level VI should also be treated for tumors with esophageal extension. In tumors of the pharynx, the risk of contralateral neck metastases increased with involvement of the ipsilateral neck [84]. Bilateral neck metastasis may develop because of rich submucosal lymphatics, which cross the midline. One could recommend restricting the treatment to the ipsilateral neck for tumors of the lateral wall of the pyriform sinus only. In the other situations, prophylactic contralateral neck treatment is recommended. The selection of the node levels to be treated should follow similar rules to those for the ipsilateral neck.

Elective ND and elective neck irradiation are equally effective in controlling the N0 neck. The choice between these two procedures will thus generally depend on the treatment modality chosen for the primary tumor, which in turn mainly depends on the institutional policy. The basic rule that should guide the choice between surgery and RT is to favor the use of a single modality treatment to avoid overtreatment. For instance, for a T1N0 pyriform sinus carcinoma, conservation surgery plus selective neck dissection (SND) or primary RT on the hypopharynx and the neck are equally effective therapeutic options. For such stage disease, the need for PORT is indeed quite low.

Conversely, for a patient staged T1N2b, a conservative treatment with (CH) RT should be favored, because of the necessity of PORT in case of primary surgery and the non-superiority of the surgical approach.

SND were initially proposed for clinically node-negative patients and, later on, extended to clinically node positive patients. Originally, SND was typically considered as a method to accurately stage the neck but without impact on regional control and survival. After SND, the rate of neck failure in undissected levels is low, typically below 10 %. In our hands, the overall neck failure rate was 3 % [85]. This low rate of neck failure is in accordance with most series reporting neck failure rates ranged from 3.5 to 15 % [80, 82, 86–88]. SND can be actually considered as the optimal procedure to manage surgically the N0 neck in patients with a high risk of occult lymph node metastasis.

The surgical management of the N1 neck is more controversial. Traditionally, radical neck dissection (RND) and modified radical neck dissection (MRND) have been the standards for patients presenting with neck disease. Andersen et al. reported that the rate of regional recurrences in the dissected neck following RND or MRND type I for N1 or N2 disease was similar [89]. Selective procedures have however gained popularity. Schmitz et al. reported a regional failure rate of 8 % in necks staged pN1 without better regional control in the necks treated with PORT, suggesting that PORT is not justified in pN1 necks without ECS [85]. Accordingly, it appears that SND for patients with limited neck disease is a safe procedure, providing that PORT is given in the presence of risk factors for regional relapse. In patients who were found to have more than one pathologically invaded lymph node following SND, PORT is clearly indicated. Despite the use of aggressive treatment protocols, patients with advanced metastatic neck disease still have poor prognosis because of high risk of regional failure and distant metastases [19]. However, the concept of less than radical procedure has gained acceptance during the last decade even in advanced regional disease. Khafif et al. reported the results of 118 patients with N2–N3 disease, treated with RND or MRND, and were not able to find any difference in overall survival between the two groups [90]. In a study comparing RND and MRND (type I) in 212 patients with stages N2 and N3, the MSKCC group reported an overall 86 % 5-year neck control rate and 61 % 5-year actuarial survival rate [89]. No difference was found between the two groups. PORT enhances regional control but does not seem to significantly improve survival [91]. Clark et al. reported the outcome of 181 patients who had 233 NDs for N2-N3 disease (163 extended

RND, RND or MRND, and 70 SNDs) [92]. PORT to the neck was given in 82 % of the patients. At 5 years, the control of disease in the treated neck was achieved in 86 %. Adjuvant RT improved neck control but did not improve overall survival. The benefit of postoperative RT combined with CH was demonstrated for patients with ECS in two prospective trials conducted by the EORTC and the RTOG and is discussed further [93, 94].

28.5 Intensity-Modulated Radiotherapy

28.5.1 Patient Setup

Typically, patients treated by RT for HNSCC will lie in supine position with the head and neck immobilized by some form of thermoplastic mask. They will undergo a planning CT scan in treatment position. The use of intravenous contrast medium and reconstruction in thin (e.g., 2.0–2.5 mm) slides is recommended.

With the use Intensity-Modulated Radiation Therapy (IMRT), there is no standard recipe anymore on how to set up the field sizes and borders according to bony landmarks. Instead, the irradiation technique should be selected and adapted so that the entire PTV receives the prescribed dose within the adopted dose–volume constraints and in full respect of the ICRU recommendations.

In that respect, it should be mentioned that a new ICRU report has been published integrating recommendations on dose prescription, specification, and reporting for IMRT [95].

28.5.2 Delineation of Target Volumes

The macroscopic tumor or Gross Tumor Volume (GTV) is typically delineated on contrast-enhanced CT. The use of FDG-PET/CT has been shown to translate into smaller GTV and thus could be of additional value [30]. The delineation of the primary tumor prophylactic Clinical Target Volume (CTV) is based on the compartmentalization of the head and neck area (e.g., parapharyngeal space, pre-epiglottic space) and on the presence of weak (e.g., epiglottis) or strong (e.g., hyo-epiglottic ligament, bone cortex) barriers. For hypopharyngeal tumors, it is recommended to include between 10 and 15 mm of mucosa from the GTV owing to the submucosal infiltration described in those tumors [96]. For piriform sinus tumor, it is recommended to include the ipsilateral thyroid cartilage. For the therapeutic CTV, a 5–8 mm margin from the GTV is typically recommended with correction for air cavities.

Regarding the delineation of the neck node CTV, in collaboration with representatives of the major European and North American clinical cooperative groups, an international set of guidelines has been published in the early 2000s for the node-negative neck [97]. In the late 2000s, a few amendments were proposed to take into account the specific situation of a node-positive and postoperative neck [98]. More recently, a task force comprising opinion leaders in the field of head and neck radiation oncology from European, Asian, Australian/New Zealand, and North American clinical research organizations (DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG) was formed to review and update the previously published guidelines on nodal level delineation [99]. The updated 2014 consensus guidelines for neck node delineation are presented in Fig. 28.7. The volumes delineated in this figure correspond to the CTV and do not include margins for organ motion or setup inaccuracy. The boundaries are based on a patient lying supine with the head in a "neutral" position.

It is beyond the scope of this chapter to discuss in depth these guidelines. The reader is referred to the original publication. In short, based on the nomenclature proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery, and in alignment with the TNM atlas for lymph nodes in the neck, 10 node groups (some being divided into several levels) were defined with a concise description of their main anatomic boundaries, the normal structures juxtaposed to these nodes, and the main tumor sites at risk for harboring metastases in those levels. Emphasis was placed on those levels not adequately considered previously (or not addressed at all); these included the lower neck (e.g., supraclavicular nodes or levels IVb and Vc), the scalp (e.g., retroauricular and occipital nodes, or levels Xa and Xb, respectively), and the face (e.g., parotid nodes and buccofacial or levels VIII and IX, respectively). The proposal for the node level delineation is valid irrespective of the nodal status of the patient, i.e., node negative or node positive. However, the translation from the node levels to CTV delineation may need some adjustments as a function of the nodal status setting. In the node-negative patients and in patients with a single small lymph node or with several small lymph nodes not abutting one of the surrounding structures (e.g., muscle, salivary gland), the CTV will be defined by the association of one or several of the node levels. For larger lymph nodes abutting or infiltrating one of the surrounding structures (e.g., sternocleidomastoid muscle, the para-spinal muscles, or the parotid gland), CTV delineation may need to take into account macroscopic and microscopic tumor infiltration outside of the node. Based on experts' opinion, an isotropic expansion by 10–20 mm into these structures from the visible edge of the node (i.e., the nodal GTV) appears reasonable, excluding bone and airway [100]. Last, the proposal for the node level delineation still holds for the postoperative situation, at least from a conceptual point of view.

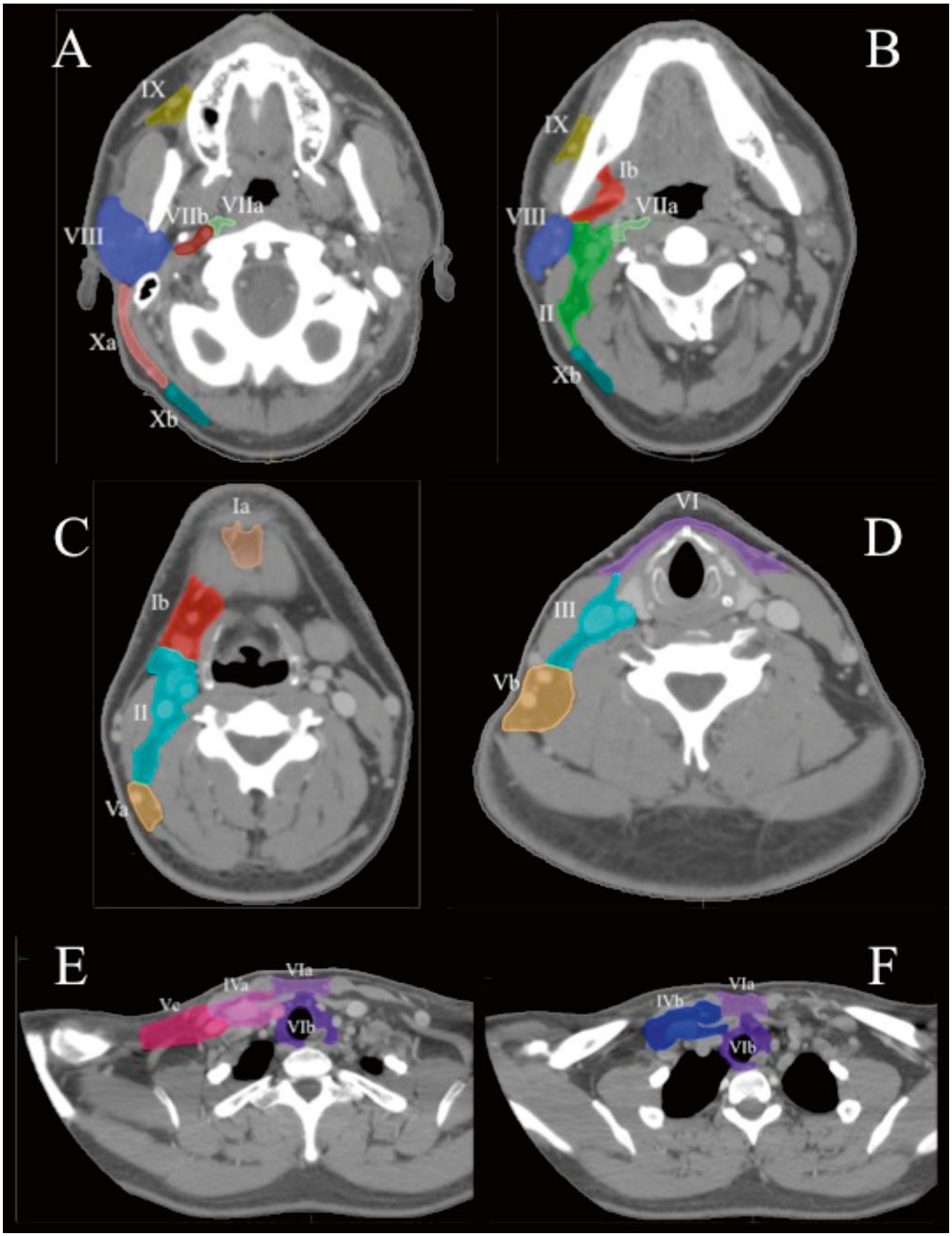

Fig. 28.7 Consensus guidelines for the delineation of neck node levels. Each LN level corresponds to the clinical target volume and does not include any security margin for organ motion or setup inaccuracy. Reprinted from Grégoire et al. [99]. With permission from Elsevier

28.5.3 Dose Prescription, Fractionation, and Overall Treatment Time

The dose prescription depends on various factors, e.g., prophylactic versus therapeutic RT, the use of combined modality treatment, planned ND, PORT, etc., which is beyond the scope of this section for comprehensive review. Typically, for early tumor stage (e.g., T1 or small T2, node-negative neck), a prophylactic dose in the order of 50 Gy in 2 Gy per fraction over 5 weeks and a therapeutic dose in the order of 64–66 Gy in 2 Gy per fraction over 6.5 weeks will be prescribed.

For these small tumors, a simultaneous integrated boost (SIB) technique has been reported, using a therapeutic dose of 69 Gy delivered in 30 daily fractions of 2.3 Gy and a prophylactic dose of 55.5 Gy delivered in 30 daily fractions of 1.85 Gy [101].

For larger T stage (e.g., T3 and T4) and node-positive neck, a therapeutic dose in the order of 70 Gy in 2 Gy per fraction over 7 weeks will be typically prescribed combined or not with concomitant chemotherapy or targeted agents such as epidermal growth factor receptor (EGFR) inhibitor. In this setting, a prophylactic dose of 50 Gy (delivered as 25 daily fractions of 2 Gy followed by a 20 Gy boost dose to the therapeutic volume) or of 54.25 Gy (delivered as 35 daily fractions of 1.55 Gy using a SIB technique) is typically proposed. In some clinical situations, hyperfractionation or accelerated fractionation may be proposed. Typically, hyperfractionation will deliver a therapeutic dose of 80.5 Gy in 70 fractions of 1.15 Gy delivered twice daily; a moderately accelerated regimen will deliver 70 Gy in 6 weeks using 2 Gy per fraction 6 times a week; very accelerated regimens will deliver a lower total dose in overall time that may range from 10 days to 3–4 weeks.

For PORT with or without concomitant CH, depending on the risk factors, doses will range from 60 to 64–66 Gy, in 2 Gy fraction over 6–6.5 weeks. There is still a debate whether a lower dose (e.g., 50 Gy) should be prescribed in low-risk areas. Also should PORT always include both sides of the neck or only the side where the risk factors have been individualized? There is no firm answer to these questions, but there are some unpublished data to suggest that more selective irradiation could be safely delivered in a postoperative setting.

28.6 Chemotherapy

Platinum-based CH is the backbone of systemic treatment in HNSCC. Untreated HNSCC is a chemosensitive disease and therefore chemotherapy is frequently administered in combination with RT as a part of the multimodal curative treatment. Cytotoxic agents are often used in recurrent and/or metastatic disease for palliation. In the curative indications, CH has been investigated before (induction), after (adjuvant), or concomitantly to RT.

When part of the multidisciplinary approach, cisplatin, 5-fluorouracil (5-FU), and docetaxel (TPF) combination is currently the standard of care as induction CH. Three phase III trials in which induction therapy was followed by RT have demonstrated the superiority of TPF over cisplatin and 5-FU (PF) in unresectable disease, low surgical curability (stage 3 or 4) disease, or larynx preservation [42, 102, 103]. Objective response rate (ORR) after CH was 68–80 % with TPF compared with 54–64 % with PF [42, 102, 103]. The main clinically relevant adverse event is grade 3 and 4 neutropenia occurring in 76–83 % of the patients. Antibiotic (ciprofloxacin 500 mg, orally twice daily, day 5–15) and/or granulocyte-colony stimulating factor (G-CSF) prophylaxis is recommended. The rate of febrile neutropenia despite the use of antibiotic prophylaxis, however, remains between 5 and 10 %.

The most frequent regimen given concomitantly with radiation therapy is high-dose cisplatin (100 mg/m^2, 3 times during RT). Due to toxicities, only two-thirds of the patients are able to receive the three planned injections of cisplatin in randomized clinical trials. Weekly cisplatin administration, with a cumulative dose beyond 200–240 mg/m^2, might be an alternative. However, no prospective randomized trials with enough power have compared 3-weekly and weekly cisplatin administration and this invalidated regimen is not recommended on a routine basis. Cisplatin or carboplatin in combination with 5-FU and other polyCH regimens including either platin or 5-FU were shown to be equally effective to high-dose cisplatin in a meta-analysis [104, 105].

Mono-CH regimens with another drug than cisplatin are inferior and should not be used in clinical routine. Adding CH to RT increases toxicity, mainly mucositis. Grade 3–4 mucositis occurs in more than 60 % of the patients treated with CH-RT [106–108]. Nausea, vomiting, renal deficiency, and hematotoxicity are typical adverse events related to CT. To limit treatment interruption or delay, this acute morbidity requires intensive supportive care including feeding tubes when appropriate, adequate hydratation (sometimes in hospitalization), and pain management.

CT has been studied in the palliative disease. The most frequently used regimens are cisplatin or carboplatin combined with 5-FU and weekly methotrexate.

28.7 Targeted Therapy

28.7.1 Epithelial Growth Factor Receptor Inhibitors

The EGFR is a member of the HER tyrosine kinase growth factor receptor family. It is a transmembrane glycoprotein, which is commonly expressed in many normal human tissues.

The intracellular domain of EGFR is activated upon ligand fixation and triggers tyrosine kinase signal transduction pathways involved in tumor proliferation, apoptosis, angiogenesis, and cell migration/invasion [109]. Its expression is frequently dysregulated in many cancers including HNSCC. Preclinical studies as well as phase I and II trials have demonstrated that pharmacologic interventions that abrogate EGFR dysfunction have antitumor activity [110]. In addition, some inhibitors of EGFR have synergism with CH and RT in preclinical models [110, 111].

The most studied and investigated EGFR inhibitor is Cetuximab. Cetuximab is a chimeric IgG1 monoclonal antibody that specifically binds to the EGFR with high-affinity, blocking ligand-induced EGFR phosphorylation [112]. The main side effects of Cetuximab monotherapy are acne-like skin reactions and rarely hypersensitivity. The recommended dose is a loading dose of 400–500 mg/m^2 and a maintenance weekly dose of 250 mg/m^2.

Panitumumab and Zalutumumab are two other monoclonal antibodies targeting EGFR that have been investigated in phase III trials for HNSCC [113, 114]. In contrast to Cetuximab, Panitumumab and Zalutumumab are fully human monoclonal antibodies limiting the risk of hypersensitivity. However, neither Panitumumab nor Zalutumumab has been shown to improve overall survival in HNSCC and so they are not used routinely.

EGFR tyrosine kinase inhibitors are orally available small molecules. The two main compounds are erlotinib and gefitinib. No significant activity has been detected in randomized trials in HN cancer [115]. More recently, a new generation of HER inhibitors, the irreversible small molecule pan-HER inhibitors including afatinib and dacomitinib, have shown promising activity in palliative HNSCC [116, 117]. By covalently binding and irreversibly blocking all kinase receptors from the ErbB family, a prolonged inhibition is obtained with the aim of improving clinical activity.

28.7.2 Treatment Selection

Despite advances in treatment modalities, hypopharyngeal SCC remain the most lethal cancer of the upper aerodigestive tract. Overall poor results are related to an anatomic disposition predisposing to silent evolution and the rich lymphatic network draining the hypopharynx, increasing the risk of regional metastasis [118]. Only 30 % of patients have local disease at the time of diagnosis when 60 % have locoregional disease and 10 % present with distant metastases. More than 20 % of patients locoregionally controlled will develop distant metastases [19, 20]. Whatever the therapeutic modality used, overall 5-year survival rates do not exceed 50 % [118–120]. In selected patients with early lesions, the 5-year survival rate is about 60 % [53], but in patients with advanced stage, overall survival ranges from 25 to 40 % at 5 years [121–123]. It seems logical to favor laryngeal preservation approaches either surgically or nonsurgically without compromising locoregional control and survival.

28.8 Early Tumors (T1-N0, N1, T2-N0, N1)

28.8.1 Surgery Versus Radiotherapy

The cornerstone supporting guidelines for the selection of treatment in early tumors should favor the use of a single therapeutic modality. For patients with T1 or T2N0, conservation surgery plus SND and primary RT are equally effective therapeutic options. For such stage disease, the need for PORT is indeed quite low. Voice-sparing surgery is a reasonable option as patients may be cured with limited morbidity and no further treatment (Fig. 28.8a). For patients N1, surgery could be less an option owing to the higher risk of PORT. For a patient staged N2, N3, a conservative treatment with (CH)RT should be favored, because of the necessity of PORT or PORT combined with CH in case of primary surgery and the nonsuperiority of the surgical approach. RT is an option for nonoperable patients, patients refusing surgery, and when conservation surgery is not indicated. For T1, 64–66 Gy standard fractionation is indicated when T2 should be treated with altered fractionation.

28.9 Locally Advanced Tumors (T3, T4-Any N)

28.9.1 Voice-Sparing Surgery

Typically, surgery should be considered as the treatment of choice for patients staged T4a (Fig. 28.8b). Adjuvant PORT has been demonstrated to improve locoregional control and overall survival [124, 125].

Conservative surgery is rarely considered for advanced tumors because of either oncologic reasons or functional reasons. Reported series of voice-sparing surgery include a large majority of T1–T2 and less than 10 % of T3–T4 [53, 57, 59, 120, 126, 127]. Selected T3–T4 of the pyriform sinus are operable using sophisticated voice-sparing procedures [61, 62]. However, those procedures require considerable expertise and reported results are generally not reproducible in other institutions. NTLP can be considered in patients with T2 and T3 lesions of the pyriform sinus [68].

This operation has been used successfully by a limited number of surgeons with good results. But patients remain tracheostomy dependent. Lecanu reported a series of T3–T4 treated by conservation surgery after induction chemotherapy [128]. The laryngeal functions were preserved in 54 % of the patients who were alive at 3 years. This innovative

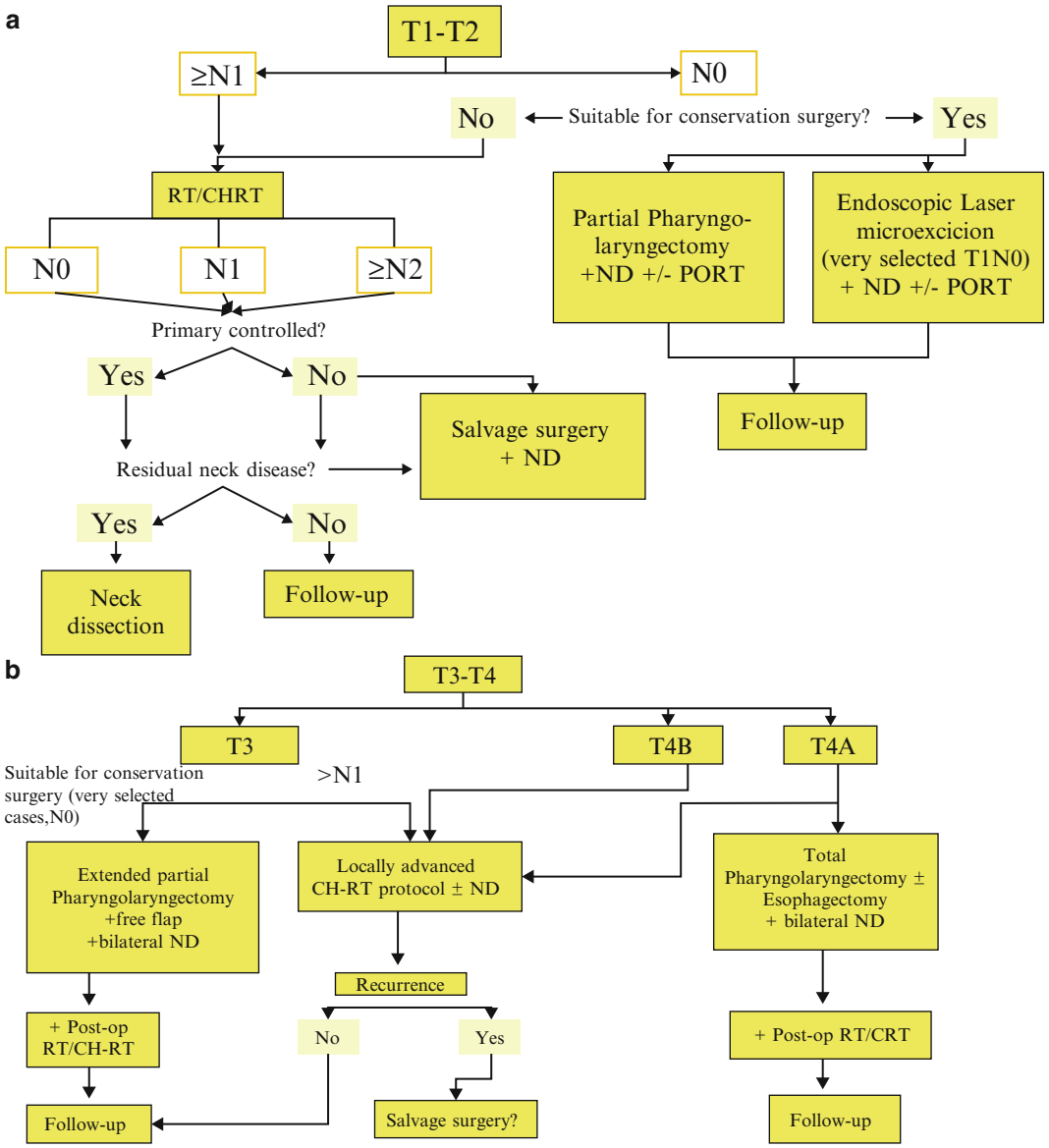

Fig. 28.8 Treatment algorithms for patients with cancer of the hypopharynx. (**a**) Early tumors, (**b**) advanced tumors

concept of "therapeutic de-escalation" allowing a less morbid surgery for good responders to an induction therapy needs, however, to be validated in prospective trials.

28.10 Organ-Preservation Strategy

28.10.1 Altered Fractionation

In the 1980s and early 1990s, several randomized studies have been conducted to validate the use of altered fractionation regimens, i.e., hyperfractionation and accelerated fractionation. A meta-analysis concluded that the use of altered fractionation was associated with an absolute increase in locoregional control by 6.4 % at 5 years and an absolute increase in survival by 3.4 % at 5 years [129]. The benefit was larger for hyperfractionation than for accelerated regimens, especially when comparing to those regimens with a reduction in total dose (very accelerated regimens). The benefit was larger for younger patients, most likely due to observation of extra deaths in the elderly population due to intercurrent diseases.

All these regimens were associated with an increase in acute mucosal toxicities, but no increase in late toxicities was reported providing that enough interfraction time was left [130–132]. Indeed, in an EORTC trial with only a 4 h interfraction time, a 50 % risk of fibrosis was documented at 5 years after treatment [133].

In summary, altered fractionation regimens (especially hyperfractionation) can be recommended for moderately advanced stage tumors (e.g., T1-N1, T2-N0, T2-N1) as well

as for locally advanced stage patients for whom there is a contraindication to the use of CH or Cetuximab in association with RT. As already mentioned earlier, for moderately advanced stage tumors, the use of SIB-IMRT is an elegant way to accelerate the radiation treatment with dose per fraction slightly higher than 2 Gy [101].

28.10.2 Concomitant Chemoradiotherapy

Concomitant CH-RT with a platinum compound is the standard of care when a nonsurgical organ-preservation approach is proposed. Most of the studies that compared concurrent CH-RT versus RT alone were generally multisites. These trials demonstrated that the addition of CH to RT improves local control and overall survival [107, 108, 134]. A meta-analysis including operable and nonoperable HNSSC patients confirmed that survival was better when CH was given concomitantly to RT compared with the neoadjuvant or adjuvant approaches [104, 105]. However, it was reported that the benefit of concomitant CH-RT might be decreased in elderly patients [105].

The reason is unknown, but might be due to reduced dose intensity in elderly patients as a consequence of acute toxicity and/or to an increase in intercurrent death. Is concomitant CH-RT better than hyperfractionation or accelerated and is the combined approach (i.e., concomitant CH-altered fractionation RT) even better? A three-arm study conducted by the French cooperative group GORTEC compared (1) concomitant CH-RT (70 Gy in 7 weeks and 3 courses of carbo-5-FU), (2) concomitant CH-accelerated RT (70 Gy in 6 weeks and 2 courses of carbo-5-FU), and (3) very accelerated RT (64.8 Gy in 3.5 weeks) [135]. No significant difference in survival was observed between the 3 arms, although there was a small advantage to concomitant chemo-RT over the 2 other arms.

All studies comparing RT to concomitant CH-RT were associated with a significant increase in acute locoregional toxicity. Typically, the percentage of grade 3 acute mucositis and pharyngitis reached values up to 80–90 %, representing thus the upper limit of what is clinically tolerable by patients [106, 108, 135]. These studies were also associated with an increase in late toxicities [136, 137]. But it needs to be emphasized that all the mentioned studies were conducted in the pre-IMRT area, and that with the systematic use of highly conformal radiation techniques, a reduction of such toxicities is expected.

In summary, the concomitant use of CH (3-weekly high-dose cis-platinum-based regimen) and RT represents the standard nonsurgical regimen for locally advanced HNSCC. It is associated with an increased acute toxicity requiring careful management and follow-up of patients during treatment.

28.10.3 Concomitant EGFR Inhibitors and Radiotherapy

RT plus Cetuximab also improves locoregional control and overall survival over RT alone: median duration of locoregional control 24.4 versus 14.9 months and median overall survival 49 versus 29.3 months, respectively [138, 139]. There is, however, no study that directly compared concomitant CH-RT to concomitant Cetuximab-RT. Regarding acute toxicity, except infusion reactions and cutaneous rash, there was no increase of the typical radiation-induced laryngitis, mucositis, and pharyngitis in the combined modality arm [140]. There are, however, some reports on dramatic increase of skin toxicities in patients treated concomitantly with RT and Cetuximab [141, 142].

In summary, the concomitant use of Cetuximab and RT represents an alternative approach to concomitant CH-RT for patients with locally advanced SCC of the head and neck. However, as there is no confirmatory trial of the Cetuximab efficacy in combination with RT, this agent might be better used in case of contraindication to CH, e.g., impaired kidney function, poor performance status, and elderly patients.

28.10.4 Role of Induction Chemotherapy for Larynx Preservation

Induction platinum-based therapy followed by RT in patients who responded to CH is an alternative to TLP for locally advanced operable hypopharynx cancers. For larynx preservation, in the RTOG 91-11 study, no difference for overall survival was detected between induction with cisplatin and 5-FU and concurrent chemo-RT, although local control and larynx preservation rates were greater with concomitant CH-RT. However, hypopharyngeal cancers were not included in this trial [106]. The EORTC 24891 study randomized 202 patients with locally advanced hypopharyngeal cancer between immediate TLP and postoperative RT versus induction CH with cisplatin and 5-FU (three cycles) followed by RT if a complete response was obtained after the three cycles of neoadjuvant CH [143, 144]. In the preservation arm, if macroscopic disease was still present after neoadjuvant CH, TLP was performed. There was no statistical difference between the arms regarding 5-year survival (preservation arm: 38 % and surgery arm: 33 %) and progression-free survival (preservation arm: 32 % and surgery arm: 26 %). The 5-year larynx preservation rate (alive with a functional larynx without local relapse or tracheotomy or feeding tube) was 22 % in the induction CH group. The GORTEC compared TPF versus PF as induction CH for larynx preservation. A higher proportion of patients with advanced hypopharynx and larynx cancer achieved 3-year larynx preservation rate with TPF than with PF: 70.3 versus 57.5 % [103].

Lefebvre and colleagues reported a phase II trial (TREMPLIN) investigating sequential CH-RT for larynx preservation to test the feasibility of combining the induction and concomitant approaches [145]. Larynx and hypopharynx cancer patients eligible for a total laryngectomy were included. TPF was given for three cycles. In case of response >50 %, patients were randomized to receive either RT plus cisplatin or RT plus Cetuximab. TPF-induced toxicity precluded further cisplatin in seven patients. TPF followed by concurrent Cetuximab plus RT was better tolerated than TPF followed by concurrent cisplatin and RT with the same larynx preservation rate at 3 months and overall survival at 18 months. Treatment compliance was higher in the Cetuximab plus radiation therapy arm. There were fewer local treatment failures in the concomitant chemoradiation arm than in the Cetuximab plus RT arm (8 local failures versus 12, respectively).

28.10.5 Concomitant Chemoradiotherapy Versus Induction Chemotherapy for Locally Advanced Disease

No study dedicated only to hypopharyngeal cancer subsite is currently available. Based on the Pignon meta-analysis and randomized trials, many consider concomitant CH-RT as the standard of care [104, 105]. Cetuximab can be used as radiosensitizer if the patients cannot tolerate platinum-based CH [138, 139]. Two phase III trials have revisited the status of induction CH for patients with "unresectable" disease. TPF was followed by RT alone in EORTC 24971/TAX323 trial and by CH-RT (weekly carboplatin) in the TAX324 [42, 102]. Both studies demonstrated that TPF significantly improves median survival compared with PF as induction therapy: 18.8 versus 14.5 months in TAX324 and 71 versus 30 months in TAX323. Therefore, TPF is considered as the standard of care for induction.

There are important differences between these two trials. First, in the TAX 323, only patients considered unresectable were included. In contrast, inclusion criteria were larger in TAX324 with the inclusion, besides unresectable disease, of patients with low surgical curability on the basis of advanced tumor stage or regional-node stage, or who were candidates for organ preservation. Second, in the TAX323, TPF was followed by RT only (70 Gy) and in the TAX 324 by concomitant weekly carboplatin (area under the curve 1.5) and RT. Of note, both studies included all HN sites. Hypopharynx cancer represented 29 % and 16 % of the patients in the TAX323 and TAX324, respectively.

There is a strong rationale to investigate if TPF induction followed by concomitant CH-RT is feasible and provides further benefit to patients with locally advanced HNSSC over CH-RT alone. So far, several randomized trials testing sequential approaches with TPF induction followed by concurrent CH-RT versus concurrent CH-RT alone have been reported [146–149]. They failed to demonstrate a statistically significant difference in OS and PFS. Paccagnella and colleagues randomized 101 unresectable patients between TPF followed by CH-RT with two cycles of cisplatin and 5-FU versus the same CH-RT regimen [146]. This small study suggested that TPF followed by CH-RT is feasible and that TPF does not compromise the subsequent delivery of CH-RT. Complete response was higher in the TPF group: 46 versus 19.6 %. Hitt and colleagues reported data from a randomized study aiming at comparing concomitant CH-RT with high-dose cisplatin (three times cisplatin 100 mg/m^2) versus induction CH with PF followed by CH-RT versus TPF followed by CH-RT [147]. Median PFS and OS were similar between the three groups. Cohen and colleagues randomized patients with nonmetastatic N2 or N3 HNSCC to concomitant CH with docetaxel, fluorouracil, and hydroxyurea plus RT versus two cycles of induction CH-RT with TPF followed by the same chemoradiation regimen [148]. Induction CH did not translate into improved overall survival compared with CH-RT alone. However, the study was underpowered because it did not meet the planned accrual target. Haddad and colleagues randomized patients to receive either induction chemotherapy with 3 cycles of TPF followed by concurrent CH-RT with either docetaxel or carboplatin or concurrent CH-RT alone with high-dose cisplatin [149]. Again, no difference was observed regarding overall survival between the patients treated with induction CH followed by CH-RT and those who received CH-RT alone, although the study was terminated early due to low accrual.

In addition, CH-RT is toxic and attempts to increase tolerability are important. In this context, targeted agents that have a better toxicity profile than CH could be nicely incorporated into the standard regimen either in combination with CH-RT or to replace CH as radiosensitizer. Ghi et al. randomized patients with unresectable stage III–IV HNSCC according to a 2 × 2 factorial design: 2 cycles of cisplatin/5-fluorouracil concomitant to RT (arm A1), cetuximab concomitant to radiotherapy (arm A2), 3 cycles of induction cisplatin, docetaxel, and 5-fluorouracil (TPF) followed by concurrent platinum-based CH-RT (arm B1), and 3 cycles of TPF followed by cetuximab and RT (arm B2) [150]. A total of 421 patients were randomized. Interestingly, no significant differences for grade 3 and 4 in-field skin and mucositis toxicities were observed, challenging the concept that Cetuximab added to RT is less toxic than cisplatin-based chemoradiation. The results of the comparison between induction and non-induction arms concluded that induction TPF followed by CH-RT or Cetuximab plus RT significantly improved the progression-free survival and

overall survival (53 versus 30 months, $p=0.015$, independently from the type of concomitant strategy) without compromising compliance to the concomitant treatments. However, the benefit of induction CH in the context of platinum-based concomitant CH-RT was not demonstrated in this study. Further trials to answer this question are therefore needed.

In summary, outside of clinical studies, the use of induction CH with TPF should remain investigational, and concomitant CH-RT should remain the treatment of choice.

28.10.6 Post-radiotherapy Neck Dissection

Organ-preservation strategy has led to controversial issues concerning the role of ND following (CH) RT for patients with advanced regional disease at initial diagnosis. Residual neck mass may be present in as much as 30 to 60 % of patients after completion of RT. For those patients, irrespective of the neck classification, there was a consensus in the literature favoring an immediate ND, because of the very low probability of achieving a neck control with salvage surgery when recurrence develops [151]. Whether an ND should be proposed to all patients initially staged N2–N3 regardless of the response [152–157] or only to those with clinical and/or radiological evidence of residual lymph node disease [158–163] is still a matter of debate.

That ND could be avoided following complete nodal response to irradiation is a consequence of a better response assessment using imaging [164] and improved regional control with CH-RT [106–108]. There are currently many arguments supporting the position that systematic planned ND is no longer justified in patients without clinically residual disease in the neck and many institutions have switched to ND for residual disease in the neck only [165].

Improvement in assessing the neck status with imaging has contributed enormously to this change in paradigm. Investigators from the University of Florida reported negative predictive value (NPV) of CT scan of 94–97 % for the detection of residual or recurrent neck metastasis, providing that very strict criteria were used [166–168]. In a large Canadian study ($n=363$), an NPV of 100 % was reported for CT scan using a regression of the initial diameter equal or more than 80 % at 6–8 weeks post-concomitant CH-RT [169]. In a previously reported study, the same group has reported that CT assessment of patients with N3 nodes was not adequate [170]. Also, in the studies mentioned above, the specificity of CT scan was found to be very low, around 28 %. In this framework, could MRI outperform CT examinations? A meta-analysis showed that CT and MRI were equivalent for the detection of pretreatment lymph node metastases in HNSCC [171]. DW-MRI was recently reported as a better tool than conventional MRI for initial regional staging and for assessment of treatment response early after the end of CH-RT [172].

The use of PET-FDG has gained some interest [173–176]. Optimum timing of PET after (CH)RT is crucial and could explain discordant results. Contrasting results could partly be explained by a lack of standardization with regard to the quality of PET imaging, the timing of PET after RT, and the timing of the ND. Despite reluctance of surgical teams to delay post-RT ND for more than 6–8 weeks because of fears that more fibrosis may develop, thus making surgery more difficult and increasing the risk of postoperative complications, it is recognized that the most appropriate time to perform PET is 12–15 weeks following RT [174–176]. In retrospective studies, PET performed 12–13 weeks post-RT showed NPV of 97–100 % and positive predictive values (PPV) of 62.5–71 %, respectively [175, 176]. Based on these data, it may be concluded that a negative PET scan closely correlates with a negative pathologic neck node status. A definitive answer on the issue of post-RT ND should come from ongoing prospective randomized studies. Recently, Porceddu et al. reported the results of a unicenter prospective study including 112 patients who underwent a 12-week post-RT assessment with PET and CT. Patients with residual CT nodal abnormalities deemed PET negative were observed regardless of residual nodal size. With a median follow-up of 28 months, all PET-negative residual CT nodal abnormalities were observed without subsequent isolated neck failure [177].

To summarize, balancing the benefit with the increased morbidity of post-CH-RT surgery, current evidence suggests that ND should be restricted to those patients with a noncomplete response after organ-preservation protocol [165].

In this situation, there is a growing evidence to support the approach of using SND even in patients with initial advanced regional disease and with clinically persistent disease, with less than 5 % of subsequent neck failure [178–182]. More, it has been recently demonstrated that SSND was a reliable surgical option for patients with residual disease confined to a single neck level [183]. In all studies reporting on post-concomitant CH-RT-selective ND, the rate of major postoperative complications was less than 10 % and comparable to the rate of complications observed after primary surgery [154, 157, 179, 184, 185].

Despite the absence of prospective study comparing SND with more comprehensive ND after organ-preservation protocols, intuitively, one would expect less fibrosis, shoulder dysfunction, and neck deformity in patients who underwent limited neck surgery.

28.11 Postoperative Radiotherapy and Concomitant Chemo-Radiotherapy

The benefit of PORT in HNSCC has progressively emerged in the 1970s and 1980s as a standard of care for patients at high risk of locoregional relapse after surgery [186–189]. Prognostic indicators for locoregional relapse after surgery have been progressively identified including the primary disease site, the surgical margins at the primary site, the presence of perineural invasion, the number of metastatic lymph nodes, and the presence of ECS [190, 191]. Based on the clustering of these pathologic factors, the MD Anderson Cancer Center proposed to stratify the patients into three risk categories conditioning the need for PORT [192]. In the absence of any risk factor, the need of PORT could not be demonstrated. Patients with extracapsular rupture or a combination of two or more risk factors were identified as being at high risk of locoregional relapse, and for those patients, a randomized study demonstrated the benefit of a radiation dose of 63 Gy (in 35 fractions) compared to 57.6 Gy (in 32 fractions). For patients with only one risk factor other than extracapsular rupture, a dose of 57.6 Gy was demonstrated as optimal. A subsequent study from the same group further validated the use of these categories of risk factors and also individualized the time between surgery and the start of PORT as well as the total treatment time (from surgery to the end of RT) as additional risk factors [193]. In this study, it was also demonstrated that patients with high risk of relapse benefited from an accelerated treatment (63 Gy in 5 weeks vs. 63 Gy in 7 weeks) in terms of both locoregional control and survival.

With the need to further improve the locoregional control after surgery and PORT, few trials combining postoperative concomitant CH and RT have been reported in the 1990s [194, 195]. Although positive in favor of the combined approach, these studies did not really influence the pattern of care of patients primarily treated with surgery. More recently, the EORTC and the RTOG conducted similarly designed studies aiming at assessing the benefit of PORT (60–66 Gy) combined with cis-platinum (100 mg/m^2) given on days 1, 22, and 43 for patients with a variety of risk factors, but slightly different between the 2 trials [93, 94]. In the EORTC study, a highly statistically significant benefit in favor of the combined treatment was observed for both locoregional control and overall survival. In the RTOG study, the benefit in locoregional control probability did not translate into a statistically significant difference in survival. An update of this latter study was recently published [196]. At a median follow-up of 9.4 years for surviving patients, no significant differences in outcome were observed in the analysis of all randomized eligible patients. However, analysis of the subgroup of patients who had either microscopically involved resection margins and/or ECS showed improved locoregional control and disease-free survival with concurrent administration of CH. The remaining subgroup of patients who were enrolled only because they had tumor in 2 or more lymph nodes did not benefit from the addition of CH to RT.

Combined modality treatment did not decrease the incidence of distant metastasis. In both studies, the concomitant use of CH significantly enhanced the acute local toxicity of RT and only half the patients could actually receive the full treatment as planned. A meta-analysis of these two studies was subsequently performed and demonstrated a statistically significant benefit of combined CH-RT but only in patients presenting with positive surgical margins and/or ECS, i.e., patients with the highest risk of relapse after surgery [197]. For the other patients, RT alone can still be considered as a standard of care.

28.12 Recurrent Disease

28.12.1 Salvage Surgery

In a few highly selected cases of early tumors treated with primary RT, conservation surgery is feasible [53, 60]. Patients suitable for this approach should have a limited local recurrence without hemilarynx fixation and cartilaginous invasion. Most patients with local recurrence, candidate for salvage surgery, require TLP. Salvage surgery for local recurrence is generally associated with high morbidity and poor oncological and functional outcome. Investigators from Princess Magaret Hospital, Toronto, reviewed a series of 72 patients with salvage pharyngectomy for radiation failure. The 5-year overall survival, disease-specific survival, local, and regional control rates were 31 %, 40 %, 71 %, and 70 %, respectively [198]. ECS was the only independent prognostic variable on multivariable analysis. This study demonstrated that salvage surgery is a viable option with high locoregional control in experienced hands. These results contrast with those reported by others [199], reporting high rates of postoperative major complications, incomplete resections, and recurrences with only 10 % of patients alive and tumor free at 3 years [199]. Patients with regional recurrence in addition to local recurrence will be unlikely successfully salvaged by surgery and should be selected for adjuvant therapy.

Is postoperative reirradiation alone or combined with CH useful after salvage surgery? A randomized study addressing this issue has shown that for patients with adverse pathologic features on the pathologic specimen, the disease-free survival but not the overall survival was prolonged after postoperative reirradiation combined with CH compared to salvage

surgery alone [200]. The regimen was, however, not common and the toxicity was substantially increased. Whether such treatment should become a standard of care should be individually assessed.

For patients doomed unresectable or unfit for salvage surgery, salvage RT in previously irradiated sites (typically only directed to the recurrent area) has been reported, but with modest or poor results depending on patient selection and extent of disease [201, 202]. Such reirradiation in previously irradiated sites has to be distinguished from a new irradiation in a previously unirradiated area that could be proposed for second primary tumor. In this latter situation, providing adequate dose could be delivered, cure rates similar to those expected in previously untreated patients are observed.

28.13 Palliative Disease

28.13.1 Systemic Treatment

Patients with distant metastases or locoregional relapse not amenable to surgery or RT are considered incurable. Pulmonary metastases account for two-thirds of these metastases [20]. It is important to distinguish between head and neck metastasis and a primary lung cancer because the latest could be treated with a curative intention. Pathology is often required to orientate adequately the diagnosis. In case of a solitary SCC pulmonary nodule, the patient should be treated surgically as for a primary lung cancer.

In the presence of a palliative disease, the prognosis is dismal with a median survival ranging between 4.5 and 10 months. Patients with good performance status, locoregional relapse only, or no previous exposure to CH have the best overall survival [203]. A small study suggested that cisplatin might improve overall survival over best supportive care although this trial did not have enough statistical power [204]. Patients who have symptoms to palliate and wish to try CH are often treated with a combination of cisplatin/carboplatin and 5-FU. Response rate ranges between 10 and 32 % [205, 206]. Cisplatin/paclitaxel combination was compared with cisplatin/5-FU in a randomized phase III trial: ORR was 22 and 29 % and median overall survival was 9 and 8 months, respectively. Methotrexate gives 10 % ORR with a median survival around 6 months. Minimal activity has been also detected with other cytotoxics (docetaxel, paclitaxel, oxaliplatin, 5 FU, capecitabine, gemcitabine, vinorelbine, pemetrexed, ifosfamide, etc.), but large randomized trials are missing with these agents.

Targeted agents have been also tested in recurrent patients. The median progression-free survival (1.3 to 4.2 months) and overall survival (4.2 to 8.1 months) remain low when these agents are given as monotherapy, maybe also because they have been mainly studied in end-stage patients with progressive disease after platinum-based therapy [207]. The most promising targeted agents are inhibitors of the EGFR pathway. Cetuximab improves survival when added to the combination of cisplatin and 5-fluorouracil (5-FU) or carboplatin and 5-FU and this combination is the current standard of care for the first palliative line of HNSSC [208].

28.13.2 Role of Local Treatment

Half of the palliative patients never develop distant metastases but experience a noncurable locoregional relapse with frequent important functional comorbidities related to swallowing, speaking, and breathing. Cutaneous cancer ulceration can also be debilitating with pain, wound healing, infection, and aesthetic problems. Therefore, it is of utmost importance to maintain a regular follow-up of these patients by the multidisciplinary team to adequately evaluate the local consequences of the recurrence and provide the best local supportive care. Systemic treatment can relieve temporally symptoms in case of response. Surgery is rarely useful and disfiguring. RT can be used to palliate symptoms such as pain and bleeding.

28.14 Follow-Up and Outcome

After the initial treatment, a comprehensive examination of the entire upper aerodigestive tract including a flexible fiberoptic endoscopy and a neck examination is recommended every 2 months for 2 years after the initial treatment, every 4 months during the third year following treatment, and 2 times per year thereafter. If PET-FDG was informative at initial diagnosis, posttreatment PET-FDG should be repeated not sooner than 12 weeks after radiotherapy to optimize the accuracy of the reading [173–177]. There is currently no high-level evidence to support routine plain chest radiography, either for improved oncologic outcomes or from a cost-benefit standpoint. However, when required, chest CT should be used rather than chest X-ray for the follow-up of hypopharyngeal cancer patients [209]. TSH level is checked once per year to detect occult hypothyroidism. Dental monitoring is important following RT, due to xerostomia and increased risk of tooth decay. Careful attention to cleaning, scaling, periodontal health, and lifelong topical fluoride treatment can reduce the risk of tooth loss and osteoradionecrosis.

Advanced hypopharyngeal SCC have still a dismal prognosis. The frequency of distant metastases is the highest of all HNSCC. During follow-up, 25 % of patients locoregionally controlled will develop distant metastases, usually in the lungs, liver, and bones [19, 20, 23]. Despite a good local control rate, most patients succumb to distant metastases, intercurrent diseases, or second primaries. Not surprisingly,

overall 5-year survival rate is approximately 30 % [118–120]. When the 5-year survival rate with early lesions is about 50–60 % [53, 210], in T3–T4 lesions or advanced regional disease, survival drops to 25–35 % at 5 years [121–123, 143]. In 1997, a survey analyzed demographics and standards of care for the treatment of hypopharyngeal SCC in the USA. Of 2939 cases, the 5-year disease-specific survival was 33.4 %. The disease-specific survival based on stage was 63.1 % for stage I disease, 57.5 % for stage II, 41.8 % for stage III, and 22 % for stage IV [211].

28.15 Perspectives

Future directions are untimely connected with advances in the management of other HNSCC. This is essentially due to the difficulties of conducting large clinical trials in patients with cancers of only a single site. Several investigations have not improved survival but have improved the quality of life. In this frame, laryngeal preservation is a typical example. What is required is developing treatments with less toxicity, promoting protocols preserving the organ function more than the organ itself, and individualizing therapy according to the molecular signature of the tumor.

The introduction of the EGFR inhibitors has demonstrated that targeted therapy combined with radiotherapy can be delivered to HNSCC without increasing mucositis. This last approach improves survival by increasing local control but did not affect the rate of distant metastases. In contrast, clinical trials have demonstrated that the addition of CH to RT decreases the risk of late distant recurrences, which is a particularly important pattern of failure in hypopharyngeal cancers.

However, CH-RT is toxic. Targeted agents have a better toxicity profile than CH and could be nicely incorporated into the standard regimen to either improve efficacy and/or decrease treatment toxicity. Ongoing studies investigating the combination of targeted agent administration during or after induction CH or with conventional CH-RT regimens will help to better define the respective role of CH and targeted agents in the multimodal treatment of this disease. In addition, efforts to identify predictive biomarker that could help to better select the patients who will benefit of a specific treatment modality are of crucial importance.

Continued improvements in conservative surgical techniques allow for the potential for further surgical resection to be performed with less swallowing morbidity. The incorporation of induction CH or targeted therapy to reduce tumor volume, allowing more oncologically sound conservative procedures, introduces an innovative concept of surgical de-escalation that should be validated in prospective trials.

Improvements in more conformal radiation techniques will continue to be limited by the need to define the extent of cancer spread. Traditional techniques have relied on alterations in the shape, size, and appearance of normal tissues. The increasing use of FDG-PET scans now allows smaller volumes of cancer spread, such as is found in normal-sized cervical lymph nodes, to be identified. This is particularly important for more conformal radiation techniques, in which underdosing areas of the neck that appear otherwise normal is possible.

Future developments in additional imaging agents that allow for more specific aspects of cancer to be detected offer the promise of smaller volumes of cancer spread to be detected and greater confidence in the use of conformal irradiation. Even more exciting is the promise of newer imaging agents and techniques that can be used noninvasively to determine various biologic aspects of the cancer. Examples include the ongoing studies of various agents that bind to areas of tumor hypoxia, which has been shown to increase radiation resistance in head and neck cancers. The ability to tag such agents with radioactive markers allows them to be used as imaging agents such as has been achieved using a hypoxia marker which has been shown to be of prognostic significance in head and neck cancers.

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Cancers of the Larynx: Tis, T1, T2 Evaluation and Management

29

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Abstract

In the USA, larynx cancer affects an estimated 1 in 250 people. Current treatment modalities emphasize obtaining a cure while maximizing the preservation of function and the quality of life. For early larynx cancers (Tis, T1, T2), these treatment options include primary radiotherapy, transoral endoscopic resection, and conservation laryngeal surgery. Current literature reports similar rates of local control and survival among these modalities, such that management decisions should incorporate the stage, extent of disease, and the anticipated functional outcomes within the context of patient social and medical factors. This chapter discusses the epidemiology, presentation, evaluation, and management of early larynx cancers, with a focus on treatment options and functional considerations.

Keywords

Larynx cancer • Conservation laryngeal surgery • Radiotherapy • Transoral endoscopic resection

29.1 Introduction

It is estimated that cancers affecting the larynx, the organ of speech, affect 1 in 250 Americans. Worldwide, the public health impact of larynx cancer is much greater, ranking as the fourteenth most common cancer among men and the second most common malignancy among head and neck cancers. In 2014, there were estimated 12,630 new cases of and 3610 deaths from larynx cancer [1]. Of these cases, roughly half originate at the level of the glottis [2]. Despite improvements in diagnostic and therapeutic techniques, the overall survival has not improved over the past 25 years [3]. In fact, there was a decline in 5-year survival for early stage supraglottic cancer from 66.7–67.5 % in the mid-1980s to 61.2–60 % in the mid-1990s. The 5-year survival for early stage glottic cancer also decreased, although to a milder degree [2]. Such trends are important to consider and reevaluate as new treatment modalities evolve and management options expand.

Both larynx cancer and its treatment heavily impact three of the major functions of this organ: phonation, respiration, and airway protection during deglutition [4]. While this facilitates earlier presentation and diagnosis of glottic tumors, it also highlights the delicate balance between sound oncologic treatment and preservation of function. The American Society of Clinical Oncology (ASCO) recommends that early stage larynx cancer (T1 or T2) be treated initially with larynx-preserving modalities [5]. Given the numerous possibilities for the treatment of larynx cancer [6], management decisions must incorporate the preservation of organ function and the anticipated patient quality of life into the goal of curing this disease. As the overwhelming majority of larynx cancers are squamous cell carcinoma [7], this chapter addresses the above considerations as they relate to the management of early stage (Tis, T1, or T2) larynx squamous cell carcinoma.

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29.2 Anatomy

The larynx is divided into the supraglottis, the glottis, and subglottis. Each level has distinct vascularization and lymphatics, as demonstrated by dye and histologic studies [8, 9], attributable to their different embryologic origins. The supraglottis encompasses the epiglottis superiorly, extending to the apices of the ventricles. Subsites within the supraglottis, which are important from a staging perspective, include the suprahyoid and infrahyoid epiglottis, aryepiglottic folds, arytenoids, and false vocal folds. The supraglottis develops from the buccopharyngeal anlage of the third and fourth branchial arches with a robust lymphatic supply both ipsi- and contralaterally. Consequently, supraglottic malignancies have a high incidence of both unilateral and bilateral cervical metastases, occurring in 25–75 % of patients across all T stages [10], with 30 % of clinically N0 necks harboring occult disease [11].

In contrast, the glottis and subglottis develop from the tracheobronchial anlage of the fifth and sixth branchial arches with relatively sparse lymphatic drainage. The glottis extends from the apices of the ventricles superiorly to 1 cm inferior to the free edge of the true vocal fold. The incidence of cervical metastases in early glottic cancer is 5–10 % and increases to up to 40 % for T4 tumors [12, 13]. The subglottis encompasses the area between the inferior limit of the glottis and the inferior border of the cricoid cartilage. The incidence of cervical metastases in subglottic cancer ranges from 4.3 to 25 %, with up to 50 % incidence of paratracheal lymph node metastases [14]. These reports may be skewed by the tendency for subglottic cancers to present in advanced stages.

The larynx contains natural boundaries to tumor spread, which tend to confine neoplasms until more advanced stages [15, 16]. These structures include the thyroid and cricoid cartilages and associated perichondrium, the conus elasticus, the quadrangular membrane, and the hyoepiglottic ligament. One area of weakness is at the anterior commissure, where the thyroid perichondrium is deficient. Another such area is the laryngeal ventricle, which is not reinforced by the quadrangular membrane. Clinically relevant spaces include the preepiglottic space, where the superior laryngeal neurovascular bundle creates a dehiscence in the thyrohyoid membrane and allows for cervical extension of tumors. Additionally, the paraglottic space, once invaded, allows tumor access to all three regions of the larynx [17].

29.3 Etiology

More than 85 % of larynx cancer can be attributed to tobacco use and alcohol consumption, with smoking being the predominant etiology and alcohol being an independent and synergistic factor [18]. The male:female ratio, once as high as 15:1, is now less than 5:1 [3], likely due to increased rates of smoking in women. Current smokers have a 10–20-fold increased risk of developing larynx cancer when compared to nonsmokers [19, 20]; those who stop smoking have a 60 % reduction in relative risk 10–15 years after cessation [21].

Other risk factors include environmental exposure to asbestos, nickel compounds, wood dust, leather products, paint, diesel fumes, and glass-wool [22]. Gastroesophageal reflux has also been identified as a risk factor for larynx cancer [23], with alkaline reflux as the causative factor [24]. Although human papillomavirus (HPV) infection (particularly types 16 and 18) may play a role in the development of larynx cancer, there does not appear to be as strong a causal association as in oropharynx cancer [25, 26]. Three to seven percent of respiratory papillomatosis cases undergo malignant degeneration to squamous cell carcinoma [27], and, interestingly, HPV types 6 and 11 prevail in these cases [28].

29.4 Clinical Presentation

In the USA, 59 % of larynx cancers arise in the glottis, 40 % develop in the supraglottis, and 1 % occur in the subglottis [29]. Tumors arising in the different regions of the larynx have varying presentations, with glottic lesions becoming symptomatic at a smaller size than supraglottic tumors. Symptoms of early larynx cancer include dysphonia, hoarseness, referred otalgia, dyspnea, neck mass, and, in larger T2 supraglottic cancers, even dysphagia and odynophagia. Regardless of tumor site, dysphonia and hoarseness are the most common symptoms with sore throat being the second most common complaint for supraglottic masses [30]. Patients with reflux laryngitis and a history of heavy smoking may not notice subtle changes and may therefore present later [17]. The duration of symptoms has not been found to have prognostic significance, perhaps because of recall bias on the part of the patient, inaccurate charting, or the aggressive nature of the malignancy. However, the number of symptoms with which a patient presents has been found to correlate with tumor stage [30].

29.5 Evaluation

A thorough history includes not only a discussion of current symptoms, but also an assessment of potential risk factors, family history, and comorbidities, with particular attention to pulmonary function and respiratory pathology if partial laryngeal surgery is planned. In addition, nutritional status and constitutional symptoms should be addressed.

A complete physical exam should be performed, including inspection and, if possible, palpation of the mucosal surfaces of the upper aerodigestive tract. Cervical palpation should

evaluate the presence of cervical lymphadenopathy and the integrity of the laryngeal framework. Tenderness of the thyroid cartilage, cricothyroid or thyrohyoid membranes, or the loss of laryngeal crepitus with horizontal movement may indicate extralaryngeal spread. Fixation of the larynx is suggestive of prevertebral fascia involvement. If indirect mirror laryngoscopy does not provide an adequate exam, fiberoptic transnasal endoscopy should be undertaken to complete the examination of mucosal surfaces and assess vocal fold and arytenoid cartilage mobility. If the appropriate equipment is available, transnasal endoscopy may also be used to obtain a biopsy; in a prospective cohort, this technique has been demonstrated to provide diagnoses congruent with biopsies obtained in the operating room [31].

Preoperative laryngeal videostroboscopy reveals abnormalities of the true vocal fold mucosal wave, which may be the earliest finding for an invasive glottic cancer. If the mucosal wave is largely normal, extensive vocal ligament invasion is improbable and a reasonable postmicrosurgical resection voice quality is more likely [32].

In a patient with a larynx tumor, an exam under general anesthesia is necessary to evaluate tumor extent, take a biopsy, assess candidacy for conservation laryngeal surgery (CLS), and exclude the presence of a second primary tumor. This is best executed using 0, 30, and 70° telescopes which can evaluate the anterior commissure, ventricles, and subglottis. Performing rigid endoscopy prior to intubation allows for an unobstructed view of all mucosal surfaces in the larynx, as well as the evaluation of cricoarytenoid mobility without the impediment of an endotracheal tube. With very superficial lesions, excisional biopsy can be both diagnostic and therapeutic [33, 34].

The patient should be assessed by a speech pathologist for preoperatively to review and arrange potential treatment rehabilitation for both speech and swallowing. If radiotherapy is being considered, the patient should undergo a dental evaluation with the management of dental problems as indicated. Pulmonary function tests are sometimes indicated if CLS is planned, although functional assessment by simply walking a flight of stairs has been shown to be equally effective in the thoracic surgery literature [35].

29.6 Imaging

Imaging is a useful adjunct to physical examination; the combination of clinical examination and computed tomography (CT) has been shown to have a higher staging accuracy than either evaluation alone [36]. Both CT and magnetic resonance imaging (MRI) provide information on potential lymphadenopathy and the extent of the primary tumor within and beyond the larynx, thereby assisting with the determination of resectability and with surgical planning [37].

CT staging of the neck has a reported 87–93 % accuracy with comparable results with MRI [17]. Thyroid cartilage invasion is difficult to assess on imaging because it often has areas of contiguous areas of chondrification and ossification [37]. Although Becker et al. identified several CT findings suggestive of cartilage invasion, no single indicator had both a sensitivity and a specificity higher than 70 %, despite several criteria having either a high sensitivity or a high specificity [38]. Although both modalities have a similar accuracy, CT has a higher specificity but lower sensitivity than MRI for thyroid cartilage invasion [39]. More recently, revised criteria to evaluate thyroid cartilage invasion on MRI significantly increase specificity [40].

For small T1 larynx cancers, imaging may not be indicated. In a small cohort of patients, Dullerud et al. reported that imaging did not alter the staging of T1 or T2 glottic cancers [41]. In a larger study, Barbera et al. found that 54 % of T1 larynx cancers showed no abnormality on CT, whereas only 20 % of T2 lesions appeared normal. Although only 6 % of T1 supraglottic cancers were upstaged because of CT findings, 25 % of T1 glottic carcinomas, 14 % of T2 glottic carcinomas, and 36 % of T2 supraglottic carcinomas were upstaged [42]. This indicates that imaging may not be warranted for a select group of patients with early T1 larynx cancers, although this patient population needs to be better defined.

A metastatic work-up is necessary, although distant metastases are unlikely in early stage disease. Chest X-ray can evaluate nonneoplastic pulmonary disease, synchronous tumors, or lung metastases. If done for a metastatic work-up, a chest X-ray should be accompanied by liver function tests with possible liver ultrasonography. Suspicious findings on preliminary imaging or a high suspicion for distant metastases should lead to CT imaging. Alternatively, positron emission tomography (PET)/CT may be used. Recently, pretreatment PET/CT has been found to alter management in 18–31 % of head and neck cancer patients [43–45] and the availability of this technology is increasingly more widespread.

In addition, if CLS is being considered, a modified barium swallow is indicated to assess the risk of aspiration and dysphagia.

29.7 Staging

The current staging system for larynx cancer is set forth by the 2010 American Joint Committee on Cancer (AJCC) Staging Manual, seventh edition [46] (Table 29.1). This system is based on tumor, node, and metastasis (TNM) criteria and, as opposed to the prior criteria, differentiates between resectable and unresectable T4 tumors (T4a and T4b, respectively). Hence, stage IV disease is divided into IVA, IVB, and IVC; the latter denotes the presence of distant metastases. For this chapter, focusing on T1–T2

Table 29.1 AJCC staging for larynx cancer

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Supraglottis	
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
T4a	Moderately advanced local disease Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck, including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Glottis	
T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3	Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space, and/or inner cortex of the thyroid cartilage
T4a	Moderately advanced local disease Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck, including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Subglottis	
T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation
T4a	Moderately advanced local disease Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck, including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

(continued)

Table 29.1 (continued)

Regional lymph nodes (N)[a]			
NX	Regional lymph nodes cannot be assessed N0; no regional lymph node metastasis		
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension		
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension		
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension		
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		
N3	Metastasis in a lymph node, more than 6 cm in greatest dimension		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

[a]Metastases at level VII are considered regional lymph node metastases

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cancers, a crucial aspect of staging is for the invasion of the paraglottic space noted on the CT scan, which would classify the tumor as T3. This leads to upstaging tumors that clinically appear as T2 (some T2 with impaired motion of the true vocal cord for instance or T2 with anterior invasion of the floor of the ventricle) [47].

This staging system begins to address important prognostic factors by recognizing differences among tumors of varying sizes and prognoses, which were grouped together by previous criteria. However, limitations still exist. Prognostic factors, such as nodal extracapsular spread, perineural or lymphovascular invasion, and histologic grade, have yet to be incorporated [13]. Another consideration includes molecular characterization [48]; for example, the overexpression of p53 as identified on immunohistochemistry lowers the rate of 5-year local control for a T1 glottic tumor from 94 to 48 % [49]. Other potential improvements include a more objective definition of vocal fold immobility, in order to differentiate among mucosal, vocal fold, and arytenoid immobility, as well as grouping severe dysplasia and carcinoma in situ (Cis) together, since these are similar in terms of histology and prognosis [48].

29.8 Management

The treatment goal for larynx cancer is the judicious use of available treatment modalities to achieve a cure while maximizing the preservation of function. The importance of maintaining function from a patient's perspective is highlighted by an oft-cited study by McNeil et al. in which one out of five patients in a cohort of firefighters and upper management executives with advanced larynx cancer would accept a 20–30 % decrease in survival in order to preserve voice [50]. Additionally, despite the paucity of randomized, controlled studies comparing treatment modalities [5, 51], guidelines designed by ASCO recommend larynx-preserving treatment options as the initial approach for T1 or T2 larynx cancers [5]. Appropriate treatment modalities are best decided by the multidisciplinary approach, in which a head and neck surgeon, radiologist, pathologist, radiation oncologist, medical oncologist, and speech pathologist convene to determine the best management strategy for an individual patient.

29.8.1 Radiotherapy

Radiotherapy alone and CLS are accepted as effective single modality treatments in the management of T1 larynx cancer. Although there are several large cohort studies evaluating each modality individually, there are no randomized, controlled trials comparing the two and not enough evidence to declare one superior to the other [51]. However, for T2 cancers, there is much less clinical equipoise, both in terms of local control, which is the key for laryngeal preservation, and long-term survival.

In general, early T1-2N0 glottic tumors are treated using narrow-field irradiation, extending superiorly to the thyroid notch and inferiorly to the inferior border of the cricoid cartilage. Local control rates for T1 glottic tumors range from 82 to 94 %; after surgical salvage, the ultimate local control rate ranges from 90 to 96 %, with an 83–95 % rate of larynx preservation. The 5-year cause-specific survival ranges from 95 to 98 % [52–60]. For T2 glottic cancer, local control rates range from 61 to 80 %, with ultimate local control after salvage ranging from 80 to 91 % and a 60–82 % larynx preservation rate. Rates of 5-year disease-specific survival range from 86 to 95 % [52–54, 56–58, 61, 62]. For this reason, the use of altered fractionation for T2 cancers is strongly recommended [58].

The outcomes of early supraglottic tumors treated with radiotherapy vary widely; those studies addressing tumor grades separately note a local control rate of 84–100 % for T1 lesions and 74–86 % for T2 tumors [63–66]. Studies evaluating these groups collectively report local control rates of 77–100 % [52], with 5-year disease-specific survival ranging from 76 to 100 % [64, 67, 68]. Studies comparing surgery with radiotherapy for early supraglottic cancer generally report better rates of local control after surgery [52, 67], although these findings may be confounded by adjuvant radiotherapy given to select surgery patients and by the selection of healthier patients who can tolerate postoperative aspiration as surgical candidates. Regardless, management of the T2 laryngeal cancer is challenging. In fact, these local control rates are the justification for including T2 laryngeal cancer in the RTOG 91-11 study [69].

Traditionally, radiation doses have ranged from 60 to 70 Gy; T1 lesions receive 66–68 Gy and T2 tumors receive a total of 70 Gy. Total doses less than 65 Gy have been associated with lower rates of local control [54, 59, 62, 70, 71]. In addition, accelerated and hyperfractionation regimens, characterized by higher daily fractions and shorter duration of treatment, have been associated with improved outcomes. Daily fraction size impacts 5-year local control rates: the local control rate for fractions of 2.25 Gy or more is 84–100 %; for 2 Gy fractions, it is 77 %; and for 1.8 Gy fractions, it drops below 50 % [53, 54, 72, 73]. The length of treatment is also an independent factor affecting local control [74]; rates of local control range from 95 to 100 % for treatment lasting fewer than 40 days and 79–84 % for treatment lasting longer than 40 days [54, 75]. Trotti et al. recently examined hyperfractionation (1.2 Gy twice daily) for T2 glottic lesions compared to standard radiation doses (2 Gy per day). The hyperfractionation cohort had a 78 % local control rate compared to 70 % for standard daily fractionation [76].

Other factors portending a worse prognosis in early larynx cancer patients treated initially with radiotherapy may include a larger number of involved subsites [54, 55, 62, 63], involvement of the anterior commissure [54, 56, 59], reduced vocal fold mobility [59, 62], and whether patients continued to smoke through treatment [63]. However, none of these is a clear prognosticator; there are contrasting studies showing no association between these factors and local control for each of these considerations.

Complications from radiotherapy include early and late subgroups. Early complications include edema, mucositis, hoarseness, and dysphagia, while late complications include fibrosis, xerostomia, stenosis, and hypothyroidism. The growing use of intensity-modulated radiation therapy (IMRT) has been found to reduce the incidence of xerostomia and dysphagia while preserving survival outcomes [52, 77]. Xerostomia, which affects as many as 80 % of patients receiving radiotherapy [78], may be ameliorated by agents such as pilocarpine and amifostine. The incidence of hypothyroidism, reported to be as high as 48 % [79], highlights the importance of close follow-up. Although compelling intellectually, the efficacy of IMRT has yet to be demonstrated in a randomized prospective trial [80]. More recently, intensity-modulated proton therapy (IMPT) has gathered interest based on potential to more effectively spare normal tissue and theoretically reduce toxicity. No randomized control trials to date have assessed IMPT therapeutic or toxicity equivalence with IMRT or standard radiation. Likewise, IMPT studies examining treatment for laryngeal carcinoma are sparse [81].

For recurrence after primary radiotherapy, surgical options range from CLS to total laryngectomy [82–86]. Recurrence has been correlated with T stage, degree of histologic differentiation, and patients' overall health. The rate of recurrence after primary radiotherapy for T1 tumors is 5 %, and for T2 tumors, it is 17 %. Unfortunately, roughly three-quarters of patients who recur ultimately require total laryngectomy [87]. Holsinger et al. compared outcomes of salvage CLS with those of salvage laryngectomy, demonstrating no significant differences in recurrence rates or disease-free interval between the two approaches, but a lower rate of survival in patients undergoing salvage laryngectomy [88]. The latter finding may reflect more extensive disease or degree of comorbidities in the salvage laryngectomy group.

Nonetheless, surgical salvage enhances local control rates; for example, the local control rate for T1 glottic lesions is 82–94 % with primary radiotherapy and 90–96 % after surgical salvage. Additionally, Steiner et al. reported that 71 % of early stage recurrences were cured after salvage CLS (although some patients required multiple surgeries), citing a 5-year disease-specific survival of 86 % for those treated with CLS or total laryngectomy. In its review of the literature, this article cites a 50–100 % cure rate [86]. However, local control through salvage surgery often necessitates a total laryngectomy; for this reason, primary surgery is encouraged for early stage laryngeal cancer.

29.8.2 Chemotherapy

Chemotherapy has been evaluated as a monotherapy and in combination with either surgery or radiotherapy. While not currently the standard of care, chemotherapy has been investigated as a single agent modality for larynx cancer. Laccourreye et al. examined the curative effects of chemotherapy in N0 patients with all tumor grades of squamous cell carcinoma of the pharyngolarynx who had undergone induction chemotherapy with complete response. Patients presenting with glottic cancer had a local control rate of 66 % (100 % after salvage treatment), larynx preservation rate of 100 %, and a 5-year survival rate of 85 %. Those with cancer of the pharyngolarynx fared worse with a local control rate of 38 % (83 % after salvage treatment), a larynx preservation rate of 64 %, and a 5-year survival rate of 55 % [89].

The combination of neoadjuvant chemotherapy and CLS was evaluated by Laccourreye et al. They retrospectively evaluated the use of cisplatin-fluorouracil (PF) induction chemotherapy in combination with CLS for patients having T2 glottic cancer, reporting a 5-year survival rate of 92 % and a local recurrence rate of 6 % [90]. Compared with previous management with CLS without neoadjuvant chemotherapy at their institution, they demonstrated a 22 % increase in local recurrence together with a significant increase in overall laryngeal preservation and long-term survival [91].

There is no role for chemoradiotherapy for T1 larynx cancer. However, in the Radiation Therapy Oncology Group (RTOG) randomized, controlled trial 91-11, patients with T2 tumors comprised 11–16 % of each study population. Patients either received radiation alone, induction chemotherapy followed by radiation, or concurrent radiation and chemotherapy. Initial analysis demonstrated that there was no significant difference in overall survival among these treatment strategies while concurrent chemoradiotherapy had significantly better rates of both locoregional control and larynx preservation [69]. A 10-year evaluation of the long-term results confirmed no difference in overall survival (39 % for induction, 28 % for concomitant, and 32 % for radiation) while the concomitant group maintained improved locoregional control (41 % risk reduction relative to radiation and 34 % risk reduction relative to induction) and laryngeal preservation (54 % risk reduction relative to radiation). There was no difference in laryngectomy-free survival between the induction arm and concurrent arm. Interestingly the concurrent arm had significantly more deaths at 10 years from causes not related to laryngeal cancer relative to the induction arm (52.8 % vs. 69.8 % respectively) [92].

Expanding on the efficacy of induction chemotherapy in laryngeal organ preservation therapy, a laryngeal subgroup analysis of the TAX 324 prospective phase III trial examined the effect of adding a third induction agent, docetaxel, on survival and laryngectomy-free survival compared to PF. The docetaxel–cisplatin–fluorouracil (TPF) group compared to the PF group demonstrated significantly improved 3-year laryngectomy-free survival rates of 52 % versus 32 % and greater median progression-free survival times of 21 months

versus 11 months respectively. There was no significant improvement in overall survival [93]. However, there have been no randomized trials comparing TPF induction chemotherapy versus concomitant therapy.

Groups in Japan have investigated the use of chemoradiotherapy specifically for early larynx cancer. Nagahashi et al. demonstrated similar 5-year survival rates for patients with stage II supraglottic cancer treated either with radiotherapy alone or with chemoradiotherapy using carboplatin, but found a significant increase in the rate of larynx preservation in the latter group [94]. More recently, Nishimura et al. reported analogous findings in patients with T1 or T2 larynx cancer treated either with radiotherapy alone or with chemoradiotherapy using uracil-tegafur with or without carboplatin; they reported similar 5-year survival rates among the groups, and an organ preservation rate of 93 % in the chemoradiotherapy group versus 67 % in the radiotherapy alone group [95].

Biologic agents have recently demonstrated improved outcomes compared to radiation alone while offering improved toxicity [96]. Lefebvre et al. recently examined the use of the biologic agent cetuximab as an alternative to cisplatin in the treatment of laryngeal carcinoma. In this phase II trial, the cetuximab + radiation group demonstrated equivalence with the cisplatin + radiation group for larynx preservation, larynx function preservation, and overall survival. There was no difference in toxicity; however, patients in the cetuximab arm had improved compliance [97].

Despite the promising findings of these studies, further study is needed to determine the role of chemotherapy in the management of early stage larynx cancer and to identify the patient population that would most benefit.

29.8.3 Surgery

Options for surgical extirpation of early larynx cancer include transoral endoscopic resection, with cold steel technique or transoral laser microsurgery (TLM), and open CLS procedures.

29.8.3.1 Endoscopic Resection

As mentioned earlier, excisional biopsies may be performed for very superficial, minimally invasive lesions of the larynx [33, 34]. These cases, however, must be carefully selected; as many as 20 % of T1 glottic lesions with invasion of the vocal ligament may display normal mobility [98].

In 1972, Jako and Strong described the utilization of the carbon dioxide (CO_2) laser during microlaryngeal surgery to remove larynx cancer [99]. As the use of TLM has become more widespread [100], its application has been expanded both to other regions of the upper aerodigestive tract and to larger tumors [101]. TLM entails piecemeal excision of the tumor which, advocates argue, enables a better appreciation of the interface between tumor and healthy tissue, as determined by tissue-specific properties encountered during dissection with the CO_2 laser [102, 103] (Fig. 29.1a, b). This piecemeal approach, however, requires very close follow-up. Jackel et al. reported a 30 % revision rate for T1–T4 lesions of the upper aerodigestive tract treated with TLM, mostly for inadequate margins on final histopathology. 82 % of the re-resection specimens were negative for residual tumor, and these cases had similar rates of local control as those patients in whom revision was not necessary. Residual tumor on revision surgery specimens correlated with worse locoregional control and larynx preservation rates but did not significantly alter the duration of survival [104].

For the management of T1–T2 glottic cancer, TLM has outcomes comparable to other organ-preserving treatment modalities. Rates of local control range from 77 to 92 % for T1 lesions and 61 to 88 % for T2 tumors, with a local control rate after salvage of 97–98 % and a 5-year disease-specific survival of 86–98 % [71, 105–110]. Larynx preservation rates in many studies range from 90 to 99 % [71, 105–107, 109, 110], although one group reported a larynx preservation rate of 97 % for T1 tumors and 82.5 % for T2 lesions [108]. In general, TLM for the treatment of early larynx cancer has local control and larynx preservation rates on par with open approaches [100].

Since each endoscopic surgery is tailored for the tumor being excised, it is difficult to delineate distinct procedures. The European Laryngological Society (ELS) developed a classification system pertaining to the endoscopic removal of glottic cancer. In this schema, endoscopic cordectomy is categorized into four types, ranging from subepithelial to anterior Commissurectomy with bilateral anterior cordectomy, and four subtypes of extended cordectomy, inclusive of such subsites as the contralateral vocal fold, the false vocal fold, the arytenoids, and the subglottis [111, 112] (Table 29.2). More recently, ELS has proposed a classification system for endoscopic supraglottic laryngectomy (SGL) with four main types, ranging from limited excision to a lateral supraglottic laryngectomy [113] (Table 29.3).

The limitations of endoscopic resection include inadequate endoscopic exposure, caused by factors such as micrognathia, macroglossia, or arthrosis; the potential for poor functional outcomes, as determined by such findings as gross infiltration of the tongue base and circumferential infiltration of the hypopharynx or esophageal inlet; and extralaryngeal spread [100, 114].

Short-term benefits of an endoscopic approach include the avoidance of a tracheotomy and early return to oral intake, which is reflected by short hospital stays. In most cases, endoscopic surgery broadens the management possibilities for persistent or recurrent disease; salvage can be

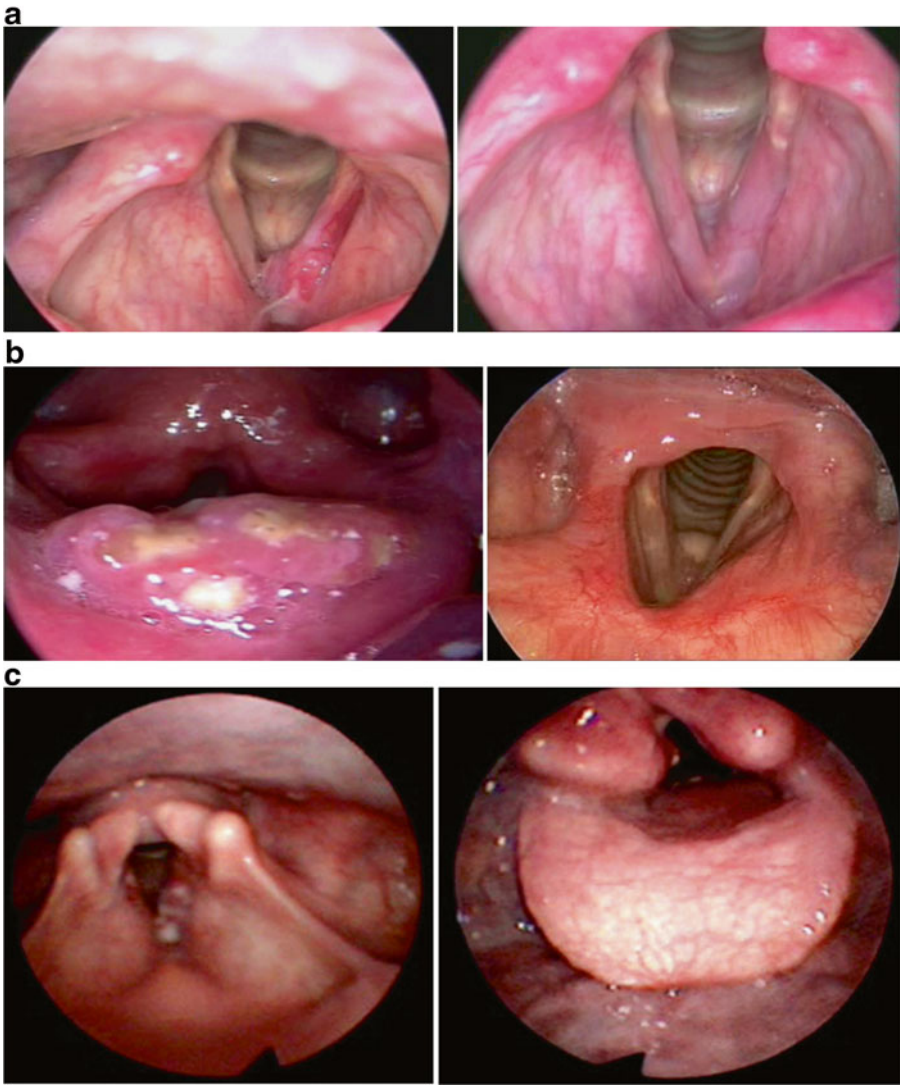

Fig. 29.1 Surgical approaches for early larynx cancer. Laryngoscopy preoperatively (*left*) revealing a laryngeal cancers arising in the anterior third of the left vocal cord and involving the anterior commissure and postoperatively (*right*) demonstrating preservation of both arytenoids and neoaryepiglottic folds, which have formed from the arytenoids to the epiglottis, permitting normal swallowing function and voice without tracheostomy. (**a** and **b**) After TLM extirpation. (**c**) After SCL for tumor ablation with CHEP reconstruction. [Reprinted from Holsinger FC, et al. Current concepts and new horizons in conservation laryngeal surgery: an important part of multidisciplinary care. Head Neck. 2010;32(5):656–65. With permission from John Wiley & Sons, Inc.]

approached with endoscopic or open surgical procedures or with radiotherapy [34, 103].

Complications of endoscopic resection include infection, bleeding, granuloma formation, cutaneous fistula, cervical emphysema, dysphagia, aspiration, and laryngeal chondritis in the setting of previous radiation. For early stage larynx cancer, the complication rate is 0.3–6 % [115, 116].

The recent introduction of transoral robotic surgery (TORS) in the surgical management of head and neck cancer offers a novel approach to minimally invasive endoscopic laryngeal surgery. Ozer et al. examined their experience with 13 TORS cases for supraglottic laryngectomy and proved feasibility with good functional outcomes [117]. Early results for highly selected patients are encouraging, but studies are limited to proof-of-principle case series with limited assessment of survival and functional outcomes [118, 119]. However, the paucity of published literatures suggests that the role of TORS for supraglottic cancer, at least with the current generation of robotic technology, appears limited.

Table 29.2 Classification of endoscopic cordectomy

I	Subepithelial cordectomy
II	Subligamental cordectomy
III	Transmuscular cordectomy
IV	Total cordectomy
V	Extended cordectomy Va including contralateral vocal fold Vb including the arytenoids Vc including the ventricular fold Vd including the subglottis
VI	Anterior commissurectomy with bilateral anterior cordectomy

Table 29.3 Classification of endoscopic supraglottic laryngectomy

I	Excision of small, superficial lesions confined to a single subsite within the supraglottis
II	Medial supraglottic laryngectomy with preservation of the preepiglottic space IIa with superior hemi-epiglottectomy IIb with total epiglottectomy
III	Medical supraglottic laryngectomy including the preepiglottic space IIIa with preservation of the ventricular fold IIIb with resection of the ventricular fold
IV	Lateral supraglottic laryngectomy IVa with resection of the ventricular fold IVa with resection of the arytenoid

29.8.3.2 Conservation Laryngeal Surgery

CLS ranges from laryngofissure with cordectomy to supracricoid laryngectomy (SCLs). There are four fundamental tenets of CLS that determine patient eligibility in order to optimize both oncologic and functional outcomes: (1) maintain satisfactory rates of local control, (2) accurately predict the extent of the tumor, (3) respect the cricoarytenoid unit (defined as 1 arytenoid, cricoid cartilage, associated muscles, and corresponding innervation by the superior and recurrent laryngeal nerves) as the basic functional unit of the larynx, and (4) understand that the resection of normal tissue is necessary to achieve consistent functional outcomes [120].

Laryngofissure with cordectomy is best suited for small, mid-vocal fold lesions with no impairment of vocal fold mobility in patients in whom endoscopic exposure is inadequate [48, 121]. This approach involves splitting of the thyroid cartilage to gain access to the endolarynx and excise the affected vocal fold. Although this procedure was previously characterized by the need for a perioperative tracheotomy [121], Laccourreye et al. reported a series of 33 cases in which no tracheotomies were needed. In this cohort, the local control rate was 100 % and the 5-year survival rate was 97 % [122].

Vertical partial laryngectomy (VPL), or vertical hemilaryngectomy, entails extending a laryngofissure with cordectomy to include resection of the corresponding thyroid ala with the affected vocal fold, sparing the ipsilateral arytenoid. If the lesion approaches or involves the anterior commissure or the anterior one-third of the contralateral vocal fold, a VPL may be extended to a frontolateral vertical hemilaryngectomy. Similarly, the ipsilateral arytenoid may be included in the resection in a posterolateral vertical hemilaryngectomy. For T1 lesions treated with VPL, local control rates are 89–100 % [123–126]. Involvement of the anterior commissure decreases local control; one study reported that anterior commissure involvement decreased local control from 93 to 75 %. In addition, the same study found that local recurrence decreased the 10-year survival rate from 63 to 31 % [125]. T2 tumors treated with VPL have local control rates of 74–86 % [123–125, 127]. Studies reporting better rates of local control select patients without impairment of vocal fold immobility or significant extension to the subglottis or supraglottis [128].

In a supraglottic laryngectomy (SGL), or horizontal partial laryngectomy, the laryngectomy is resected between the preepiglottic space and the ventricles, with the preservation of both true vocal folds, both arytenoids, and the hyoid bone. Extended procedures may include resection of the tongue base, arytenoids, aryepiglottic fold, or superior medial pyriform wall. Contraindications to SGL are involvement of the glottis, thyroid or cricoid cartilage invasion, tongue-base involvement within 1 cm of the circumvallate papillae, and deep musculature involvement in the tongue base [128]. Local control rates after SGL are 92–100 % for T1 lesions and 85–100 % for T2 tumors [129–132].

Supracricoid laryngectomy (SCL) involves the resection of both true and false vocal folds, the entire thyroid cartilage, both paraglottic spaces, and one partial or full arytenoids (Fig. 29.1c). The epiglottis may or may not be included. This procedure is reconstructed with either a cricohyoidoepiglottopexy (CHEP) or a cricohyoidopexy (CHP), depending on whether the epiglottis is resected (Fig. 29.2). In early larynx cancer, SCL is used for T1b and T2 carcinomas. Contraindications to SCL include cricoarytenoid joint fixation, invasion of the cricoid or posterior commissure, subglottic extension to level of the cricoid, and extension beyond the outer perichondrium of the thyroid cartilage [128]. For T1 and T2 lesions, the 5-year actuarial estimate of local control is as high as 98 % [133]; another study reported rates of 96 % and 91 % for T1 and T2 tumors, respectively [134]. Overall, local control rates range from 87 to 98 % [135–137] and overall 5-year actuarial estimates of survival range from 73 to 79 % [135–137], with disease-specific survival estimated at 94 % [136]. The mortality rate for SCL is 1–3.7 %, with a 9.6–11 % postoperative morbidity rate [133, 138].

Complications of CLS include infection, bleeding, adhesions, cutaneous fistulae, stenosis, aspiration pneu-

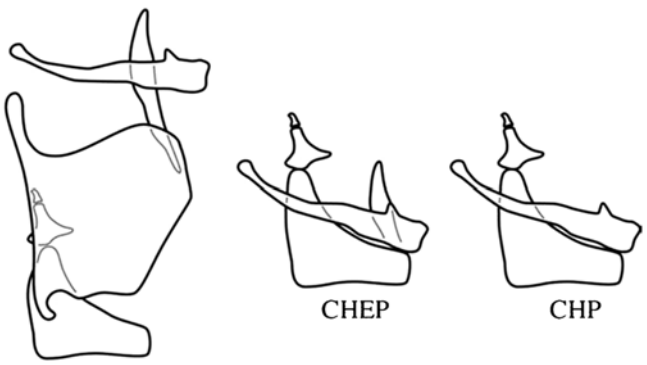

Fig. 29.2 Schematic for SCL with CHEP and CHP reconstruction. A diagram indicating the extent of resection with SCL and the optimal mechanical cricohyoid impaction for reconstruction using CHEP or CHP. [Reprinted from Holsinger FC, et al. Technical refinements in the supracricoid partial laryngectomy to optimize functional outcomes. J Am Coll Surg. 2005;201(5):809–820. With permission from Elsevier.]

monia, feeding tube or tracheotomy dependence, granulation tissue, and tracheocutaneous fistulae [103, 128]. The incidence of postoperative morbidity correlates with a previous history of irradiation, especially in the instances of local wound healing complications and laryngocutaneous fistulae [139].

29.8.3.3 Management of the Neck

As discussed earlier, supraglottic cancers present with a higher incidence of cervical metastasis; up to 30 % of N0 patients have occult lymph node metastases [11]. It is, therefore, recommended that the levels II–IV of the neck be addressed bilaterally for all supraglottic tumors, either surgically or with radiotherapy [140, 141]. On the other hand, only 5–10 % of early glottic tumors present with nodal metastases [13] and a retrospective review reported a 0 % incidence of occult cervical metastases with T1 and T2 glottic cancer [142]. Therefore, treatment of the neck is not indicated for early glottic cancer with N0 disease.

Management guidelines from ASCO state that patients with N1 disease who have a complete response to definitive radiotherapy or chemoradiotherapy do not need elective neck dissection. Patients with N2 or N3 disease, however, require surgical management of the neck regardless of response to radiotherapy or chemoradiotherapy [5].

29.9 Functional Outcomes

Larynx preservation does not guarantee functional status. Whether voice quality is superior after surgery or after primary radiotherapy remains controversial. There are currently no randomized trials comparing posttreatment voice quality after transoral endoscopic resection, open CLS, or radiotherapy; most studies are retrospective series that report conflicting findings. In general, open CLS is thought to have worse voice outcomes, with the main controversy between which of radiotherapy and endoscopic procedures results in better voice quality [104]. Recently, Sjogren et al. compared two cohorts of patients with T1a mid-cord glottic cancer treated either with laser excision or radiotherapy. They reported no significant difference in posttreatment findings of both groups with respect to the voice handicap index scores and perceptual, acoustic, aerodynamic, and stroboscopic analyses [143]. Hirano et al. evaluated similar cohorts, reporting no significant difference between the two modalities with regard to functional conversational speech, despite that TLM resulted in a higher incidence of hoarseness, incomplete glottal closure, and altered vocal fold vibration [144]. Other reports support this finding of similar voice outcomes after either radiotherapy or laser surgery [145, 146], including a meta-analysis evaluating voice handicap index scores for patients with T1 glottic cancer [146].

Factors that worsen voice outcomes after radiotherapy may include the continuation of tobacco use through treatment, as well as extensive surgical manipulation (e.g., vocal cord stripping and multiple biopsies) [52, 147]. With regard to endoscopic procedures, resections extending to or into the vocalis muscle are associated with worse postoperative voice quality [145, 148]. Likewise, greater postoperative changes in stroboscopic, objective, and perceptual analyses correspond with more extensive cordectomies [149].

Swallowing is another measure of organ function that greatly impacts a patient's posttreatment quality of life. In a study evaluating swallowing outcomes after radiotherapy for larynx cancer, Hutcheson et al. reported that 78 % of patients required feeding tubes during treatment, although of these, 52 % were eventually removed. This group found aspiration in 84 %, with nearly half of these cases having silent aspiration. They determined a significant association between pre- and posttreatment degrees of feeding tube dependence and a significant correlation between whether a patient could safely swallow liquids at initial assessment and the ability for oral intake at final evaluation. Although only 25 % of the evaluated patients had early stage disease, there was no significant correlation between T stage and these findings [150]. Recommendations for optimizing swallowing recovery after radiotherapy include avoiding unnecessary mucosal irradiation or using the minimal required dose; minimizing xerostomia through the use of IMRT, cytoprotective agents, and sialogogues; encouraging the largest tolerated bolus size; delaying feeding tube placement as long as is safely possible; and using a nasogastric tube instead of a gastrostomy tube whenever possible [151].

After TLM, nasogastric tubes are usually removed within 3 weeks [4]. Bernal-Sprekelsen et al. found that 28 % of their postoperative patients had a temporary cough with oral intake. While that statistic included patients of all T stages, only 23.2 % of early stage tumors had postoperative nasogastric tube feeding for an average of 2.5 days. 3.8 % of all patients had a tracheotomy, with 75 % of these being permanent. 6.2 % of all patients required gastrostomy tubes for dysphagia, with 38 % of these being permanent. The need for a gastrostomy tube correlated with higher T stage, radiotherapy, and the location of the primary tumor [152]. The association of irradiation with postoperative dysphagia has been reported by others [153].

In general, endoscopic procedures are associated with a more rapid return to swallowing that open CLS, and return to swallowing is dependent on the extent of the surgery [4, 128]. Endoscopic SGL is associated with a lower incidence of dysphagia with a more rapid return to normal swallowing, likely because laryngeal innervation is not as at risk in endoscopic approaches [4]. Sasaki et al. found that the glottic closure reflex returned within 72 h after endoscopic SGL, as opposed to more than 3 weeks with an open SGL in histori-

cal controls [154]. The average time to regain swallowing after VPL is 28 days, as compared to 91 days for nonextended SGL and greater than 335 days for SGL including tongue-base resection [153]. After SCL, 75–100 % of patients achieve full oral diets, with the duration of feeding tube dependence ranging from 19 to 210 days [138, 155–159]. Within the first postoperative month, 65 % of patients attain normal swallowing [138], with 81–92 % of patients having oral intake within 1 year [138, 159].

29.10 Conclusion

Current multidisciplinary guidelines for early larynx cancer emphasize both oncologic and functional outcomes [5, 6]. These organ preservation treatment modalities include primary radiotherapy, transoral endoscopic resection, and open CLS. There are currently no well-designed randomized, controlled trials comparing surgery with radiotherapy to guide treatment decisions [51]; however, current literature reports similar rates of local control and survival among these modalities. Treatment decisions should consider the stage and extent of disease and the likelihood of good functional outcomes within the context of patient social and medical factors.

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Diagnosis and Multidisciplinary Treatment of Laryngeal Cancers

30

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Abstract

Laryngeal cancer is the second most common respiratory cancer after lung cancer in the United States. Most laryngeal squamous cell carcinomas result from prolonged exposure to carcinogens that stimulate mucosal hyperplasia and ultimately lead to carcinoma. The treatment of laryngeal cancer has evolved through several phases, initially relying on surgery as a single modality and then evolving to adjuvant therapies complementing surgery, and more recently, true multimodality approaches tailored to the patient. In this chapter, we will discuss in depth the sequencing of nonsurgical therapies for advanced disease, the role of systemic therapy in general, and the development and approval of anticancer agents. In addition, we will touch on novel, truly investigational approaches and cover aspects of staging and diagnosis, radiation and surgical techniques, as well as supportive care issues.

Keywords

Larynx • Head and neck cancer • Larynx cancer • Laryngeal cancer • Carcinoma of the larynx

30.1 Epidemiology and Etiology

Laryngeal cancer is the second most common respiratory cancer after lung cancer in the United States [1]. Its incidence is increasing in much of the world, and this increase is generally accepted to be related to changes in tobacco and alcohol consumption [2, 3]. Other implicated risk factors include occupational hazards, such as asbestos [4, 5], inorganic acids, cement dust, and possibly free crystalline silica [6–8]. Dietary factors seem to play a role, as salted meat and total fat intake have been linked to elevated risk of laryngeal cancer [9, 10], whereas intake of raw leafy vegetables and legumes may have a protective effect [11]. Even though laryngopharyngeal reflux (LPR) has been suggested as a causative irritating factor in the development of laryngeal carcinoma, the association between LPR and laryngeal carcinoma remains unclear [12] and has been recently questioned [12–16]. Some genetic polymorphisms, such as of genes that code for glutathione S-transferase, have been linked to laryngeal cancer risk [17, 18]. There is a weak association between human papillomavirus (HPV) and laryngeal cancer, and recent evidence suggests an improved outcome for this subset of patients [19, 20].

Most laryngeal neoplasia results from prolonged exposure to carcinogens that stimulate mucosal hyperplasia. The risk of developing malignancy appears to correlate with the severity

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of dysplasia present on initial biopsy [21]. Among patients with laryngeal papillomatosis, dysplasia has been reported in 28 % and is linked mostly to low-risk HPV subtypes [22].

The treatment of advanced laryngeal cancer has evolved through several phases, initially with wide surgical resection, and evolving in many cases to multimodality nonsurgical treatment. Nonsurgical approaches have emerged over the past decade, including a focus on the sequencing of radiation and systemic therapy, and the development and approval of novel anticancer agents such as epidermal growth factor receptor inhibitors. These have been used in combination with radiation or other systemic agents for advanced disease. Finally, definitive chemotherapy for highly selected early-stage patients has been attempted, but remains a truly investigational strategy. Advances in radiation therapy have also been noted and have focused mainly on fractionation schedules [23, 24] or techniques such as intensity-modulated radiation therapy (IMRT) [25]. Advances in surgical techniques include endoscopic laryngeal surgery, use of laser resection for early and late tumors, and use of robotic technology in the resection of these tumors [26].

Sixty-two percent of laryngeal cancers present as Stage III or IV disease and require multimodality therapy [27]. In this chapter, we will discuss therapeutic approaches for laryngeal carcinoma in general and focus our discussion on multimodal therapy for locally advanced and metastatic disease.

30.2 Pathology and Patterns of Spread

30.2.1 Anatomy

The larynx (Fig. 30.1) is situated anterior to the fourth to sixth cervical vertebrae in adults and is composed of a framework of cartilages held in position by a series of intrinsic and extrinsic musculature and is lined by an epithelial layer that is arranged in different folds [28]. For the purpose of assessment and treatment of neoplastic diseases, the larynx is clinically divided into three areas: the supraglottis, the glottis, and the subglottis. The supraglottis is derived from the buccopharyngeal anlage, and the glottis and subglottis organize around the pulmonary diverticulum [29]. The supraglottis extends from the vallecula of the base of tongue to the apex of the ventricle. Its different components include the arytenoid cartilages, the aryepiglottic folds, the false vocal folds, the ventricles, and the infrahyoid and suprahyoid epiglottis. The glottis is composed of the true vocal cords, the posterior commissure between the two cords, and the anterior commissure. The subglottis extends from the undersurface of the true cords at the respiratory and squamous epithelial juncture to the inferior border of the cricoid cartilage [30] Though definitions vary, the AJCC manual [31] describes the glottis as a 1-cm horizontal plane extending inferiorly from the lateral apex of the ventricle. Practically, this puts the glottic–subglottic junction 5 mm inferior to the true vocal cords. The majority of laryngeal tumors arise from the surface epithelium and are therefore squamous cell carcinomas (SCCs). The thyroid cartilage opposes the inferior larynx anteriorly and laterally. The hyoid bone is connected to the thyroid cartilage by a thyrohyoid membrane. The hyoid bone serves as the upper boundary of the laryngeal framework.

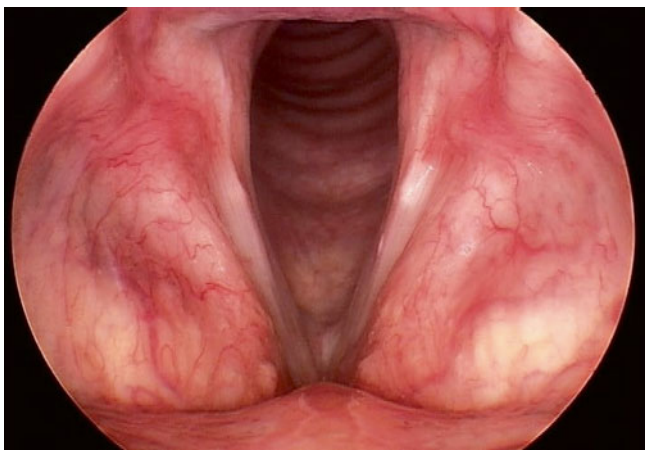

Fig. 30.1 Picture of a normal larynx

Unlike the rest of the larynx which is lined by respiratory epithelium, the vocal cords are covered by pseudostratified epithelium. Because of the sparse lymphatic supply to the glottis, true vocal cord lesions rarely present with cervical nodal metastases. On the other hand, supraglottic tumors involve neck nodes in about 17.5 % of cases with a rate of occult metastases in the contralateral neck as high as 44 % when the ipsilateral neck is pathologically involved [32]. The rate of occult cervical nodal involvement is dependent on T stage. Stage I and II tumors with clinically negative neck have a 32 % reported rate of occult cervical nodal involvement. With radiation therapy to both sides of the neck, the rate of relapse in nodal areas is reduced substantially to an estimated rate of 3.3 % [33, 34]. Patterns of growth and spread of cancer within the larynx were found to be influenced by fibro-elastic ligaments and membranes which confine the tumor to anatomic compartments, and which provide margins of safety when performing a partial laryngectomy [35]. Two barriers to periventricular extension contiguous with the quadrangular membrane superiorly and the conus elasticus membrane inferiorly have been described [36]. Consequently a high rate of local control can be obtained by surgeons performing horizontal supraglottic laryngectomy [37].

30.2.2 Supraglottic Cancer

Lesions of the supraglottis tend to spread locally. The majority of these lesions arise from the epiglottis. Lesions arising from the infrahyoid portion of the epiglottis tend to have an endophytic pattern which may spread to the preepiglottic space, whereas lesions from the upper portion of the epiglottis tend to be exophytic [35]. Modern imaging technologies, such as CT, have provided increased ability to recognize tumors that have spread to the preepiglottic space and unenhanced T1-weighted magnetic resonance (MR) images are highly sensitive for the detection of neoplastic infiltration of the preepiglottic space [38]. When the preepiglottic fold is uninvolved, patients may be treated conservatively with radiation therapy or local surgery, whereas deep invasion into the preepiglottic space may necessitate a supraglottic or total laryngectomy [39].

It has been reported that the contralateral undissected neck is a common site of failure in patients treated for SCC of the supraglottic larynx [40]. Routine bilateral neck dissection decreases cervical recurrence and appears to improve survival in the management of supraglottic cancer [40, 41].

30.2.3 Glottic Cancer

Glottic or true vocal cord carcinomas often demonstrate infiltrative growth patterns, and about two-thirds are confined to the vocal folds (glottis), with the majority of these confined to the anterior two-thirds of that structure. About 34 % of glottic tumors involve the anterior commissure, and close to 11 % involve the posterior commissure [42–44]. The anterior commissure influences growth spread of the tumor, initially retarding invasion of tumors and possibly causing diversion into the epiglottis [37]. When vocal cord lesions progress, they may invade the subglottic region or penetrate through the thyroid cartilage, penetrate the thyrohyoid membrane, or just expand superiorly to involve the base of tongue. Early glottis carcinomas may be treated with external radiation or endoscopic laser techniques. For larger glottis tumors with unilateral ventricle extension or involvement of the vocal process, a vertical laryngectomy may be used [45]. A supracricoid partial laryngectomy with cricohyoidoepiglottopexy (SCPL-CHEP) is a partial horizontal laryngectomy for selected patients with glottic cancers. It offers an alternative to TL and has a single method of reconstruction [46]. A low recurrence rate of 10 % has been reported for patients with T3 lesions following induction chemotherapy and SCPL-CHEP [47]. However, few surgeons are skilled in this technique, and the functional consequences are unpredictable; therefore, many patients who would otherwise be candidates for CHP/CHEP procedures are instead often treated nonsurgically.

30.2.4 Subglottic Cancer

Tumors arising in the subglottic area of the larynx tend to be poorly differentiated and often are quite infiltrative. They are rare tumors and do not exceed 1–7 % of all laryngeal carcinomas [48, 49]. As discussed above, the subglottis is practically considered to begin 5 mm below the free margin of the vocal cords and extends to the inferior border of the cricoids cartilage. The incidence of nodal metastasis from subglottis cancers is estimated to be close to 16 %; however, this may be an underestimation as the primary drainage pattern of these lesions is to the para- and pretracheal lymph nodes which are more difficult to detect [49]. Surgeons should, however, be aware of the relatively high incidence of micrometastases in patients with laryngeal cancer. Just as elective neck treatment is recommended for supraglottic tumors staged T2 or higher, and T3 or higher glottic cancer, subglottic cancers of stage T3 or higher merit elective regional treatment [50].

30.3 Diagnosis and Staging

Accurate staging is imperative for laryngeal carcinomas, as minute differences in tumor size and location may have a significant impact on overall stage, prognosis, and therefore choice of treatment. Staging is initiated clinically with thorough examination, usually with the aid of a flexible fiberoptic nasopharyngoscope. Further clinical examination under anesthesia with direct laryngoscopy may be necessary. In addition to the clinical examination and endoscopy, imaging techniques, including CT, magnetic resonance imaging (MRI), and PET scans, play a crucial role in pretherapeutic and posttherapeutic diagnostics [51]. MRI is useful in determining submucosal transglottic spread and is also very sensitive in detecting cartilage [51, 52] and preepiglottic space invasion [53]. Interpretation of CT and MR images requires a thorough knowledge of the patterns of submucosal spread and familiarity with recognizing signs of invasion. Both CT and MR imaging are highly sensitive for the detection of neoplastic invasion of the preepiglottic and paraglottic spaces, as well as cartilage invasion [54]. CT imaging of advanced laryngeal cancer is surprisingly inaccurate [55]. In the past, MRI has also been unreliable, but new MRI interpretation techniques which help differentiate peritumoral edema from tumor invasion are promising [52, 56].

The staging of laryngeal cancer follows the current AJCC guidelines using standard TNM stratification [31] (Table 30.1). T staging is performed differently for each subsite and is therefore separated into supraglottic, glottic, and subglottic sections (Fig. 30.2).

A T1 designation is reserved for small, localized tumors in each respective subsite. Transition to T2 indicates involve-

Table 30.1 Staging of laryngeal cancer

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Supraglottis	
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex)
T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Glottis	
T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a	Tumor limited to one vocal cord
T1b	Tumor limited to both vocal cords (Fig. 30.2)
T2	Tumor extends to supraglottis and/or subglottis, or with impaired vocal cord mobility (Fig. 30.4)
T3	Tumor limited to larynx with vocal cord fixation and/or invades the paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex) (Fig. 30.3)
T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Subglottis	
T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation
T4a	Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node, more than 6 cm in greatest dimension
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

ment of another laryngeal subsite. Similarly, a T3 tumor exhibits vocal cord fixation and/or involvement of one or more of the potential spaces within the laryngeal framework (Fig. 30.3). This is particularly important when evaluating the larynx radiographically as involvement of the preepiglottic and paraglottic spaces is often difficult to detect clinically, yet has significant bearing on the stage and therefore treatment of the disease. T4 tumors are noted by involvement of extralaryngeal structures, penetrating through the thyroid cartilage or other organs within the visceral compartment. T4b tumors are considered "unresectable," often because of prevertebral invasion (Fig. 30.4).

An excellent discussion on the role of imaging for staging of advanced larynx cancer was recently published by Becker et al. [51]. The N and M stages are similar to those of other head and neck subsites.

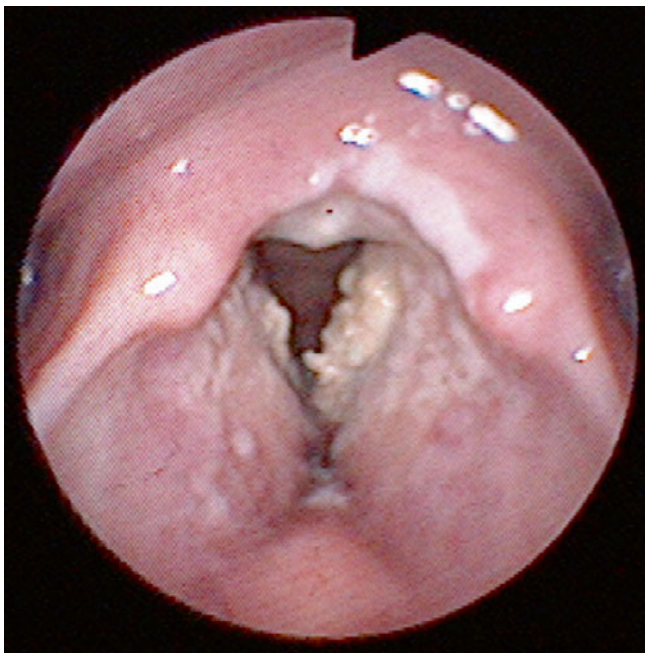

Fig. 30.2 A T1b glottic tumor

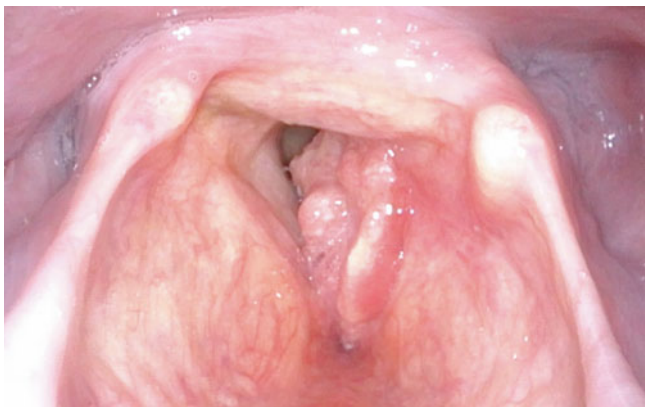

Fig. 30.3 A T3 glottic tumor

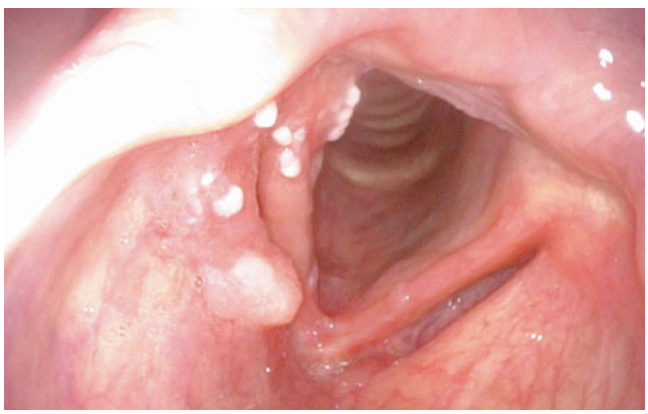

Fig. 30.4 A T2 glottic tumor with extension to the supraglottic area

30.4 Treatment and Outcome for Advanced Stage Disease

30.4.1 Supraglottic Cancers

30.4.1.1 Advanced Stage

The success of supraglottic laryngectomy for T3 and T4 lesions has been variable with poor predictability for recurrence. However, a local control rate of 70–85 % has been reported [57]. A supraglottic laryngectomy can be successfully performed for T3 cancers with preepiglottic space invasion since the preepiglottic space is removed during the procedure. The poor predictability for recurrence may be a result of poor appreciation of tumor extent preoperatively. In addition, patients who experience recurrence after nonsurgical therapy frequently have advanced stage disease at recurrence [58]. As a result, caution and selectivity should be exerted when treating T3 and T4 lesions with supraglottic laryngectomies. In an attempt to spare the patient postoperative radiation therapy, elective bilateral neck dissections should be considered in the T3N0 setting. A near total laryngectomy is another less commonly performed surgery for supraglottic tumors with cord fixation or glottis tumors with subglottic extension [59]. A local control rate similar to that reported with TL or laryngopharyngectomy with conversational voice was achieved in 85 % of patients surviving beyond 1 year [59]. In this procedure, there is preservation of the posterior half of the hemilarynx with a long-term tracheostomy, with the major advantage being maintaining the voice and avoiding synthetic prostheses. A local recurrence rate of 7 % was noted [59].

Though laser surgery has been performed on selected post-radiotherapy cases, this approach requires very careful patient selection and ought to be limited to localized recurrences after radiotherapy for early-stage glottis cancer. A supraglottic laryngectomy is usually not recommended in patients who have had prior radiation therapy because of associated wound healing problems or in patients whose pulmonary function cannot tolerate aspiration. Recurrent advanced stage disease generally requires a TL [58].

30.4.2 Glottic and Subglottic Cancers

30.4.2.1 Advanced Stage

Advanced stage glottic tumors tend to present with nodal involvement with a probability of cure of 60 %. Whenever possible, the goal should be laryngeal preservation. However, if there is evidence of aspiration or a need for a tracheostomy because of airway compromise, TL is often required. There is a lack of randomized studies comparing surgery with radiation therapy alone for T3–T4 lesions. A subtotal laryngec-

tomy with the advantage of maintaining the airway may be achieved with a subtotal laryngectomy and cricohyoidopexy or cricohyoidoepiglottopexy [46, 60–62]. Radiation therapy as a single modality is not usually given for curative intent. Combined modality therapy is the nonsurgical approach of choice as discussed in the following section.

30.4.3 Treatment of Locally Advanced Disease

30.4.3.1 Trials of Laryngeal Preservation

Primary chemoradiotherapy in patients with advanced laryngeal cancer can achieve high rates of organ preservation without sacrificing survival compared with radiation alone [63] or conventional laryngectomy [64]. Appropriate selection of patients for organ preservation approaches could enhance overall treatment outcome and quality of life.

A major shift in treatment for patients with advanced laryngeal cancer occurred with the publication of results, indicating that successful organ preservation, with survival rates similar to those with primary laryngectomy, could be achieved with definitive radiation therapy in patients responding to neoadjuvant chemotherapy [65, 66]. The landmark Veterans Affairs' (VA) laryngeal cancer study, initially published in 1991, provided the best initial evidence to support cisplatin-based, induction chemotherapy as part of a larynx-preserving treatment approach. In the VA laryngeal study, 332 patients were randomly assigned to receive either three cycles of chemotherapy (cisplatin and fluorouracil) and radiation therapy for responders or surgery and radiation therapy. The clinical tumor response was assessed after two cycles of chemotherapy, and patients with a response received a third cycle followed by definitive radiation therapy (6600–7600 cGy). Patients in whom there was no tumor response or who had locally recurrent cancers after chemotherapy and radiation therapy underwent salvage laryngectomy. After a median follow-up of 33 months, the estimated 2-year survival was 68 % (95 % confidence interval, 60–76 %) for both treatment groups ($p=0.9846$). Patterns of recurrence differed significantly between the two groups, with more local recurrences ($p=0.001$) and fewer distant metastases, 11 % versus 17 % ($p=0.016$), in the chemotherapy group than in the surgery group. The 66 % rate of laryngeal preservation in the chemotherapy group suggested that a treatment strategy involving induction chemotherapy and definitive radiation therapy can be effective in preserving the larynx in a high percentage of patients, without compromising overall survival [65].

The similarly designed European Organization for Research and Treatment of Cancer (EORTC) larynx preservation study, which focused on patients with advanced cancer of the hypopharynx, further supported the principles of the VA trial. Induction chemotherapy followed by radiation with surgery reserved for salvage came to be considered a new standard treatment for patients with locally advanced cancer of the larynx [66].

The Radiation Therapy Oncology Group and the Head and Neck Intergroup conducted a randomized trial (RTOG 91-11) to investigate three radiation-based treatments for nonbulky advanced laryngeal cancers: induction cisplatin plus fluorouracil followed by radiotherapy if there was a response to the chemotherapy (a regimen identical to that given in the VA laryngeal trial), radiotherapy with concurrent administration of cisplatin, and radiotherapy alone. The purpose was to determine the contributions of chemotherapy and radiotherapy to larynx-preserving treatment. Patients were eligible if they had biopsy-proven, previously untreated stage III or IV SCC of the glottic or supraglottic larynx that would otherwise require a total laryngectomy. Patients were excluded if they had a T1 primary tumor or large-volume stage T4 disease (defined as a tumor penetrating through the cartilage or extending more than 1 cm into the base of the tongue). A total of 547 patients were randomly assigned to one of the three study groups. The median follow-up period was 3.8 years. At 2 years, the proportion of patients who had an intact larynx after radiotherapy with concurrent cisplatin was significantly improved compared with the groups given induction chemotherapy followed by radiotherapy (88 % versus 75 %, $p=0.005$) or radiotherapy alone (70 %, $p<0.001$), suggesting that cisplatin was an active radiosensitizer [63]. Concurrent chemoradiation became the new standard of care for advanced laryngeal cancer without massive base of tongue involvement.

Clearly chemotherapy-based concurrent regimens are the therapy of choice for laryngeal preservation; eventhough there are no randomized phase III trials comparing the different systemic therapy regimens cisplatin remains the most widely accepted standard chemotherapy agent used in the concurrent setting for laryngeal preservation. The Tremplin study is a randomized phase II trial that compared cisplatin 100 mg/m^2 per day on days 1, 22, and 43 of RT versus cetuximab 400 mg/m^2 loading dose and 250 mg/m^2 per week during conventional radiotherapy (RT; 70 Gy) for stage III to IV larynx/hypopharynx squamous cell carcinoma. Patients needed to have more than 50 % response to 3 cycles of induction chemotherapy with docetaxel and cisplatin 75 mg/m^2 each on day 1 and fluorouracil 750 mg/m^2 per day on days 1 through 5 [67]. Though there was no clear difference in outcome between the 2 arms, there was an observed trend to increased local failures in the cetuximab arm [67].

30.4.3.2 Chemotherapy

Induction Chemotherapy

It has been shown that outcome for patients with locally advanced SCC of the head and neck (SCCHN) may differ according to the type of induction therapy they receive. As compared with induction chemotherapy using cisplatin and

fluorouracil, induction chemotherapy with the addition of docetaxel significantly improved progression-free and overall survival in patients with unresectable SCCHN, as shown in the TAX 324 study [68]. Outcomes were analyzed in the subgroup of assessable laryngeal and hypopharyngeal cancer patients enrolled in TAX 324, a phase III trial of sequential therapy comparing docetaxel plus cisplatin and fluorouracil (TPF) against cisplatin and fluorouracil (PF), followed by chemoradiotherapy. Among operable patients (TPF, $n=67$; PF, $n=56$), laryngectomy-free survival (LFS) was significantly greater with TPF (HR: 0.59; 95 % CI: 0.37–0.95; $P=0.030$). Three-year LFS with TPF was 52 % versus 32 % for PF, and fewer TPF patients had surgery (22 % versus 42 %; $p=0.030$), supporting the use of sequential TPF followed by carboplatin-based weekly chemoradiotherapy [69].

In another study originating in Europe, TPF was compared to PF as induction chemotherapy in patients with locoregionally advanced, unresectable SCCHN. A total of 358 patients underwent randomization, with 177 assigned to the TPF group and 181 to the PF group. At a median follow-up of 32.5 months, the median progression-free survival was 11.0 months in the TPF group and 8.2 months in the PF group (hazard ratio for disease progression or death in the TPF group, 0.72; $P=0.007$). Treatment with TPF resulted in a reduction in the risk of death of 27 % ($P=0.02$), with a median overall survival of 18.8 months, as compared with 14.5 months in the PF group, showing that the addition of docetaxel significantly improved progression-free and overall survival in patients with unresectable SCCHN [70]. The Gortec (TREMPLIN) study looked at 3 cycles of TPF chemotherapy followed by either concurrent cisplatin or cetuximab with radiation therapy in responders, or TL in nonresponders with a primary endpoint being laryngeal preservation 3 months after therapy. A total of 116 patients (79 % of those enrolled) were randomized between the two concurrent arms. As indicated, no clear difference in outcome between the two arms was noted [67]. Of note, however, is that the overall approach of induction therapy has failed to show an improvement in overall outcome for different primary sites including larynx cancer in two phase III randomized trials [71, 72]. In both studies, however, the lack of benefit has been attributable partly to an underestimation of survival in the control arm in the setting of changing demographics in oropharyngeal SCC. In a very recent report presented at the 2014 American Society of Clinical Oncology meeting (ASCO) meeting, HPV-negative patients appear to better benefit from the induction approach [73]. The option of concurrent therapy with cetuximab was, however, added as an option making this a 2-by-2 factorial design. The discussion of the future of sequencing therapy is, however, beyond the scope of this chapter.

An interesting approach to select patients for organ preservation was based on response to a single cycle of induction chemotherapy [74]. Patients with stage III and IV larynx cancer were treated depending on their response to chemotherapy with surgical or nonsurgical approaches. The overall survival rate at 3 years was 85 %. The cause-specific survival rate was 87 %. Larynx preservation was achieved in 69 patients (70 %), indicating that excellent survival results achieved with a targeted approach to patient selection may be a result of the early selection for laryngectomy of patients likely to fail chemoradiotherapy. No solid conclusions could, however, be reached from phase II studies [74].

30.5 Definitive Chemoradiotherapy

An exciting but as yet investigational concept is the use of definitive chemotherapy for laryngeal cancer [75]. A total of thirty-one previously untreated patients with laryngeal cancer (stages T2-4, N0-1, M0), who were deemed resectable with conservation laryngeal surgery (CLS), received four cycles of paclitaxel, ifosfamide, and cisplatin (TIP) chemotherapy with or without CLS. Response was assessed histologically. With TIP chemotherapy alone, 11 patients (37 %) achieved a pathologic CR, 10 of whom (33 %) remained alive with durable disease remission and no evidence of recurrence over a median follow-up time of 5 years. Nineteen patients (63 %) treated with TIP alone achieved PR. The overall laryngeal preservation (LP) rate was 83 %, and only five patients (16 %) required postoperative RT. It is of note, however, that this patient group was carefully selected, with predominantly stage II disease, and was suitable for CLS from the outset. Also, supracricoid laryngectomy was performed which is not widely applied worldwide. This raises the question of the generalizability of this approach for T3 and T4 lesions where the standard of care remains concurrent chemo and radiation therapy or a total laryngectomy.

30.5.1 Recurrent Disease

30.5.1.1 Surgical Management

Despite many surgical options, the standard of care for surgical management of recurrent disease and/or persistent disease after attempted organ preservation treatment remains a TL [76]. Some of the best data available are those from the VA Study and follow-up studies, in which the survival rates of patients treated with organ preservation radiation and chemotherapy were not significantly different than those patients treated with primary surgery, specifically because treatment failures were still able to undergo the gold standard of TL for salvage [65]. Indeed, most organ preservation protocols involve radiation and chemotherapy for advanced stage III or IV laryngeal disease, the recurrences of which are often not amenable to less than total laryngectomy, either from tumor

size, inability to differentiate tumor from treatment effect on the tissues, or a nonfunctional organ.

Lessons learned from the VA Study also include the necessity of evaluating the neck separately from evaluation of the primary site. Early neck salvage after induction chemo followed by radiation failures was recommended [77].

However, more studies are emerging with preliminary data indicating that less than TL may be oncologically feasible in select patients with early-stage disease who have failed initial nonsurgical treatment and are still amenable to a conservation surgery attempt. In one recent study, 55 patients with laryngeal cancer that were previously treated underwent transoral surgery salvage with comparable outcomes to traditional TL [78]. Similarly, in 2006, Holsinger et al. reviewed 105 cases undergoing salvage surgery with TL ($n=73$) versus partial laryngectomy ($n=32$) and found no statistically significant difference in oncologic outcome [79]. Obviously, the key to such results is careful selection. Finally, in a large study of 662 patients with T1 or T2 initial disease who failed radiation therapy and underwent either salvage total or partial laryngectomy, up to 50 % of patients undergoing partial laryngectomy had to be yet again salvaged by TL due to disease progression [80]. Thus, current data are promising that select patients may be able to be salvaged surgically without a total laryngectomy, but the surgeon and patient must both be aware that although salvage partial laryngectomy may sometimes be feasible, a TL may yet be necessary due to disease recurrence or aspiration.

Although TL is still considered the gold standard method of surgical salvage, the current NCCN guidelines do not delineate which surgical intervention is suggested for salvage after primary nonsurgical treatment for laryngeal cancer and, instead, leave the decision to the surgeon. The choice of surgery is made on an individual basis predicated by the initial stage, the amount of residual disease, the functional status of the larynx, and the performance status of the patient [81].

30.5.1.2 Systemic Therapy

Most of the information in this section applies to recurrent metastatic SCCHN in general. Several phase II trials combining cetuximab with a platinum agent in patients who were refractory to the platinum-based combination have reached an objective response rate that does not exceed 10–13 % [82]. Cetuximab has been approved by the FDA for treatment of platinum-resistant disease as well as in combination with radiation for the treatment of locally advanced disease. In the EXTREME trial, adding cetuximab to platinum-based chemotherapy for recurrent or metastatic SCCHN significantly prolonged median overall survival from 7.4 to 10.1 months (HR = 0.8 $p=0.04$), with a prolongation of median progression-free survival from 3.3 to 5.6 months (HR = 0.54 $p<0.001$). This study showed for the first time an improvement in overall survival with the addition of cetuximab to platinum-based therapy and resulted in the longest reported survival ever seen in a phase III study, resulting in a practice-shifting change toward the use of the cetuximab combination [83]. Other targeted agents under development include newer anti-EGFR agents such as the fully humanized antibody panitumumab [84], novel anti-angiogenic therapies [85], dual EGFR and ErbB2 inhibitors [86], mTOR inhibitors [87], and inhibitors of insulin-like growth factor-1R [87], as well as c-MET inhibitors. Recent efforts are under way to better elucidate the mechanisms of resistance to EGFR monoclonal antibodies.

30.6 Radiation Therapy Techniques for Laryngeal Cancer

Early glottic cancer is best treated with simple fields, usually parallel opposed, though many patients need angulation of the beam to avoid entrance shoulders (Fig. 30.5). The use of CT-guided treatment planning as well as wedges (virtual or physical) brings the inhomogeneity of the field to 3–4 % for most patients. Schwaibold first demonstrated that fraction sizes of <2 Gy/day are associated with inferior results. For T1 disease, 63 Gy in 2.25 Gy daily fractions is a standard dosing schedule. For T2 disease, the RTOG has investigated hyperfractionation, and though not statistically significant, hyperfraction may improve local control [24].

For more advanced laryngeal cancer, being treated definitively with external radiation and chemotherapy IMRT allows salivary sparing for most patients (Fig. 30.6). Involved necks should be covered from levels 2–6 and the lateral retropharyngeal nodes. Bulky disease may dictate that level IB may need to be covered in selected cases. Contralateral coverage of the clinically negative neck may begin superiorly at the transverse process of C1 or where the posterior belly of the digastrics crosses the jugular vein. Coverage of the medial retropharyngeal nodes may not be necessary and sparing this region may be functionally important [88, 89].

For patients treated postoperatively, it is important to boost the dose to the laryngeal stoma, as tolerated, and this is conventionally done with bolus. A tracheostomy tube or aquaplast may be an effective bolus [90].

After supraglottic laryngectomy, postoperative radiation may impair the functional results. Since local failures on the glottic side are particularly uncommon, if neck dissection has not been performed, nodal irradiation with sparing of at least the laryngeal anastomosis may be the best treatment technique.

Fractionation has been an area that radiation oncologists have investigated with good results [91–94]. RTOG 9003 [91] randomized patients with locally advanced head and neck cancer to (1) standard fractionation at 2 Gy/fraction/day, 5 days/week, to 70 Gy/35 fractions/7 weeks; (2)

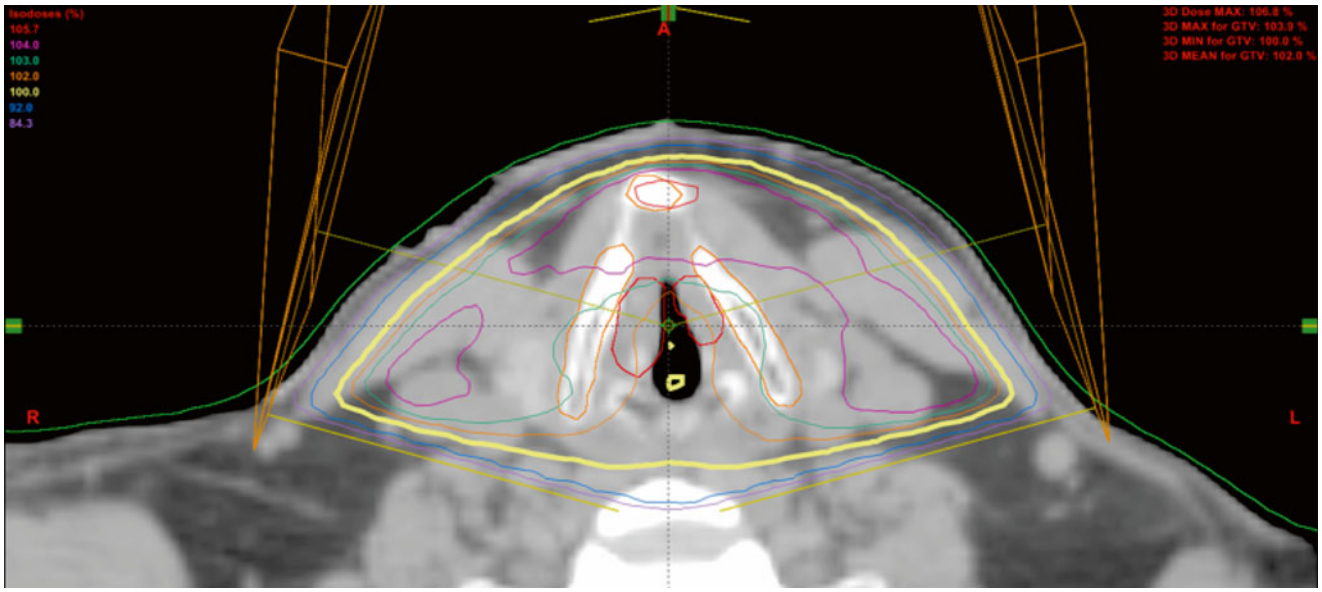

Fig. 30.5 External radiation therapy for T1N0 Glottic Cancer Isodose Plan; angled, conventional fields with wedges and inhomogeneity corrections were used

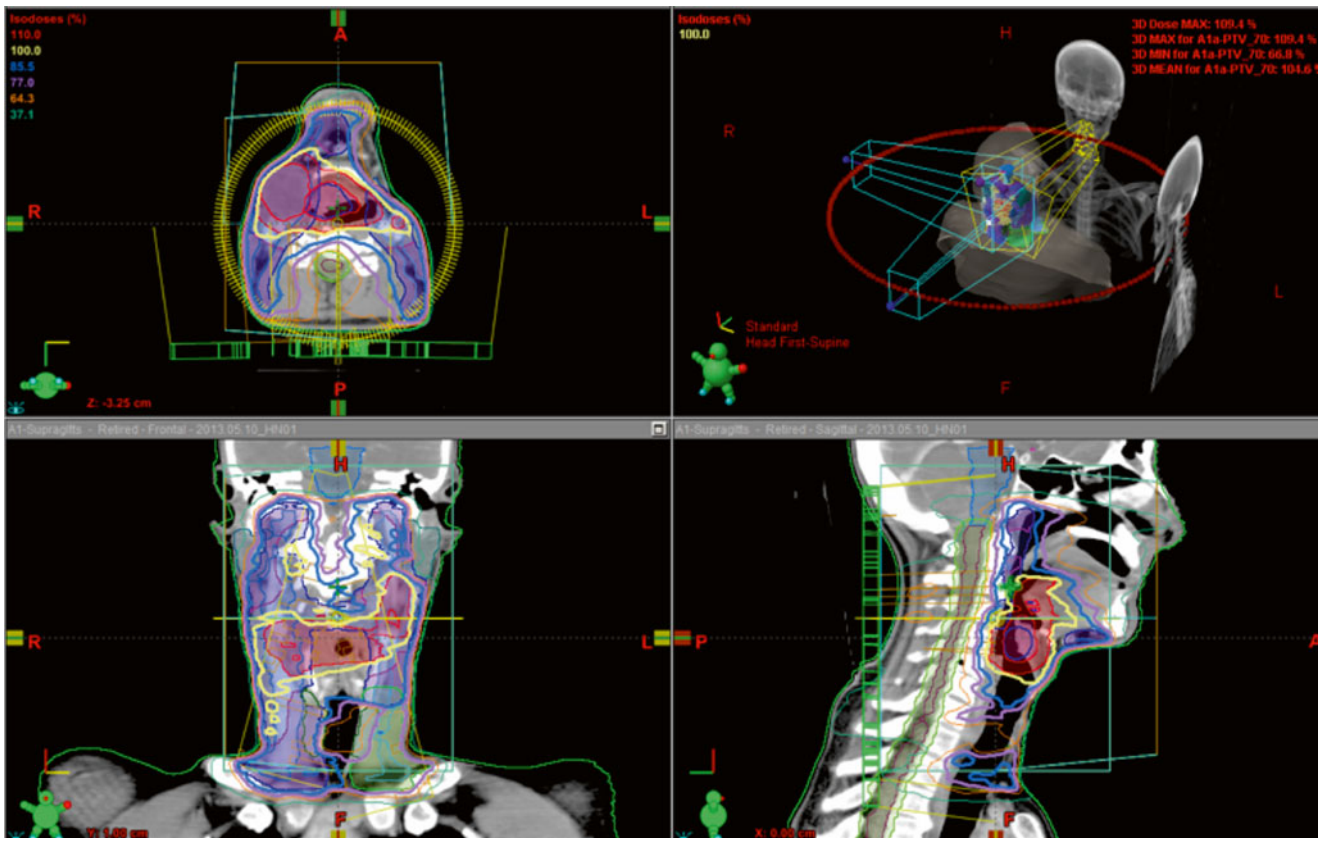

Fig. 30.6 Patient with advanced supraglottic laryngeal cancer with preepiglottic space invasion; treatment delivered with Vmat arc rotations. Tissue inhomogeneity corrections applied

hyperfractionation at 1.2 Gy/fraction, twice daily, 5 days/week, to 81.6 Gy/68 fractions/7 weeks; (3) accelerated fractionation with split at 1.6 Gy/fraction, twice daily, 5 days/week, to 67.2 Gy/42 fractions/6 weeks including a 2-week rest after 38.4 Gy; or (4) accelerated fractionation with concomitant boost at 1.8 Gy/fraction/day, 5 days/week, and 1.5 Gy/fraction/day to a boost field as a second daily treatment for the last 12 treatment days to 72 Gy/42 fractions/6 weeks. Later follow-up suggested that hyperfraction improved locoregional control without increased late toxicities [23].

RTOG 9003 was performed in the era before IMRT. IMRT allows radiation oncologists to increase the dose per fraction to gross disease while keeping dose per fraction to clinical target volumes smaller. Simultaneous in-field boosts have thus become the present-day result of some of the lessons regarding fractionation.

Most oncologists believe that concurrent chemoradiation is more effective than hyperfractionation alone for advanced disease. Data is available showing that hyperfractionation plus concurrent cisplatin improved overall survival compared to hyperfractionation alone and hyperfactionation with concurrent docetaxel, cisplatin, and 5-fluorouracil produced significantly better local-regional control than standard fractionation and the same chemotherapy [95, 96]. RTOG 0522 assessed the addition of cetuximab to IMRT radiation plus concurrent cisplatin, and those results are pending. Since RTOG 0522 required years to complete, and toxicity data was monitored by a data safety monitoring committee, it is reasonable to conclude that both regimens were tolerated.

Specific to laryngeal cancer patients, DAHANCA 6 and 7 [97] showed that six compared to five fractions per week improved voice preservation among patients with laryngeal cancer (80 versus 68 %, $p=0.007$).

30.7 Surgical Techniques

A traditional laryngectomy approach involves a U-shaped or "apron" incision in the anterior neck from mastoid tip to contralateral mastoid tip, encompassing a planned stoma just above the sternal notch. This allows exposure to the visceral compartment of the neck while also allowing both neck nodal basins to be approachable via a single incision. The visceral compartment is then separated from the rest of each neck by dividing the blood vessels and nerves entering the larynx from the hyoid bone to the trachea. The suprahyoid musculature is then dissected free from the hyoid bone superiorly, while the trachea is entered inferiorly with care taken to be well below the inferior-most extent of tumor. The stoma is then created in an appropriate position. The aerodigestive tract is then usually entered at the vallecula, depending on the superior limit of the tumor. This allows retraction of the larynx anteriorly for direct visualization of the tumor and facilitates further mucosal cuts around the tumor with adequate margins. The thyroid lobe ipsilateral to the tumor is often left in continuity with the larynx. The last mucosal cuts along the postcricoid region fully deliver the specimen from the patient. Once negative margins are reached, the mucosal defect can usually be closed primarily, traditionally by hand sewing the defect, or sometimes with an automatic linear stapler [98]. More widely resected tumors may result in defects too large for primary closure, requiring reconstruction of the pharyngoesophageal defect with regional flaps (pectoralis major myocutaneous flap) or free fasciocutaneous flaps (radial forearm flap, anterolateral thigh flap).

Neck dissection is performed concurrently if there are clinically known positive nodes, or if there is a high probability of occult nodal metastases. In advanced disease, a selective neck dissection of levels II–IV is likely adequate for N0 necks with formal modified neck dissections likely reserved for clinically N+ necks [99].

On the near horizon, a promising adjunct to traditional surgical treatment of laryngeal cancer is emerging in the form of transoral robotic surgery with carbon dioxide laser (TORS). The use of laser with transoral approach has been established as a viable method for treating select laryngeal tumors for many years and even in some advanced diseases [100]. However, with the addition of robotic technology, the application of the transoral approach is broadened due to the finer control and more advantageous angle of dissection than is possible with traditional transoral exposure. Although not currently FDA approved at the time of this writing, several institutions have shown feasibility and potential benefits in experimental use [101, 102]. Whether this technique eventually replaces the traditional external approach, much like laparoscopic surgery and robotic urologic surgery have in their respective specialties, remains to be seen.

30.8 Voice and Swallowing Changes

Total laryngectomy is one of the surgical procedures most feared by patients. Body image reintegration is critical to subsequent quality of life after head and neck cancer surgery. When disfigurement and dysfunction is associated with treatment, quality of life may be profoundly and adversely affected [103, 104]. To determine how head and neck cancer patients prioritize potential treatment effects in relationship to each other, 131 patients were assessed pretreatment using standardized quality of life (QOL) measures (Functional Assessment of Cancer Therapy-Head and Neck) and performance (Performance Status Scale for Head and Neck Cancer). Patients were also asked to rank a series of 12 potential head and neck cancer treatment effects. The data suggest that, at least in the pretreatment period, survival is of primary importance

to patients. Patients might be more willing than nonpatients to undergo aggressive treatments and endure acute distress in the interest of potential long-term gains [105].

Effective treatment for laryngeal cancer concerns the preservation of voice. Supracricoid partial laryngectomy can have a significant social and professional impact. Patients may find themselves withdrawing from society and the work force in which vocal involvement is essential. The potential postsurgical social voice impact should be taken into consideration before proposing surgery, and it is essential to estimate the possible impacts of the vocal handicap according to the patient's professional or other activities. Progress has been made in treatment, rehabilitation, restoration of the airway, and nonsurgical treatments. With the introduction of tracheo-esophageal speech and voice prosthesis, many treated patients acquire socially acceptable speech after TL and maintain satisfactory quality of life [106]. Successful voice restoration can be attained with any of three speech options, namely esophageal speech, electro-larynx, and tracheo-esophageal (TO) speech using an artificial valve. Although no single method is considered the best for every patient, the tracheo-esophageal puncture (TEP) has become the preferred method in the past decade [106]. It remains unclear, however, as to whether a primary TEP during the TL would be better in comparison to a secondary procedure. Recent evidence suggests that even though it provides immediate satisfactory voice rehabilitation, primary TEP may be associated with a shorter prosthesis lifetime [107].

Even in the absence of symptoms, if nonsurgical therapy is being considered, patients with advanced laryngeal cancer should undergo a swallowing assessment, to detect possible aspiration and initiate therapeutic maneuvers and swallow precautions. Pretreatment swallowing assessment results in measurable improvements in posttreatment swallowing in patients undergoing concomitant radiation and chemotherapy [108, 109].

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Programs of Organ and Function Preservation

31

Jean Louis Lefebvre

Abstract

An intensive clinical research has been carried out over the past three decades aiming to avoid performing a total laryngectomy. Large partial open procedures or endoscopic laser CO_2 surgery may be an alternative to total laryngectomy in very highly selected cases. Altered fractionated radiotherapy has proved to be more efficient than conventional radiotherapy. However, most of the research has been done by combining chemotherapy and radiotherapy. The first programs used induction chemotherapy (cisplatin and 5-fluorouracil with or without docetaxel) followed by radiotherapy in good responders. Toxicity was acceptable, neither disease control nor survivals were compromised, and larynx could be preserved in at least two-thirds of the cases. The second programs used concomitant chemoradiotherapy. Concurrent chemoradiotherapy provided higher larynx preservation rates but at the price of a substantial acute and late toxicity potentially compromising the larynx function. Alternating chemoradiotherapy did not increase toxicity, but larynx preservation was similar to induction chemotherapy. Whether concurrent or alternating, there was no improvement of survival. A recent randomized phase II has assessed induction chemotherapy followed by radiotherapy with either concurrent chemotherapy or concurrent biotherapy without difference between both arms. One ongoing phase III trial assesses induction chemotherapy with or without biotherapy followed by chemoirradiation with or without this biotherapy.

Keywords

Larynx • Hypopharynx • Chemotherapy • Biotherapy • Radiotherapy • Surgery

31.1 Introduction

Surgery has been the first treatment of larynx and hypopharynx cancers. This surgery was initiated at the end of the nineteenth century for larynx cancer and quite simultaneously consisted of either partial or total laryngectomy. At the very beginning of the twentieth century, radiotherapy was also used for the treatment of laryngeal malignancies. As a result, from the start there were two major options: surgery or radiotherapy. All along the twentieth century, an intensive surgical research has allowed fine-tuning the indications and techniques of the various partial surgery procedures. With time some large partial procedures have been validated for cases that were until then only amenable to a total laryngectomy. That is the case, for example, of the supracricoid partial laryngectomies. Endoscopic laser surgery has also been a major advance. But open and endoscopic partial surgeries are indicated most often for quite limited tumors. Radiotherapy techniques have also been improved (better conformation of irradiated fields to the tumor volume, modification of the fractionation).

Larynx preservation has been a major advance in head and neck cancer management over the past three decades.

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The goal of larynx preservation is to control the disease and to maintain in place a functioning larynx. This definition of larynx preservation is only meaningful if indicated for advanced larynx and hypopharynx cancers that are, if surgery is considered, only resectable by a total laryngectomy. These cases have been until the 1980s treated either by total laryngectomy with postoperative radiotherapy if indicated or by definitive radiotherapy with surgery in reserve in case of failure. These two options have never been compared in a randomized trial that should have been the first larynx preservation program. Each option was indicated according to institutional policies. The appearance of active chemotherapy regimen in the early 1980s has had a definite impact on this discussion.

31.2 Programs with Partial Surgery

Some teams have explored the reliability of supracricoid laryngectomy in selected T3 and T4 larynx cancers [1, 2]. Some other teams have extended the indications of endoscopic laser surgery to T3 or T4 larynx or hypopharynx cancers [3–7]. Both have got undisputable satisfactory results but on quite limited series. Clearly, there is a room for these indications but for highly selected cases and for very experienced surgical teams and they are not on a large scale a real alternative to total laryngectomy. Transoral robotic surgery is under evaluation but again for early diseases.

31.3 Programs with Definitive Radiotherapy

Many reports have shown the improvement of radiotherapy results thanks to a modification of the fractionation. The goal is either to increase the total dose by means of delivering more than one fraction per day (hyperfractionated radiotherapy) or to decrease the overall treatment time (reducing the ability of tumor cell repair and repopulation). A recent meta-analysis [8] has assessed the impact of altered fractionated radiotherapy on survival. A total of 6515 patients enrolled in 15 randomized trials were included in the analysis. There was a significant 3.4 % benefit in survival at 5 years as well as there was a significant better local control. The major improvement in 5-year survival was found for hyperfractionated radiotherapy (8 %). The effect of altered fractionated radiotherapy on tumor control did not differ according to the primary site. However, the impact of altered fractionation on larynx preservation is probably limited. The acute toxicity of these treatments may be a limit due to the cartilaginous structure of the larynx, due to the impact of mucositis on larynx function and due to the vulnerability of the cricoarytenoid joints.

31.4 Programs Based on Chemotherapy and Radiotherapy

31.4.1 Programs with Induction Chemotherapy

In the early 1980s, the Wayne State University team reported their experience with platinum-based induction chemotherapy and in particular with the cisplatin and 5-fluorouracil regimen. Previously, untreated patients demonstrated impressive response rates at the primary tumor site. When subsequently treated with radiotherapy good responders to induction chemotherapy appeared to be also good responders to irradiation while poor responders to induction chemotherapy were also poor responders to the subsequent irradiation [9, 10].

These reports had a tremendous impact on the daily practice and induction chemotherapy was widely used for head and neck cancer. But a large meta-analysis [11] failed to find a significant advantage of induction chemotherapy in terms of survival. However, it must be stressed that when induction chemotherapy consisted of cisplatin and 5-fluorouracil, there was a significant 5 % improvement of the 5-year survival.

But the undisputable merit of induction chemotherapy has been to reopen the discussion on larynx preservation. If the discussion on a randomized comparison of radical larynx surgery versus definitive irradiation had not get the consensus between surgeons and radiation, on the contrary comparing radical surgery versus definitive irradiation in good responding patients after induction chemotherapy appeared acceptable. The first program on larynx preservation could really start.

31.4.2 Programs with Cisplatin and 5-Fluorouracil (PF) Induction Chemotherapy

The goal was to compare total laryngectomy with neck dissection with or without postoperative irradiation versus PF induction chemotherapy followed by irradiation (keeping total laryngectomy in reserve for salvage if necessary) in good responders or by total laryngectomy with or without postoperative irradiation in poor responders.

The Department of Veterans Affairs Laryngeal Cancer Study Group reported in 1991 the first randomized trial on larynx cancers [12]. Three hundred and thirty-two patients were randomly assigned to be treated by total laryngectomy or to receive two cycles of PF followed in responders (partial or complete responders) by a third cycle and irradiation or by total laryngectomy in nonresponders. In this trial 63 % of the patients had a supraglottic tumor and 37 % had a glottic cancer, and 57 % had larynx fixity. There was no significant

difference in survival between both arms (68 % at 2 years). At 4 years, two-thirds of the survivors in the chemotherapy arm had retained their larynx. These data were updated regularly in various meetings and these results did not vary with time. A quality of life study has been carried out on 46 survivors of this trial (25 in the surgery arm and 21 in the chemo arm). Better scores were found in the chemotherapy arm patients as regards more freedom of pain, better emotional well-being, and lower levels of depression. But surprisingly there was no correlation between quality of life scores and preservation of the speech function.

The European Organization for Research and Treatment of Cancer (EORTC) published in 1996 a similar trial on hypopharynx (78 %) and lateral epilarynx (22 %) tumors only eligible for a total laryngectomy with partial pharyngectomy [13]. Two hundred and two patients were enrolled in this study comparing the standard treatment (surgery and postoperative irradiation) versus two or three cycles of PF followed in clinically complete responders at the primary site by irradiation or, for other patients, by the conventional treatment. For the 194 evaluable patients, there was no significant difference in survival, despite a notable difference in median survival favoring the experimental arm (44 months) when compared with the surgery arm (25 months). Finally, at 3 and 5 years, half the survivors in the chemotherapy arm had retained a functional larynx. This trial was updated with a 10-year follow-up and these results were confirmed [14]. Of note in this trial there was a specific analysis of the impact of induction chemotherapy on tolerance and quality of the subsequent treatments. Radiation therapy was not compromised by the previous chemotherapy as well as there was no unforeseen treatment interruption due to acute toxicity. Salvage surgery in poor responders had similar postoperative courses and similar quality of surgical margins when compared with patients treated in the surgical arm.

The French group (GETTEC) published also in 1998 a randomized trial on larynx cancer. Patients were randomized to receive either the standard treatment (total laryngectomy) or three cycles of PF followed by irradiation in case of clinical response over 80 % or by total laryngectomy in the other cases [15]. In this trial, the selection was more restrictive than in the North-American study since all tumors were classified T3 and all patients had larynx fixity while only 31 % had a supraglottic tumor and 69 % had glottic or transglottic tumor and all had larynx fixity. The trial was prematurely closed due to a poor accrual. The 2-year survival was significantly higher in the surgery arm (84 vs. 69 %), but 15 of the 36 patients (42 %) enrolled in the chemotherapy arm avoided surgery.

These three trials were pooled in a subset analysis of the abovementioned large meta-analysis [11]. It appeared that there was a nonsignificant 6 % decrease in survival in the chemotherapy arms when analyzed together that was balanced by a 56 % larynx preservation rate.

31.4.3 Programs with Docetaxel, Cisplatin, and 5-Fluorouracil (TPF) Induction Chemotherapy

In 2007, two randomized trials comparing the PF induction regimen with the TPF one were simultaneously published. The TAX 323 [16] trial assessed this comparison for nonresectable tumors to be treated after the induction phase with radiotherapy alone. The TAX 324 trial [17] assessed this comparison for either resectable or nonresectable tumors to be treated thereafter with radiotherapy and concurrent weekly carboplatin. Both trials concluded that the overall survival and locoregional control were significantly higher in the TPF arm with a reduction as high as 30 % in risk of death. This superiority of the TPF regimen was also supported by another specific meta-analysis. The TPF regimen is considered as the new standard for induction chemotherapy.

The French group GORTEC published in 2009 a randomized trial comparing PF and TPF as induction chemotherapy followed by irradiation in case of response of at least 50 % in larynx and hypopharynx cancers [18]. A total of 213 patients were enrolled in this study. With a median follow-up of 3 years, there was no difference in terms of survival, but the 3-year actuarial larynx preservation rate was 70.3 % with TPF versus 57.5 % with PF (p=0.03). J Natl Cancer Inst; 2015 Dec 16;108(4). pii: djv368. doi: 10.1093/jnci/djv368. Print 2016 Apr

31.5 Conclusions for the Programs with Induction Chemotherapy Followed by Irradiation in Good Responders

- The addition of induction chemotherapy for larynx preservation did not compromise the survival when compared with upfront surgery.
- Induction chemotherapy did not compromise subsequent treatment (either salvage surgery of definitive irradiation) in terms of tolerance or of efficacy.
- None of the different induction chemotherapy regimens (PF or TPF) has been able to improve survival in larynx preservation programs.

31.5.1 Programs with Concomitant Chemoradiotherapy

Concomitant chemoradiotherapy may be delivered with two different schedules.

Chemotherapy may be given either during irradiation without interruption in radiotherapy (concurrent chemoradiotherapy) or alternatively with radiotherapy during the radiation protocol (alternating chemoradiotherapy).

The advantage of concurrent chemoradiotherapy has been demonstrated by the meta-analysis and the administration of cisplatin at the dose of 100 mg/m^2 on days 1, 22, and 43 of a conventional 70 Gy irradiation has been shown as the highest advantage [11, 19].

Alternating chemoradiotherapy delivering four cycles of PF (on weeks 1, 4, 7, and 10) and three courses of radiotherapy at the dose of 20 Gy in 2 weeks (weeks 2–3, 5–6, and 8–9) for a total of 60 Gy has been reported as feasible and able to improve survival and disease control [20, 21].

31.5.2 Programs with Concurrent Chemoradiotherapy

The RTOG published in 2003 a large three-arm randomized trial [22]. In this trial, 547 patients were randomized to receive in one-arm PF induction chemotherapy followed in responders by irradiation in another arm concurrent chemoradiotherapy (with cisplatin) or in the third-arm radiotherapy alone. With a median follow-up of 3.8 years, the highest 2-year larynx preservation rate was found in the concurrent arm (88 %), while there was no difference in 5-year overall survival between the three arms. As regards acute toxicity, the grade 3–4 mucositis was twice higher in the concurrent arm when compared with the two others. The complication rate after salvage laryngectomy did not differ between the three arms. This trial was updated and the final results were published in 2013 [23] with a median follow-up of 10.8 years. Both the induction and the concurrent arms provided a significantly better laryngectomy-free survival (primary end point) over radiotherapy alone (induction vs. radiotherapy HR .75 for a 95 % CI of .59–.95, concurrent vs. radiotherapy HR .78 for a 95 % CI of .78–.98). However, the highest rate of larynx preservation was found in the concurrent arm. As regards overall survival, there was no significant difference between both arms despite a trend for a worse survival in the concurrent arm due to a significantly higher rate of noncancer-related deaths.

There was no increase in late toxicity reported for this trial. However, the RTOG reported a combined study [24] of three concurrent chemoradiotherapy arms from three randomized trials conducted by this group (RTOG 91-11, RTOG 97-03, and RTOG 99-14). The aim of this study was to assess severe toxicity that occurred in 43 % of patients. Severe late toxicity was found in particular for larynx and hypopharynx cancer.

31.5.3 Programs with Alternating Chemoradiotherapy

The EORTC published in 2009 a randomized trial comparing induction chemotherapy and alternating chemoradiotherapy in patients with advanced tumor of the larynx or hypopharynx candidates for a total laryngectomy [25]. In the induction arm, patients with a 50 % or more reduction in primary tumor size after two cycles of PF received another two cycles, followed by radiotherapy (70 Gy total). In the alternating arm, a total of four cycles of PF (in weeks 1, 4, 7, and 10) were alternated with radiotherapy with 20 Gy during the three 2-week intervals between chemotherapy cycles (60 Gy total). A total of 450 patients were enrolled in this trial. With a median follow-up of 6.5 years, survival with a functional larynx was similar in sequential and alternating arms as were similar larynx preservation rates and overall or progression-free survivals. The acute toxicity was slightly lower in the alternating arm, but there was no difference in late toxicity.

31.6 Conclusions for the Programs with Concomitant Chemoradiotherapy

- Concurrent chemoradiotherapy provides the highest larynx preservation defined as the larynx in place.
- Concurrent chemoradiotherapy generates a substantial acute toxicity.
- Late toxicity after concurrent chemoradiotherapy may compromise the laryngeal function. It is important to stress that for quality of life only the preservation of a functioning larynx is meaningful.
- Neither concurrent nor alternating chemoradiotherapy improves survival.

31.6.1 Programs with Sequential Chemoradiotherapy (I.E. Induction Chemotherapy Followed by Concurrent Chemoradiotherapy)

The TAX 324 trial (PF vs. TPF before radiotherapy and concurrent weekly carboplatin) showed the feasibility of sequential chemoradiotherapy [17]. Meanwhile, a randomized trial on biotherapy comparing radiotherapy alone and radiotherapy with concurrent administration of a monoclonal antibody targeting the EGFR (cetuximab) showed that this combined treatment provided a significantly higher overall survival and locoregional control than radiotherapy alone, this improvement being in the range of that observed with concurrent chemoradiotherapy but without an increased acute mucosal toxicity [26].

31.6.2 Programs with Sequential Chemoradiotherapy

A subset analysis of the TAX 324 trial was carried out on 166 patients with larynx or hypopharynx cancer [27]. The same improvement in overall survival and progression-free survival in the TPF arm was found for this subgroup of patients as for the overall population. Among the 123 operable patients, the laryngectomy-free survival was also significantly greater.

The Ann Arbor group explored larynx preservation in 36 patients with T4 larynx cancers [28]. Usually these tumors are excluded from larynx preservation trials. Patients received one cycle of PF. In case of response of at least 50 % the patients received thereafter chemoradiotherapy with adjuvant PF in case of clinically complete response. The larynx preservation rate was of 58 %.

31.6.3 Programs with Sequential Biotherapy

The GORTEC group reported in 2013 the results of a randomized phase II trial in patients with larynx or hypopharynx tumor [29]. One hundred and fifty-three eligible patients were enrolled to receive three cycles of TPF. In case of response of at least 50 % they were randomized to receive either concurrent chemoradiotherapy with cisplatin or concurrent radiotherapy and cetuximab. Only 74 % of patients could receive the planned induction chemotherapy protocol. After induction chemotherapy 76 % of patients were randomized: 60 in the chemoradiotherapy arm and 56 in the bioradiation one). Only 45 % of patients randomized in the cisplatin arm could receive the planned three cycles of cisplatin, while 71 % of patients randomized in the cetuximab arm could receive the full protocol. With a median follow-up of 36 months, there was no obvious difference between both arms as regards the primary end point (larynx in place without persistent disease 3 months after treatment): arm cisplatin 95 % for a 95 % CI 86–98 and arm cetuximab 93 % for a 95 % CI of 83–97. There was no obvious difference in secondary end points at 18 months: larynx function preservation (87 %; 95 % CI, 76–93 % in the cisplatin arm and 82 %; 95 % CI, 70–90 % for the cetuximab arm) or in overall survival (95 % CI, 82–96 % in the cisplatin arm and 89 %; 95 % CI, 79–95 % in the cetuximab arm). Despite there were fewer local failures in the cisplatin arm, salvage surgery was successful only in the cetuximab one resulting in a similar ultimate local control. A longer term evaluation is ongoing.

Another phase III trial is ongoing in Germany, the DeLOS II trial. 170 patients with only laryngectomy-operable laryngeal/hypopharyngeal SCC were randomized between 3 cycles of induction docetaxel cisplatin and 5-fluorouracil with or without cetuximab followed by irradiation with or without cetuximab. In case of response below 30 % after the first cycle patients underwent immediate salvage surgery. In the interim analysis due to toxicity 5-fluorouracil was removed from the induction chemotherapy. Very preliminary results were published in 2014 with promising survival with a functional larynx that was reached in 31.4 % vs. 17.0 %, favoring the cetuximab arm (HR 0.502 [0.267–0.944]; $p = 0.0289$) but that require a much longer follow-up [30].

31.7 Conclusions for the Programs with Sequential Chemoradiotherapy

- Sequential chemoradiotherapy is potentially a new option, but delivering the standard induction chemotherapy followed by the standard concurrent chemoradiotherapy generates a substantial overall toxicity.
- The integration of biotherapies may overcome this concern, but clearly sequential chemoradiotherapy (either with cisplatin or a biotherapy such as cetuximab) remains to be evaluated on a large phase III trial specifically designed for larynx preservation.

31.8 Discussion

Larynx preservation is an important new concept that has been developed for tumors of the larynx and of the hypopharynx that can be removed only by a total laryngectomy. Extensive tumors (T4) and very infiltrative transglottic tumors are at least for the moment better controlled by an upfront total laryngectomy.

If the concept of larynx preservation is nowadays considered as a validated option, the best larynx preservation protocol remains to be defined. It is noticeable that all these trials even if they were conducted with the goal of larynx preservation had different definitions of larynx preservation: from the simplest one (larynx preservation = larynx in place) to the most complex one (survival with a larynx free of tumor and without tracheotomy or feeding tube). A detailed quality of the function of the preserved larynx is often missing. A consensus should be reached in designing future trials [31, 32].

None of the larynx preservation protocols has had an impact on survival. This means that none provided a better survival than an upfront total laryngectomy. Whatever the protocol, distant metastases remain a concern.

It must be underscored that these larynx-preserving protocols did not compromise disease local control and survival because the surgeons performed salvage surgery. It must be kept in mind that surgery plays an important role in this research. To this extent much attention must be paid to acute and late toxicity not only for the quality of the function of the larynx but also for the feasibility and reliability of salvage surgery.

Larynx preservation is a challenging approach that is permanently moving. Induction chemotherapy has the advantage

of allowing adapting the subsequent treatment quite early in the treatment program. Concurrent chemoradiotherapy provides high local control but at the price of a substantial acute and late toxicity. Both has advantages and disadvantages; combining both is a logical new step in this clinical research, but the balance between the induction and the concurrent phases remains to be defined. Finally, biotherapies have a role to play in this research. More than ever a multinational–multidisciplinary collaboration is requested.

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Principles and New Approaches in Surgical Reconstruction

32

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Abstract

The reconstruction of oncological defects remains a critical element in the surgical treatment of head and neck cancer. Goals of reconstruction are wound healing, vital structure protection, function, and cosmoses. In this chapter, we discuss the reconstructive ladder as it applies to defects of the oral cavity, or pharynx, nose, orbit, misfile, hypopharynx, larynx, and cervical esophagus. Patient cases are shown to illustrate outlined principles. New approaches in surgical reconstruction are discussed, including salvage surgery after failed chemoradiotherapy, the use of perforator flaps, and the frontier of transoral laser microsurgery defects that require flap reconstruction.

Keywords

Transoral laser microsurgery • Tongue reconstruction • Facial reconstruction • Radial forearm free flap • Laryngeal organ preservation • Hypopharynx reconstruction • Oral cavity defect

32.1 Reconstruction of Surgical Defects: Principles and Goals

The scientific community that is concerned with head and neck cancer had to face that alternative multimodality treatment of squamous cell carcinomas of the head and neck (HNSCC) also has handicaps like early and late toxicities, reduced functional outcome, and treatment failure leading to high-risk salvage surgery with several complications in many cases. To address this problem, Lefebvre and Ang [1] worked out a list of guidelines for better outcome specification after organ preservation therapy, which should be used (not only) in further clinical trials. These guidelines describe a new endpoint: "laryngoesophageal dysfunction-free survival," implicating the highly important issue of late functional outcome. Today's main guidelines for treatment in HNSCC are still based on phase III trials and comprehensive meta-analyses (MACH; [2]), with excess of radiation or chemoradiation studies at the expense of surgical trials. As stated by Higgins and Wang [3], clinical recommendations for HNSCC treatment based on evidences are difficult due to a disproportion of surgical and nonsurgical trials. This conflict is triggered by the fact that instruments for evaluating best surgical practice are different from methodological standards in nonsurgical phase II or III trials. But, going back to clinical routine, well-established and proven standards in surgery of HNSCC are defined as state-of-the-art tumor resection procedures and reconstruction, following consented resection criteria like clear margins (R0 resection) [4]. In general, as recently proposed by Wittekind et al. (2009), the inclusion of the minimal distance between tumor

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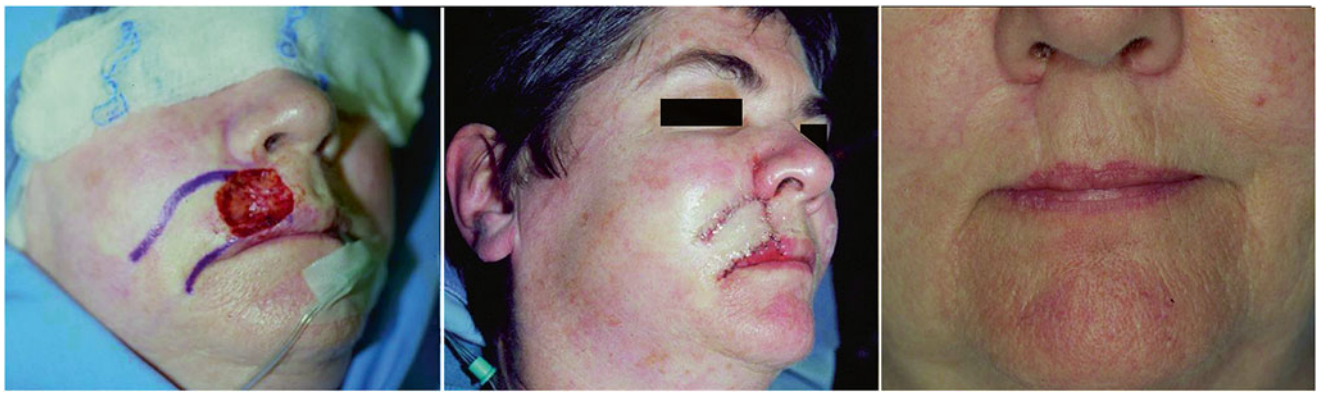

Fig. 32.1 The principle of subunits in facial reconstruction. A right upper lip defect is shown following the excision of a skin cancer. A local tissue advancement flap was designed along relaxed skin tension lines and used to reconstruct the upper lateral lip subunit. The medial suture line was placed along the philtral ridge. The resulting scars are camouflaged

tissue and resection margins into the current R classification would be useful [5]. In HNSCC a distance of 5 mm in minimum (except tumors of the glottis fold) is highly recommended. Also standardized neck dissection [6] should be included into the tumor stage-related surgical concept. Altogether, primary surgery and additional adjuvant treatment of HNSCC is ever recommended if R0 resection is possible (also consequently ignoring biomolecular tumor configurations in today's clinical routine). Therefore, the choice of either surgery or multimodality treatment is mainly based on clinical experience and medical culture since there is still a high degree of haziness in view of the best biology-based treatment. To conclude, the treatment decision should be based on an interdisciplinary view (tumor board) on best tumor-specific and overall survival, best late functional outcome, and best consideration of individual patient's needs.

In case of decision for primary surgery, the reconstruction of a surgical defect follows a generalized set of principles applied to the patient's anatomic and functional deficit(s). These principles allow the surgeon to reconstruct a wide variety of defects to achieve optimal functional and aesthetic outcomes for patients, implication of high-level surgical skills, and competence as indispensable part of the interdisciplinary treatment team. Before a patient is ever taken to the operating room, the potential defect and postoperative functional and cosmetic results should be known and accepted by both the patient and the surgeon. In addition, a consequent oncologically sound resection must be performed, meaning the surgeon must not compromise the complete excision of neoplastic disease, even if a larger or more challenging reconstructive defect may result.

The first and most basic principle in reconstructive surgery applies to the creation of a defect. When planning to make incisions, these should be made in areas of low tension to facilitate optimal wound healing. If incisions are made in a cosmetic area, such as the face, this is especially important. The facial relaxed skin tension lines, such as the melolabial crease, are often diagrammed in textbooks to convey this point. Further, the creation of surgical defects should be mindful of aesthetic and functional subunits (Fig. 32.1).

Incisions should not cross subunits if this can be prevented, and in surgeries involving facial or neck tissue, the excision of an entire subunit often allows for better reconstructive results. In the creation of a surgical defect, the surgeon should be mindful of its functional, aesthetic, and psychological impact upon the patient. A reconstructive plan should be made before a resection ever takes place.

The second principle in reconstructive surgery applies to the repair of a defect and follows a sequence often referred to as the "reconstructive ladder." As this analogy suggests, wound management should begin with the most simple technique first and then progress to more complex rearrangement and transfers as needed. The strategy ultimately chosen should provide the best functional and cosmetic outcome for patients, yet pose the least surgical risk. The dense anatomical structures in the head and neck, coupled with limited soft tissue redundancy, must be allowed for in surgical planning.

The lowest rung of the ladder, and therefore the simplest option for defect closure, is to allow a wound to heal on its own with no intervention, so-called secondary intention. In the head and neck, some limited mucosal and superficial cutaneous or scalp defects will heal well by secondary intention. The next option is to reapproximate wound edges in a primary closure, although when tissue is missing, this method effectively becomes repair by local advancement flaps. When tension or tissue loss negates this type of repair, skin grafting or tissue expansion techniques may be used. Alternately, local or regional tissue can be inset into a wound bed by creating transposition, advancement, or rotation flaps. If wounds involve multiple tissue layers, such as the skin, subcutaneous fat, muscle, and mucosa, the use of a skin graft or local flap may lack adequate volume, strength, or function;

in these cases, the use of composite grafts, composite local flaps (e.g., the Gilles fan flap), pedicled flaps, or microvascular free flaps must be considered.

A "flap" refers to tissue that is moved from a donor to recipient site and carries its own blood supply. Although there are multiple classification schemes for flaps, the two main types that will be discussed here are pedicled flaps and microvascular free flaps. These two flaps differ from each other in that pedicled free flaps remain connected to their native blood supply, either random or axial, while microvascular free flaps are tissue units with axial vessels, completely separated from their donor site and then connected to a recipient vein and artery at the defect.

A pedicled flap offers some advantages in head and neck reconstruction. As exemplified by the pectoralis major myocutaneous flap popularized in 1979, pedicled flaps can be inset into a wound in a single stage and bring with them a robust and reliable blood supply [7]. Pedicled flaps are best suited for defects requiring tissue bulk for a multilayer tissue closure in which minimal tissue folding is required. They are also potentially a good choice for reconstruction when a patient has vascular disease or donor site morbidity that would preclude the use of a microvascular free flap. However, the arc of rotation for a pedicled flap is limited, and the pedicled nature of the blood supply limits tissue molding, sculpting, and tubing. The bulk of pedicled flaps also limits their functional use when used in the oral cavity or alimentary tract. Other pedicled flaps used in head and neck reconstruction include the latissimus dorsi flap, trapezius flap, deltopectoral flap, temporoparietal flap, and scapular flap [8–12].

Microvascular free tissue transfers offer distinct advantages in head and neck reconstruction for use in scalp, facial, oral cavity, osteocutaneous defects, and pharyngeal defects. The ability to mold and sculpt microvascular free flaps to three-dimensional forms allows them to be used in a multitude of settings. Although first described in case reports, such as the use of a free jejunal segment for cervical esophageal reconstruction in 1959 [13], subsequent angiosome mapping has inspired many different free flaps for reconstructive use [14]. By understanding angiosomes as discrete subunits of vascularized tissue with identifiable and reasonably predictable zones of blood supply, free flaps with both bone and soft tissue from all over the body can be designed and tailored to suit a specific defect. High-utility flaps in head and neck reconstruction have been the radial forearm and anterolateral thigh free flaps, which afford low donor site morbidity, and vascular pedicles with good length and vessel caliber (recommended artery caliber 2–2.5 mm) [15, 16]. For defects requiring bony and soft tissue reconstruction, a fibular osteocutaneous free flap can be used to bridge large or mandibular defects and provide a skin paddle for intra-, extraoral, or combined use [17, 18]. For shallow defects requiring tissue coverage without excess bulk, the thinned anterolateral thigh flap is ideal [19].

Although free flap success has been the rule due to advances in microsurgical techniques and technologies, flap "salvage" is necessary if arterial or venous flow is compromised [20–22]. Impairment of the flap macrocirculation can be addressed by exploring and revising vascular anastomoses, with the removal of any occluding thrombi. To minimize mainly venous problems, end-to-side anastomosis of the flap vein to the internal jugular vein proved to be highly sufficient. Moreover, new coupler systems offered smooth adaption of the veins and could reduce the operation time (Bild). Damage to the microcirculation or interstitial areas of the flap can be more difficult to remedy, with techniques ranging from thrombolytic agents, hyperbaric oxygen, to leeching of the flap [23–25]. In principle, operation time (cut to suture) and intraoperative blood loss turned out to be independent risk factors for postoperative morbidity, and therefore, two teams should work in parallel (tumor and flap team) to save time and to keep the ischemic period as short as possible.

As transferred tissue heals and inosculates, revising the flap may be necessary to improve function and contour. Bulky flaps may need to be thinned in order to improve functional results, and tethered tissues may need to be released. Flap revision is especially important for reconstructions of the tongue for speech or to afford swallowing if tissue transfer has caused dysphagia and obstruction from excess bulk in the pharynx [26].

Ultimately, the choice of reconstructive technique must afford patients with the best functional outcome that poses the least surgical risk, and these factors must be carefully weighed for each individual. By applying basic principles and carefully negotiating the reconstructive ladder, patients can have restored aesthetics and function after the resection of disease.

32.2 Goals of Reconstruction: Wound Healing, Vital Structure Protection, Function, and Cosmesis

The overarching goal of reconstructive surgery is to create new tissue arrangements that serve in place of native structures, allowing for form to follow function. Because of the enormous complexity and interrelatedness of the deep tissue function, surgery of the head and neck poses unique challenges in achieving reconstructive results that go beyond simple wound healing. The reconstructive surgeon must devise strategies that preserve a patient's ability to eat, speak, swallow, and breathe, in addition to yielding an acceptable aesthetic outcome and quality of life. A site of defect-based approach to reconstruction will be discussed here and will incorporate general principles and techniques in treating defects of the oral cavity, oropharynx, hypopharynx, esophagus, larynx, midface, and orbit.

32.2.1 Oral Cavity

The mouth or oral cavity encompasses the lips, alveolar ridges, floor of the mouth, retromolar trigone, buccal regions/cheeks, and hard palate. These structures rest on the foundation of the mandible. The primary functions of the oral cavity include mastication, speech, facial expression, and early deglutition. The oral preparatory stage and oral phase of swallowing take place in the mouth. Oral cavity malignancy can leave a patient with a postsurgical defect that impairs any one of these essential functions. Reconstructive efforts should focus on maintaining oral competence, tongue bulk and mobility, and the ability to initiate a swallow.

Beginning with defects of the lip or oral soft tissue, the surgeon needs to consider the wound in terms of location, size, and thickness. Due to the highly cosmetic impact of lip reconstruction, few areas should be left to heal by secondary intention, but include superficial vermillion and cutaneous and inner mucosa lip defects, especially those that are in close proximity to the alar–cheek junction. A local advancement design with linear repair may be considered when the defect occupies less than 30–35 % of the lip. Limitations to primary closure include potential for microstomia as well as cosmesis. Full-thickness skin grafts can be used for superficial cutaneous defects, but often do not provide a cosmetically favorable result compared to local flap options. A wide variety of local flap options exists for lip reconstruction and are designed based on the involvement of the mucosal, vermillion, or cutaneous lip, in addition to involved lip subunits (see Fig. 32.1). These include the Abbe or Estlander flaps for redistributing full-thickness tissue from the unaffected lip to the operated lip [27, 28], cheek rotation or advancement flaps (e.g., Gilles flap, Johansen flap) [29], and the Karapandzic flap which acts as a circumferential rotation/advancement flap with partially preserved muscle function and sensation for large full-thickness defects [30]. If a cancer resection results in a loss of >40 % of the total lip area, or >80 % of either lip, any local reconstructive technique will result in undesirable microstoma, which is especially problematic for those with dentures. In these cases, total or subtotal lip reconstruction must be undertaken and is best accomplished with a microvascular tissue transfer, such as the radial forearm free flap [31].

In addition to lip reconstruction, tongue reconstruction must be carefully planned in order to preserve a patient's ability to eat, speak, and swallow. Defects of the oral tongue often include a lateral or anterior floor of the mouth wound, a hemiglossectomy defect, or a total/subtotal oral glossectomy defect (very rare, selected situations) in which complete reconstruction is necessary to restore optimal function (which is limited due to the complex motility pattern of the tongue and the limitations of complete reconstruction). For small superficial mucosal defects, healing by secondary intention is often possible. Occasionally, a skin graft may be used. In partial tongue resections which create a small anterior or a longitudinal defect, primary closure can provide excellent results. However, in considering primary closure, or advancement of limited local tissue, the surgeon needs to be cautious about creating a lateral or anterior tethering effect on the tongue that would impair speech or swallowing. Pedicled myocutaneous flaps may play little or no role in tongue reconstruction. However, for patients who have undergone a total or hemiglossectomy, or will have an unacceptable functional deficit from remaining tissue, a microvascular tissue transfer usually affords the best results (see Fig. 32.2a). The reconstruction of the oral tongue is a

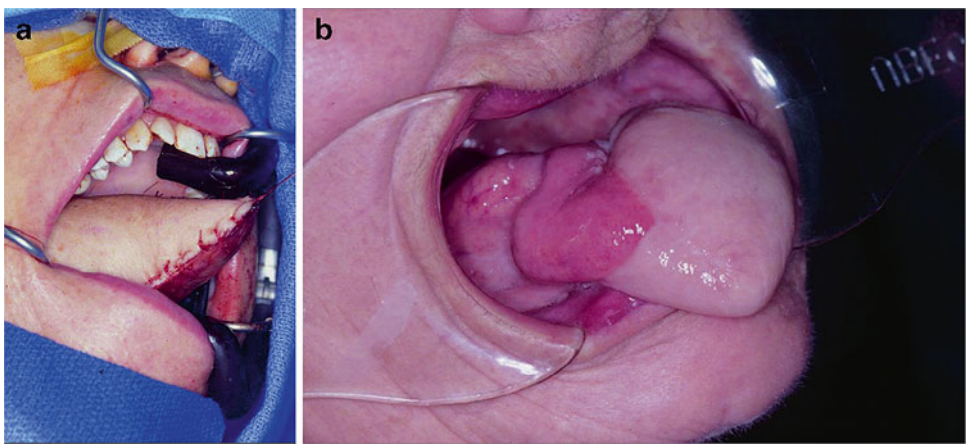

Fig. 32.2 (**a**) Functional tongue reconstruction. Fifty-three-year-old patient with a T2N0M0 squamous cell carcinoma of the right lateral tongue. He underwent a two-thirds anterior glossectomy and floor of the mouth resection, followed by a radial forearm free flap reconstruction with a neurorrhaphy between the lingual nerve and the lateral antebrachial cutaneous nerve. (**b**) "Fold-and-roll" tongue reconstruction. Final healed result of the fold-and-roll technique at 8 months postoperatively (preoperative radiation therapy only). The native tongue remnant is atrophied from a previous anastomosis of cranial nerves XII to VII

prime example of where a free flap bestows a distinct functional advantage compared to other choices on the reconstructive ladder. In using a free flap, the surgeon is able to mold the tissue to form a tubed or rolled structure that can ultimately approximate with the palate, lips, or teeth to allow speech and facilitate a functional swallow [32–36] (Fig. 32.2b). Reconstructive options include fasciocutaneous flaps, such as the radial forearm free flap, and the fasciocutaneous version of the anterolateral thigh flap [37]. If a concomitant mandibular defect is being reconstructed, a fibular free flap can also be employed in the reconstructive effort [38] (Fig. 32.3). For defects of bone reconstruction, the readers are referred elsewhere [39]. In case of defects after subtotal glossectomy including parts of the floor of the mouth, reconstruction can be improved by combination of free and pedicled flaps. Remmert described a highly suitable technique by using pedicled infrahyoidal flaps of both sides which can be pulled through the defect of the floor of the mouth and fixed to the remnant parts of the base of the tongue. Additionally radial forearm flap can be applied to create an epithelialized lining of the dorsum and suitable coverage of the floor of the mouth. The infrahyoidal flaps provide sufficiently the lacking volume of the tongue which cannot be substituted by the free flap alone [40]. In case of bilateral use of the infrahyoidal flap, the surgeon has to keep in mind the supplying pedicle from the superior thyroid artery which may not be used for the arterial anastomosis of the free flap.

32.2.2 Oropharynx

The oropharynx, similar to the oral cavity, plays an essential role in swallowing and also maintains velopharyngeal competence. The oropharynx extends from the plane of the posterior hard palate to the horizontal plane of the pharyngoepiglottic folds and contains the soft palate, base of the tongue, and the lateral oropharyngeal walls, including the tonsils and their arches. Contact of the soft palate to the posterior pharyngeal wall effectively separates the oropharynx from the nasopharynx superiorly and allows food and air propulsion to occur without nasal regurgitation. The palate also aids in controlling airflow during speech and respiration. A surgical defect of the soft palate or pharyngeal walls can cause a patient to reflux food into the nasal cavity during swallowing efforts and can also make speech unintelligible. Reconstructive goals in this zone are designed around maintaining the separation of the nasopharynx from the oropharynx and preserving velopharyngeal competence with speech and deglutination. Base of the tongue reconstruction is designed to protect the airway against aspiration, promote swallowing, and avoid oral tongue tethering. As such, a well-tailored fasciocutaneous flap is the best option if more than 2/3 of the tongue base is missing [32].

Due to the rising relevance of HPV16-related disease and consecutive dramatically increase of incidence in North America and Western Europe, current trials suggest that surgery could be substituted by radio- or chemoradiation

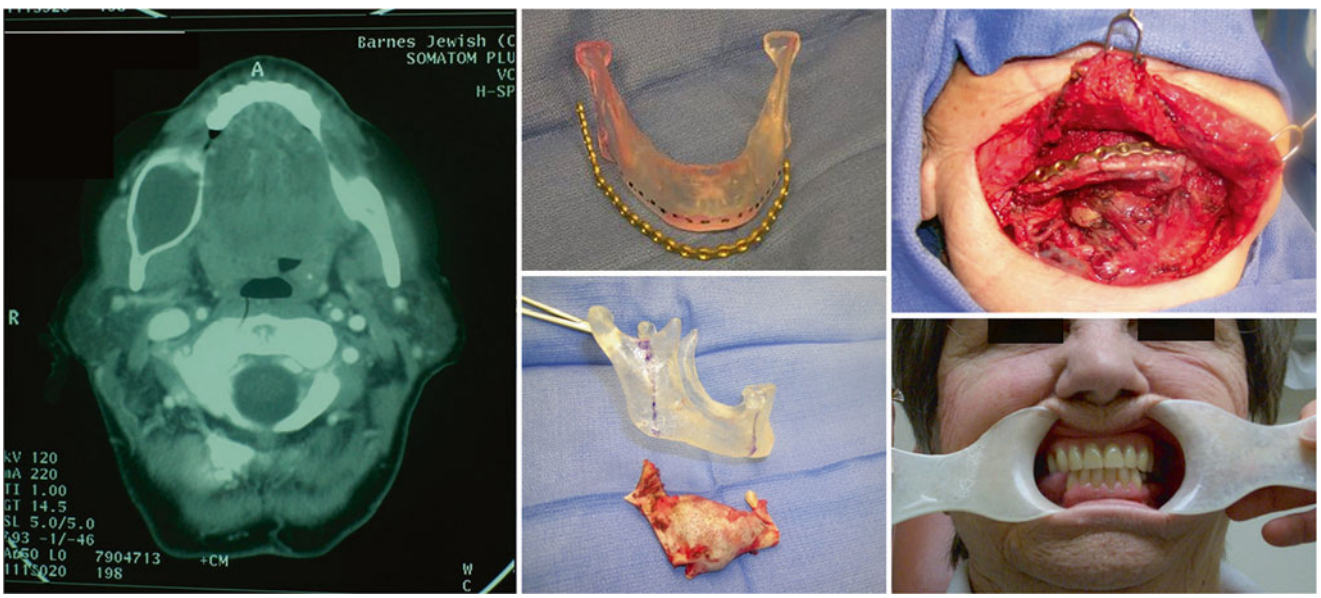

Fig. 32.3 Medical models for reconstruction. Advances in three-dimensional imaging and technologies allow precise models to be created for preoperative reconstruction planning. An axial CT image reveals an expansile cystic lesion (*left image*). Surgical planning to remove this dentigerous cyst includes a generated mandibular model for precise reconstruction bar fitting (*upper middle image*) and planning of segmental mandibulectomy (*lower middle image*, tumor specimen shown). Fibular free flap reconstruction is then performed followed by successful postoperative placement of dental implants (*right-sided images*)

treatment since response to nonsurgical treatment raised significantly. Moreover, treatment de-escalation trials including nonsurgical and surgical treatment are on the way implicating minimal invasive surgical techniques (TLM, transoral robotic surgery (TORS)) as acceptable choices to minimize functional deficits in HPV16-positive disease. Today, there are no data showing in direct comparison superiority of surgical or nonsurgical treatment. Nevertheless, current data (based mainly on p16 testing) show that HPV16-positive oropharyngeal cancer patients do much better than HPV16 negative regardless of both treatment directions, primary surgery and chemoradiation. Therefore, current evidence is not adequate to abolish primary surgery in HPV16-positive patients and to change routine treatment options beyond clinical trials.

Recently, TORS (transoral robotic surgery) has been approved for small (T1, 2) oropharyngeal lesions and is used in routine treatment for lesions of the tonsillar region and base of the tongue in many North American centers with good results. In Europe, TORS is in strong competition to TLM which is limited especially in base of the tongue lesions but highly sufficient in well-trained hands in most regions of the upper aerodigestive tract. Since TORS is still new and neither evidence for superiority toward TLM does not exist nor reimbursement in Europe does cover the terrific costs, this technique is not recommended for first-choice routine treatment.

The small volume of the oropharynx and limited tissue redundancy restrict reconstructive options. Healing by secondary intention may cause unwanted scarring, contracture, and stenosis if a very large or circumferential raw surface area is exposed. An open wound may pose risk to surrounding structures if a communication exists between the oropharynx and deep neck. Primary closure may be possible if there is limited tension and narrowing from reapproximated wound edges. Skin grafts can be used to restore superficial tissue loss. More involved defects of the oropharynx or soft palate are best treated with a regional flap, free flap, or prosthesis. There are some limited local flaps for soft palate reconstruction, such as the superior constrictor advancement rotation flap (SCARF) [41]. The SCARF reconstruction is a myomucosal advancement flap that aims to restore the sphincter function of the nasopharynx. Another local flap option is the palatal island flap, in which hard palate mucoperiosteum pedicled on the greater palatine artery is rotated posteromedially into the defect [42]. For larger defects, a thin free tissue transfer of fasciocutaneous tissue can be performed, and the donor tissue should be carefully designed and inset. To avoid velo- or nasopharyngeal stenosis with resultant nasal obstruction, sleep apnea, and rhinolalia clausa, the surgeon should aim to imbricate the flap tissue for soft palate reconstruction such that both dorsal and central linings of the neo-soft palate are provided, but without obstructive bulk. Free flap options for the soft palate and base of the tongue include the radial forearm free flap (working horse) [43], other fasciocutaneous flaps, and a thinned rectus abdominis flap [44] (Fig. 32.4). The use of free flaps can also be combined with local flaps as necessary [45–47].

32.2.3 Hypopharynx

The hypopharynx represents a functional junction between the passage of air from the pharynx to the larynx anteriorly and the routing of food into the cervical esophagus posteriorly. The final pharyngeal phase of swallowing occurs in the

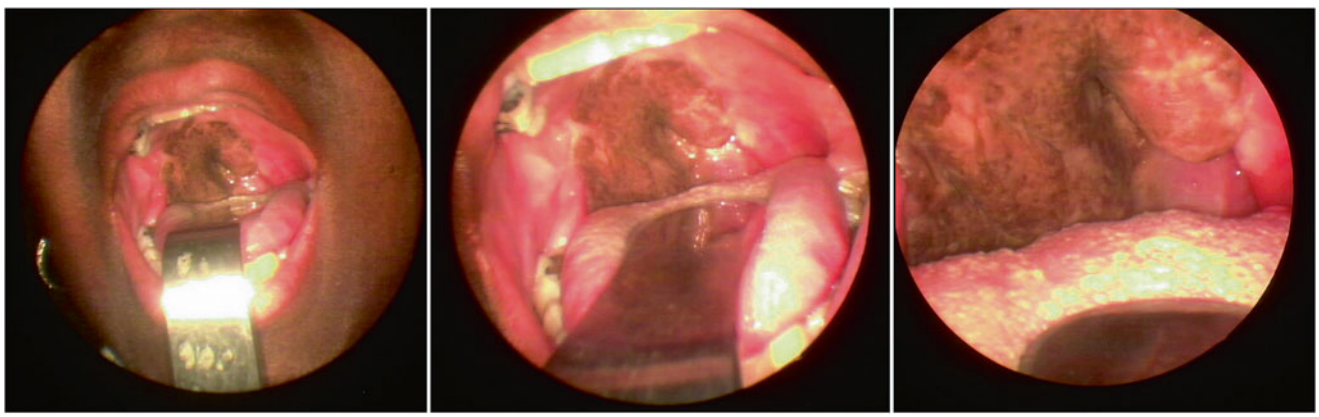

Fig. 32.4 Transoral *inset* of a free flap. Sixty-five-year-old woman s/p radial forearm free flap for reconstruction following resection of a T3N1M0 squamous cell carcinoma of the right tonsil and soft palate. The patient's resection included a transoral CO_2 laser partial pharyngectomy, parapharyngeal space resection, base of tongue glossectomy, and wide soft palate resection. A widefield view of her skin paddle inset is shown on the *left*, with *middle* and *right images* demonstrating the neo–uvula junction with the soft palate, in addition to volume recreation in her right tonsillar fossa and excellent pharyngeal wall coverage

hypopharynx, as the tongue propels food posteriorly, and local peristalsis combined with distal muscle relaxation allows food to pass inferiorly into the alimentary tract. The regions of the hypopharynx include its posterior wall, continuous above with the posterior oropharyngeal wall, the floor of the vallecula superiorly, the postcricoid area anteriorly, and the pyriform sinuses laterally.

The function of the hypopharynx relies on the circumferential movement of muscles in order to facilitate a swallow, and any reconstructive efforts must maintain this form. Creating a functional funnel or U-shaped reconstruction can pose a significant challenge in patients who have failed organ preservation therapy for hypopharyngeal cancer or who have undergone a combined pharyngolaryngectomy for advanced-stage disease. If the larynx is present, the prognosis for swallowing must remain cautious [48]. Most defects of the hypopharynx should not be left to heal by secondary intention due to risk of fistulization or contamination of deep tissue spaces with saliva. In defects that have sacrificed minimal hypopharyngeal mucosa, a primary repair may be possible. The superior hypopharynx is often more amenable to a primary repair than defects that approach the cervical esophagus, and the surgeon must be especially careful to eschew an area of dysfunctional stenosis. Historically, repairs of hypopharyngeal defects have relied on a multitude of different grafting techniques in attempts to avoid narrowing or stricture. These have included shaping skin grafts around mesh [49] or a tube [50], but were unfortunately related to high rates of fistulization and stricture. Currently, skin grafts are best used for partial, noncircumferential defects, and larger reconstructions are best repaired with pedicled or free flaps.

For circumferential defects, e.g., from a total laryngopharyngectomy, the use of a local, broadly based cervical flap was introduced by Wookey in 1942 and resulted in the first series of patients with reliable functional results following extensive pharyngeal repair [51]. Subsequently, the robust pectoralis major flap was used in pharyngeal reconstruction and excelled in importing well-vascularized muscle to aid in wound closure, even in contaminated or previously radiated fields [7]. However, the functional result and inset of the pectoralis flap is limited by its bulk, which makes tubing and circumferential shaping of the flap difficult [52].

The thin, reliable fasciocutaneous free flap has largely replaced pedicled flap reconstruction of pharyngoesophageal defects. The anatomy of the fasciocutaneous tissue lends itself to three-dimensional molding and inset, characteristics that can be used to restore function and create a circumferential repair [53–55]. These features are shared by the anterolateral thigh (ATLF) and the radial forearm flaps, which can provide a larger skin paddle, in addition to muscle tissue [55–58]. However, the ALTF is often limited by the course of its perforators (intramuscular versus intermuscular and fascial) and its degree of thickness, dependent on a patient's body habitus. However, the ALTF can be thinned peripherally. Considering the goal of laryngoesophageal dysfunction, free survival fasciocutaneous flaps seem to result in less pharyngeal stricture following surgery and adjuvant (chemo) radiation.

Occasionally, defects of the hypopharynx require a long segment of circumferential tissue for reconstruction that cannot be accomplished with a fasciocutaneous flap. Historically, this has been accomplished with the use of either a jejunal free flap or a tubed gastric pull-up. Both of these options have the increased morbidity of intrathoracic or intra-abdominal surgery for flap harvest and inset. The jejunal flap is harvested via a laparotomy, and the defect is reanastomosed end to end. The use of this flap was first described in the early 1900s [59] and later became the first free tissue transfer described in humans [13]. Functionally, the jejunal flap provides a tube of mucosal peristaltic tissue and has been used in large numbers of patients [60–65]; however, in addition to functional problems and risks associated with the pharyngeal reconstruction such as fistula and stricture [66], patients are at risk for small bowel obstruction, peritonitis, and intra-abdominal adhesions from the donor site [67]. Similarly, the transposition of proximal stomach tissue to reach the edge of a pharyngeal defect in a gastric pull-up requires exposure in the abdomen, thorax, and neck, posing increased donor site morbidity to patients. The use of a gastric transposition was described in the 1960s [68, 69] and has evolved to incorporate laparoscopic techniques to reduce complications from open abdominal or thoracic surgery. Functionally and technically, the advantages of a gastric pull-up for hypopharyngeal or esophageal reconstruction include a decreased rate of stricture, a single anastomosis, fairly although not totally reliable bloody supply, and incontinuity of mucosal surface in the alimentary tract. The main disadvantage is the failure to reach the pharynx without tension and the high rate of perioperative morbidity [70]. New techniques for better ischemic conditioning of the flap provide a two-step procedure. First step is a pure laparoscopic mobilization of the stomach including the cardia and preparation of the gastric conduit. Second step would be the pull-up procedure to connect the distal pharyngeal end with the stomach tube after tumor resection and esophagectomy. Major postoperative complications were observed in 13.3 % of the patients, and the 90-day mortality was 0 % in a series of 83 % of patients with primary esophageal cancer [71].

32.2.4 Cervical Esophagus

The cervical esophagus extends from the cricopharyngeal inlet and is a tubular striated muscle and tubed segment of mucosal, stratified squamous epithelium. Functionally, the cervical esophagus transmits food and secretions from the

hypopharynx to the distal esophagus via peristalsis coordinated with cricopharyngeal muscle relaxation. Any surgical defect of the cervical esophagus will impair a patient's ability to swallow and also puts the patient at risk for fistula and mediastinitis. Reconstructive goals include restoration of swallowing coupled with maintenance of laryngeal airway and voice production. Tissue for reconstruction should be thin and cylindrical to afford swallowing and should be with sufficient diameter to avoid stricture or dysphagia. For incomplete or partial defects (less than 50 % of circumference), reconstructive options include the use of a "patch on" flap, such as the pliable radial forearm free flap [72, 73]. For longer segment defects above the thoracic inlet, tubed fasciocutaneous flap options or the jejunal free flap may be used as discussed above [74, 75]. For defects extending below the brachiocephalic vessels, a gastric transposition flap may be used [76].

32.2.5 Larynx

Surgery of pharyngoesophageal tumors often necessitates surgery of the larynx, as disease may be isolated or confluent in these closely related structures. The larynx has a range of critical functions, including the generation of speech, regulation of airflow into the trachea and lungs, and airway protection during eating and swallowing. Defects and malfunction of the larynx can impair a patient's ability to breathe, eat, and phonate. Anatomically, the larynx has three main subunits that extend from the tip of the epiglottis to the inferior border of the cricoid cartilage. The supraglottic larynx encompasses the epiglottis, the false vocal cords, ventricles, aryepiglottic folds, and arytenoids. The glottic larynx encompasses the true vocal cords and anterior commissure and extends inferiorly by 5 mm below the free margin of the cords. The subglottic larynx is the airway segment between the vocal cords and the trachea and extends inferiorly to the distal cricoid cartilage. After surgery involving any one of these structures, goals of laryngeal reconstruction are to maintain a protected airway, to preserve airway patency with avoidance of long-term tracheostomy, and to allow for speech generation.

There has been a tremendous effort in the treatment of head and neck cancer to preserve the larynx and its functionality. Historically, and in chronological order, laryngeal organ preservation techniques have included modified surgical techniques that remove only part of the laryngeal framework involved by disease, radiation therapy, and chemoradiotherapy (CRT) [77–79]. Partial laryngectomies are accomplished by transoral endoscopic laser microsurgery (TLM), resulting in a vertical hemilaryngectomy or a supraglottic laryngectomy [80–82]. Historically, these procedures have been performed by the open techniques and more frequently committed a patient to a tracheostomy due to aspiration or upper airway obstruction. However, the TLM approach, the only minimally invasive technique available on a routine basis for larynx cancer, results in a low (<5 %) tracheostomy rate and rapid functional recovery, even for advanced disease [82]. TORS is feasible for supraglottic carcinomas but has well-known limitations and disadvantages in comparison to TLM. Therefore, TORS is not the first-choice transoral approach for the larynx [83]. In the context of well-trained modern surgical personnel and services, a total laryngectomy, by contrast, is an infrequent event [84].

Following treatment for laryngeal cancer, reconstruction is largely confined to two populations of patients: (1) patients who are undergoing surgery as a primary treatment modality and (2) patients who require a partial laryngectomy after failing CRT. The first subset of patients may require advancement of distal laryngeal structures to approximate the edges of the defect or recruitment and transposition of extralaryngeal musculature [85–91]. These types of local reconstructive options are more limited for the second subset of patients, whose local tissues are more likely to have radiation damage, including fibrosis and impaired vasculature. In these patients, pedicled myocutaneous flaps can be used to aid in wound healing, but are limited by their bulk and pedicle reach in functional reconstruction. In a radiated field, free tissue transfer may offer the best functional results in reconstructive efforts [92].

The radial forearm free flap may be used to aid in reconstruction following primary laryngeal surgery as well as in salvage efforts. The tissue can be inset into hemilaryngectomy defects, including those with concomitant pharyngeal involvement [93–95]. In addition to the radial forearm free flap, the temporoparietal flap may be utilized as a "vascular carrier" in various reconstructive efforts, meaning that it provides a blood supply to otherwise avascular graft materials, such as cartilage [92, 96–99]. A reconstructive method for patients who have undergone a standard hemilaryngectomy after radiation failure includes using the temporoparietal flap as a vascular supply in a technique described by Ralph Gilbert [92]. In this technique, a layered reconstruction is created with a buccal mucosa graft on the deep laryngeal surface, followed by the temporoparietal tissue enveloping an avascular cartilage graft superficially, effectively mimicking the native laryngeal tissue structure of mucosa, perichondrium, and cartilage [92]. A study of functional outcomes in 21 patients included 90 % resuming a normal diet within 6 weeks after surgery and 85 % of patients being discharged without a tracheotomy. No patients were reported as being tracheotomy dependent at 3 months after surgery [92].

In summary, there are multiple surgical options for laryngeal organ preservation, many of which offer patients an oncologically sound and functionally restorative outcome,

without progressive inexorable long-term tissue degeneration, which results in high late "toxicity" (i.e., swallowing failure) rates [100].

32.2.6 Orbit, Nose, and Midface

Tumors of the head and neck may involve the orbit, nose, or midface and create significant reconstructive defects that greatly impact a patient's appearance and functional capacity. The orbits are bony compartments that include the globe, periorbital fat, and extraocular muscles, bordered by 16 named maxillofacial bones. The zygomatic, frontal, sphenoid, maxillary, palatine, ethmoid, and lacrimal bones comprise the bony orbit, which is situated lateral to the ethmoid sinuses, superior to the maxillary sinus, inferior to the frontal sinus, and anterior and inferior to the cranial vault. The shape of the orbital space approximates a quadrangular pyramid with an apex at the deep surface, near the optic nerve in its bony foramen. Functionally, the orbit houses the visual organ system and provides bony support and protection of the eye. Reconstruction may follow an orbital exenteration, in which a significant volume deficit may be present along with exposed bone. An empty orbital space can be reconstructed with a split-thickness skin graft to line the orbital cavity and permits the use of an ocular prosthetic. Alternately, a local (e.g., forehead, temporalis) or free flap can be used to restore volume. The rectus abdominis muscle or other myocutaneous flaps can be used to restore contour to the orbit and obliterate dead space after extensive surgical resection, although the volume requirement is surprisingly small [101–103] (Fig. 32.5). Sometimes a thick fasciocutaneous flap will suffice.

In any reconstruction of the orbit or midface, the separation of anatomical compartments, especially the subarachnoid space, must be recreated. The skull base, bony orbit, sinuses, and oral cavity need reliable tissue or bony barriers to permit function and also restore facial form. Anatomically, the midface can be conceptualized as consisting of three subunits: lower, upper, and central [104]. The lower subunit supports the maxillary dentition and effects a separation between the midface and oral cavity, allowing for functional speech and eating. The upper subunit provides facial contour, separates the midface and maxillary sinus from the cranial vault, and supports the orbital contents. The central subunit provides structural support to counteract forces of mastication and dictates the proportions of vertical facial height. The central subunit additionally provides the scaffolding for midface soft tissue and projection. Priority in reconstruction should begin with establishing the most important barrier or functional subunit first, with meticulous care given to defects involving the skull base.

The evolution of midface reconstruction has progressed slowly due to a multitude of factors, including interval use of prosthetics, poor prognosis in advanced disease, and a wide variety of surgical paradigms. Wound healing, facial contour, and palatal competence are the basic requirements of any midfacial reconstruction. Options for reconstruction must offer appropriate bulk for facial symmetry and orbital support. Similar to other defects of the head and neck, this was initially attempted using locoregional pedicled flaps [105–108]. As techniques have progressed, midfacial reconstruction may now utilize multiple components of the reconstructive ladder to offer a comprehensive result (Fig. 32.6). A single reconstruction may employ a free tissue transfer from the radial forearm, scapula, rectus, or fibula depending on tissue bulk and bony defects [109, 110]. These may be combined with local or pedicled flaps, free bone grafts, or

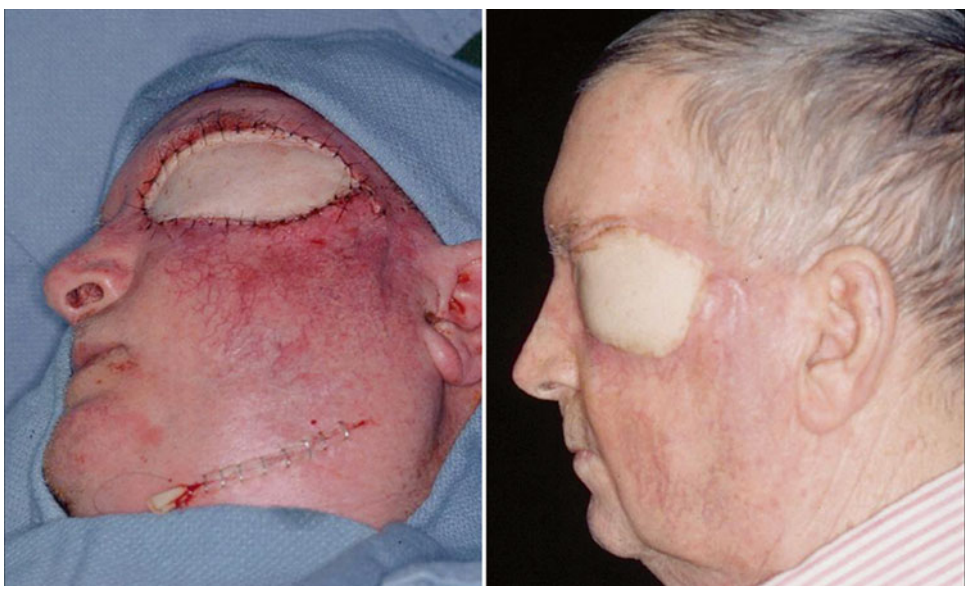

Fig. 32.5 Orbital reconstruction with a rectus abdominis free flap. Sixty-six-year-old gentleman initially presented with a history of major skin cancer, including a massive basal cell carcinoma invading the orbit and the frontal bone. This necessitated a wide excision of the frontal bone, orbital exenteration, partial excision of the maxilla, and repair with a rectus abdominis free flap. This lesion had arisen from the left lower lid

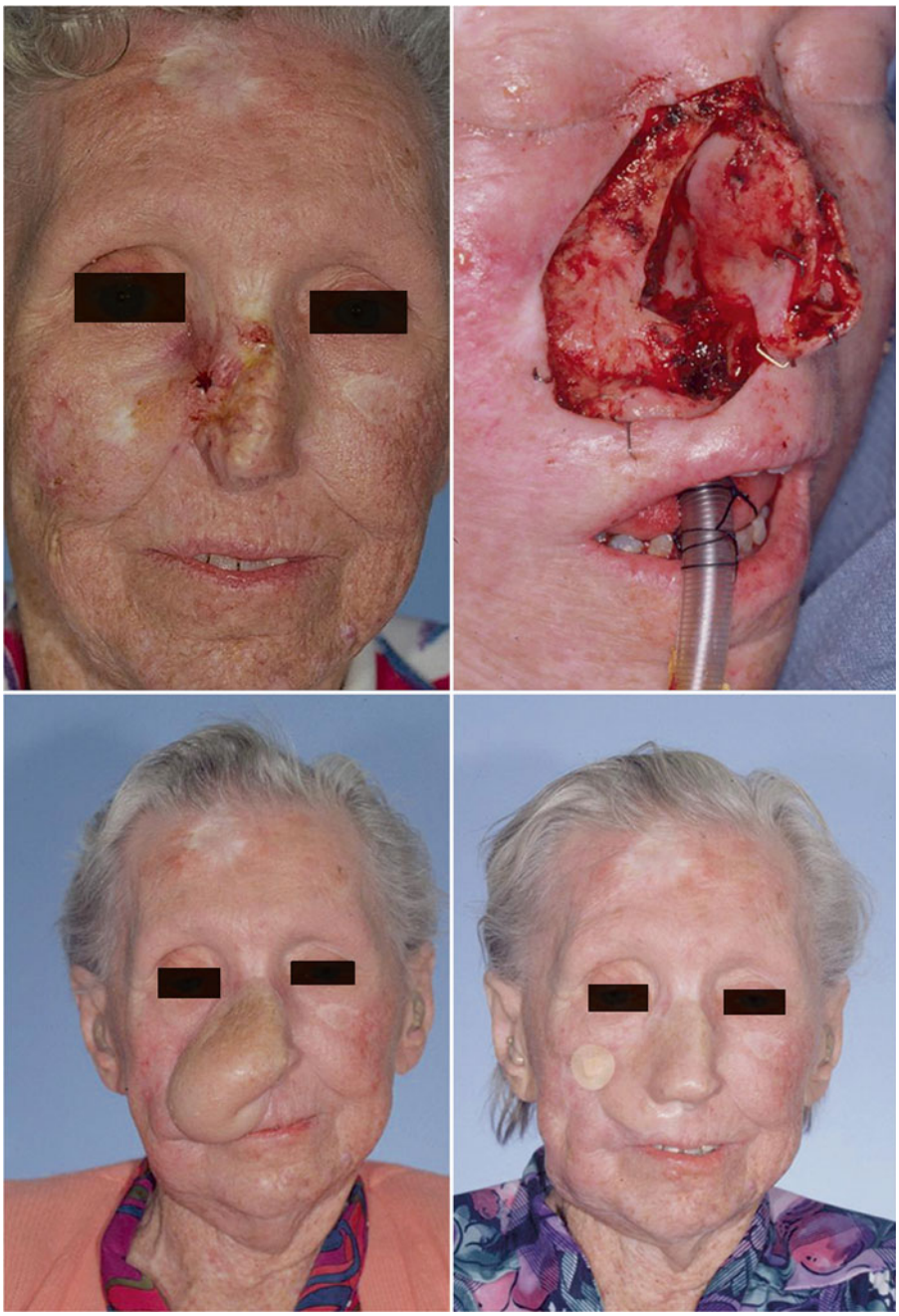

Fig. 32.6 Subtotal nasal reconstruction with radial forearm free flap and second stage debulking. Patient is an elderly woman with a history of invasive basal cell carcinoma of the right lateral nasal sidewall and ala (*top left*) who underwent Mohs excision resulting in a subtotal nasal defect, right cheek defect, and right upper lip defect (*top right*). A reconstruction for soft tissue coverage and bulk was performed using a radial forearm free flap, followed by a second stage revision of the flap, including adjacent tissue transfer, debulking, and insetting (*lower left* and *right images*). A conchal cartilage graft for alar reconstruction was also performed

prosthetics to ultimately restore function. Details of skull base reconstruction are specifically excluded in this chapter, the reader being directed to other sources [111].

32.3 New Approaches

Evolving treatment strategies for head and neck cancer have created new surgical defects and considerations after oncological resections. Specifically, a new variety of surgical defects have been introduced by the practice of surgical salvage after failed CRT, in addition to the use of TLM for organ preservation. New reconstructive options and flaps have also emerged in the surgical armamentarium for these and other previously described defects.

32.3.1 Surgical Salvage

Historically, surgical salvage after failed primary radiotherapy treatment was primarily limited by what reconstructive options were available. Today, advances in microsurgical

techniques enable more candidates to undergo resection and reconstruction, but the effects of radiation are still a major consideration before undertaking surgical salvage, in addition to what functional status and quality of life a patient may have postoperatively [112].

Radiation alters the quality of tissue at the primary site, in addition to the surrounding tissue available for reconstructive efforts. The effects of radiation on vital tissue include fibrosis, desiccation, and altered vascularity. Subsequently, patients with recurrent cancer after failed CRT or radiotherapy can have disrupted tissue planes and poor wound healing [113]. These factors must be considered in planning surgical salvage.

Local flaps and skin grafts are limited and often contraindicated in postradiated patients, but free flaps have provided reasonable success in reconstructive efforts after salvage surgery [114]. Defects can be reconstructed in a similar manner as previously outlined in this chapter, with goals of functional restoration as well as protection of vital structures. Technical advances in microsurgery have enabled more patients to undergo salvage surgery, although they have not changed the poor prognosis of patients with advanced recurrent disease [112, 115].

32.3.2 Perforator Flaps

A notable technical advance in microsurgery has been the introduction of perforator flaps [116, 117]. Research and development of the use of perforator flaps is based on the observation that a free flap of skin can be transferred without any underlying fascial plexus vessels or muscle carrier tissue if the musculocutaneous perforator vessels are carefully dissected and preserved [118]. The advantages of perforator flaps are decreased donor site morbidity, increased pliability of the flap, decreased necessity for flap revision, and improved aesthetic outcome [119]. Disadvantages are increased operative time depending on a surgeon's experience and variability in the anatomy of the perforator vessels. Perforator flaps are indicated in certain defects requiring thin, easily molded tissue, but are contraindicated in patients with perforators that are too small to safely dissect or patients who have wound healing problems or vascular disease.

Two applicable perforator flaps in head and neck reconstruction include the anterolateral thigh flap harvested as a septocutaneous flap and the large, versatile deep inferior epigastric artery perforator (DIEAP) flap harvested from the abdomen. The septocutaneous anterolateral thigh flap can be harvested with <5 mm thickness and is based off of a lateral circumflex artery perforator. It can be used for skin defects, including the auricle and neck soft tissue, in addition to other sites [120, 121]. The DIEAP flap has been described for use in the repair of glossectomy, floor of the mouth, scalp, and lateral facial defects and provides soft tissue bulk [122] (Fig. 32.7). The use of both of these, in addition to other perforator flaps, broadens reconstructive options in the head and neck, and new technologies are continuing to expand the delineation of perforator anatomy, i.e., "perforasomes," that provide individual maps to potential flaps throughout the body [123].

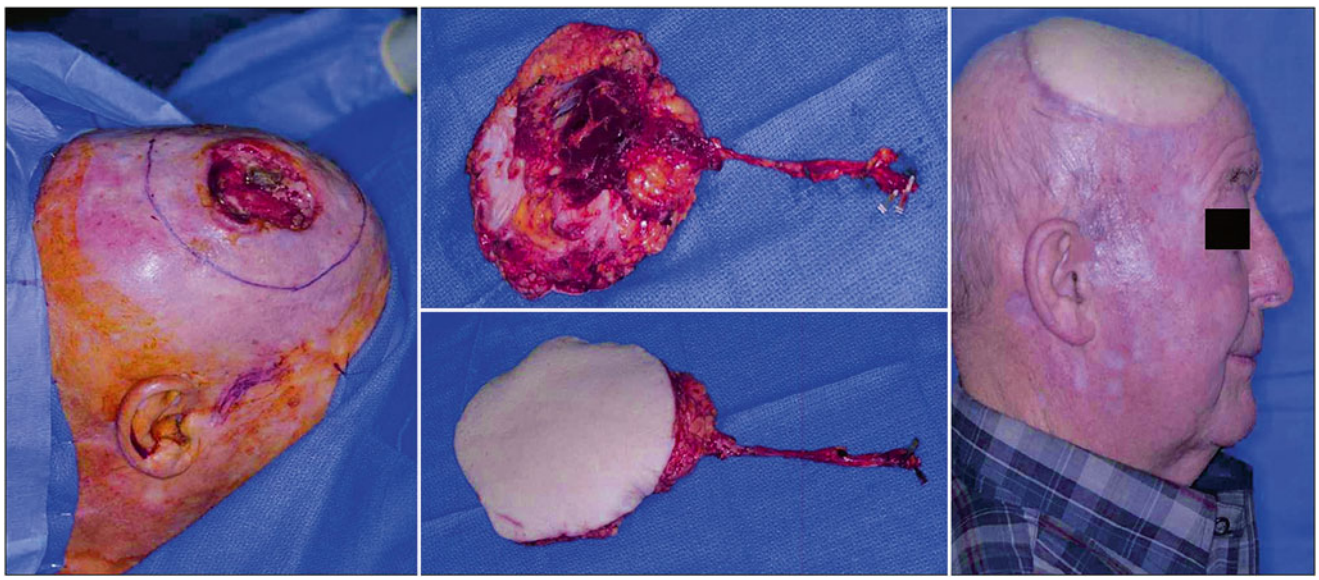

Fig. 32.7 Perforator flap for scalp reconstruction. Seventy-eight year-old gentleman who underwent resection of a squamous cell carcinoma of the scalp followed by reconstruction with a left rectus abdominis perforator free flap, in addition to an acrylic implant placed for cranial reconstruction. The preoperative view is seen on the *left*, and the dorsal and ventral surfaces of the flap in addition to the vascular pedicle are seen in the *middle images*. A postoperative view is seen on the *right*

32.3.3 Transoral Laser Microsurgery (TLM) Transnasal Endoscopic Skull Base Surgery and Transoral Robotic Surgery (TORS)

The most recent development in head and neck resectional surgery is the minimally invasive approach through natural orifices, viz., the mouth and nostrils. Various tools for resection using this approach have included retractors and endoscopes, and cutting instruments have included Bovie, laser, and cold steel. Robotic manipulation of these tools has been described for small tumors.

Data from several centers worldwide have demonstrated that transnasal endoscopic surgery performed with or without a transcranial approach is capable of achieving radical resection of selected sinonasal malignancies. As concluded by Castelnuovo et al. [124], endoscopic endonasal resection performed with or without a transcranial approach, when properly planned and in expert hands, has an accepted role with precise indications in the surgeon's armamentarium for the treatment of sinonasal and skull base malignancies.

In 2009 the outcomes report from a multi-institutional retrospective trial, led by Weinstein and O'Malley at the University of Pennsylvania, was utilized by the US Food and Drug Administration (FDA) to approve the use of the da Vinci Surgical System. TORS procedures have been described to manage pathologies at numerous anatomic sites from the glottis and hypopharynx to the nasopharynx and skull base [10–12]. The most commonly reported use of TORS for malignant disease, however, has been for oropharyngeal cancer, particularly tongue base or tonsillar cancer. Growing experience in TORS led to clear definitions of contraindications and better understanding of the technique [125]. Moreover, the transoral robotic approach pushed interesting new smaller and more handy technologies [126] since the da Vinci System is far bulky.

The operative procedures to routinely remove large tumors of the upper aerodigestive tract are currently restricted to the transoral laser microsurgical (TLM) method, in which the tumor can be taken out in pieces, with precise visualization and control of the margin at many areas around the tumor's perimeter [127]. When the volume or surface area of the defect left behind is large, tissue reconstruction will accelerate wound healing and minimize functional loss. Various local advancement flaps, such as the SCARF approach [41], have been reported. Limited advancement at the pharyngeal wall and for graft inset can also be accomplished transorally (Fig. 32.8). Free flaps are also suitable under specific circumstances. The conditions where I have used free tissue transfer for reconstructions are (a) soft palate defects, full thickness, half or greater; (b) oral tongue defects, greater than hemiglossectomy, or total deep base of tongue; and (c) full-thickness pharyngeal wall and parapharyngeal space defects with exposure of the internal carotid artery.

In brief, the free flap needs to be thin, so that the radial forearm donor site has proven the best available, although the ALT flap has been used successfully on patients with appropriate habitus (see Fig. 32.4). Vessel access and anastomosis are accomplished via the neck dissection, and a small pharyngotomy, if not already present from the resection, is created to pass the pedicle from the oral cavity or pharynx to the neck. Sometimes, this is enlarged slightly for posteroinferior suture placement. Most of the inset, however, is accomplished by transoral suturing using the same retractor systems (Dingman, Feyh-Katzenbauer) as were used for the resection. Although not technically simple, the functional advantages for extensive defects are obvious, especially in the reduction of severe velopharyngeal incompetence for soft palate resections. The indications for and techniques of reconstruction following minimally invasive resections continue to evolve.

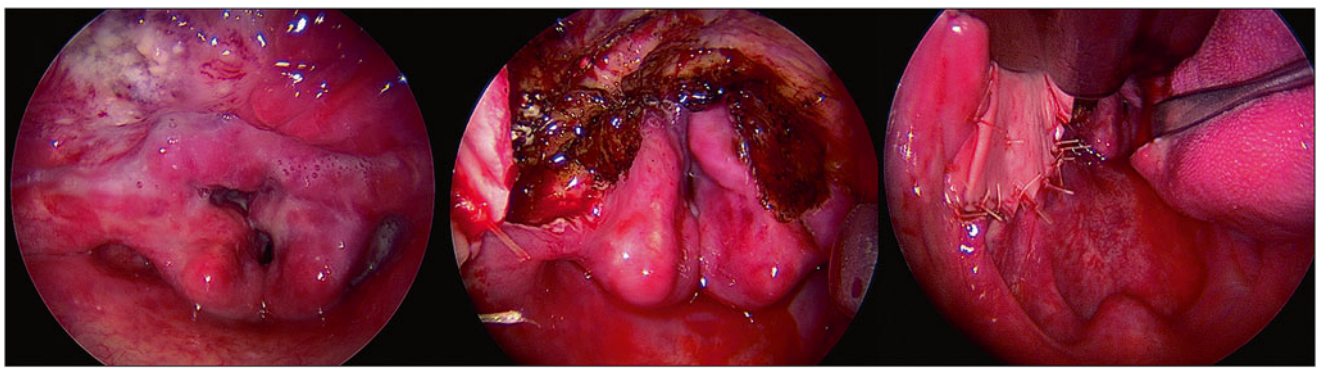

Fig. 32.8 Transoral laser microsurgery. Patient with history of radiotherapy for supraglottic squamous cell cancer presented with a second primary involving the base of tongue and pharyngeal wall (*top left*). The patient subsequently underwent transoral laser microsurgery (*middle*), with pharyngeal flap and AlloDerm graft (*top right*)

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Multidisciplinary Treatment of the Neck

33

Remco de Bree, Johannes A. Langendijk, and C.R. Leemans

Abstract

Since lymph node metastases are one of the most important prognostic factors, treatment of the neck is challenging. In clinically N0 neck, (super)selective neck dissection is indicated, whereas a more extensive neck dissection with preservation of important structures is performed in N2–N3 disease. Adjuvant treatment consists of radiotherapy with or without chemotherapy in patients with an intermediate or high risk of recurrence in the neck. Primary radiotherapy alone is effective in non-bulky disease. In more extensive neck disease, a combination of radiotherapy and chemotherapy with or without planned neck dissection is indicated. Advances in imaging and treatment as well as risk assessment have further modified the paradigm of planned neck dissection. Primary chemoradiation is effective for sterilising occult disease, and, therefore, post-treatment (super)selective neck dissection seems to be sufficient.

Keywords

Lymph node metastases • Neck dissection • Radiotherapy • Chemoradiation • Salvage surgery

Head and neck squamous cell carcinomas have a proclivity to metastasise through lymphatics to regional nodes rather than to spread hematogenously. The degree of involvement of lymph nodes with tumour is the most important prognostic factor. Patients with multiple, contralateral or bilateral metastases have markedly reduced survival rates. Because recurrence in the neck generally caries a fatal prognosis, optimal initial treatment planning is vital. Considering these factors, management of the neck has become one of the most actively debated topics in the field of head and neck oncology. Because squamous cell carcinoma is the most frequent histological tumour type within the head and neck, focus will be mainly on this tumour type.

The lymphatics of the head and neck form a rich plexus of vessels, of which the anatomy was first described by Rouvière [1]. Current standardisation of nomenclature recognises 5 nodal levels in the lateral neck, of which several levels are further subdivided into two (Table 33.1 and Fig. 33.1). The central neck consists of a sixth level, which also includes the paratracheal nodes [2, 3]. Staging of cervical lymph node metastases is based on number, size and side. In the N0 neck, no lymph node metastases are diagnosed. An N1 neck means that only one enlarged ipsilateral lymph node less than 3 cm is detected. In N2 disease multiple or contralateral lymph node metastases or lymph nodes of 3 cm or more but smaller than 6 cm are found. If lymph node metastases of 6 cm or larger are present, the neck is staged N3 (Table 33.2) [4].

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Table 33.1 Anatomical and radiological structures defining the boundaries of the neck levels and sublevels

	Anatomical boundary				Radiological boundary					
Level	Superior	Inferior	Anterior (medial)	Posterior (lateral)	Cranial	Caudal	Anterior	Posterior	Lateral	Medial
IA	Symphysis of mandible	Body of hyoid	Anterior belly of contralateral digastric muscle	Anterior belly of ipsilateral digastric muscle	Geniohyoid muscle, plane tangent to basilar edge of mandible	Plane tangent to body of hyoid bone	Symphysis ment, platysma	Body of hyoid bone	Medial edge of anterior belly of digastric muscle	Midline
IB	Body of mandible	Posterior belly of digastric muscle	Anterior border of digastric muscle	Stylohyoid muscle	Mylohyoid muscle, cranial edge of submandibular gland	Plane through central part of hyoid bone	Symphysis ment, platysma	Posterior edge of submandibular gland	Basilar edge / inner side of mandible, platysma, skin	Lateral edge of anterior belly of digastric muscle
IIA	Skull base	Horizontal plane defined by inferior border of hyoid	Stylohyoid muscle	Vertical plane defined by spinal accessory nerve	Caudal edge of lateral process of C1	Caudal edge of the body of hyoid bone	Posterior edge of submandibular gland; anterior edge of internal carotid artery; posterior edge of posterior belly digastric muscle	Posterior border of internal jugular vein	Medial edge of sternocleidomastoid muscle	Medial edge of internal carotid artery, levator scapulae muscle
IIB	Skull base	Horizontal plane defined by inferior border of hyoid	Vertical plane defined by spinal accessory nerve	Lateral border of sternocleidomastoid muscle	Caudal edge of lateral process of C1	Caudal edge of the body of hyoid bone	Posterior border of internal jugular vein	Posterior border of sternocleidomastoid muscle	Medial edge of sternocleidomastoid muscle	Medial edge of internal carotid artery, levator scapulae muscle
III	Horizontal plane defined by inferior border of hyoid	Horizontal plane defined by inferior border of cricoid cartilage	Lateral border of sternohyoid muscle	Lateral border of sternocleidomastoid muscle or sensory branches of cervical plexus	Caudal edge of body of hyoid bone	Caudal edge of cricoid cartilage	Posterolateral edge of sternohyoid muscle, anterior edge of sternocleidomastoid muscle	Posterior edge of sternocleidomastoid muscle	Medial edge of sternocleidomastoid muscle	Internal edge of internal carotid artery, scalene muscle

	Anatomical boundary				Radiological boundary					
Level	Superior	Inferior	Anterior (medial)	Posterior (lateral)	Cranial	Caudal	Anterior	Posterior	Lateral	Medial
IV	Horizontal plane defined by inferior border of cricoid cartilage	Clavicle	Lateral border of sternohyoid muscle	Lateral border of sternocleidomastoid muscle or sensory branches of cervical plexus	Caudal edge of cricoid cartilage	2 cm cranial to sternoclavicular joint	Anteromedial edge of sternocleidomastoid muscle	Posterior edge of sternocleidomastoid muscle	Medial edge of sternocleidomastoid muscle	Medial edge of internal carotid artery, scalene muscle
VA	Apex of convergence of sternocleidomastoid and trapezius muscles	Horizontal plane defined by lower border of the cricoid cartilage	Posterior border of sternocleidomastoid muscle or sensory branches of cervical plexus	Anterior border of trapezius muscle	Cranial edge of body of hyoid bone	CT slice encompassing the transverse cervical vessels	Posterior edge of sternocleidomastoid muscle	Anterolateral border of trapezius muscle	Platysma, skin	Levator scapulae, splenius capitis muscles
VB	Horizontal plane defined by inferior border of cricoid cartilage	Clavicle	Posterior border of sternocleidomastoid muscle or sensory branches of cervical plexus	Anterior border of trapezius muscle						
VI	Hyoid bone	Suprasternal	Common carotid artery	Common carotid artery	Cranial edge of body of thyroid cartilage	Sternal manubrium	Skin; platysma	Separation between trachea and oesophagus	Medial edge of thyroid gland, skin and anteromedial edge of sternocleidomastoid muscle	n.a.

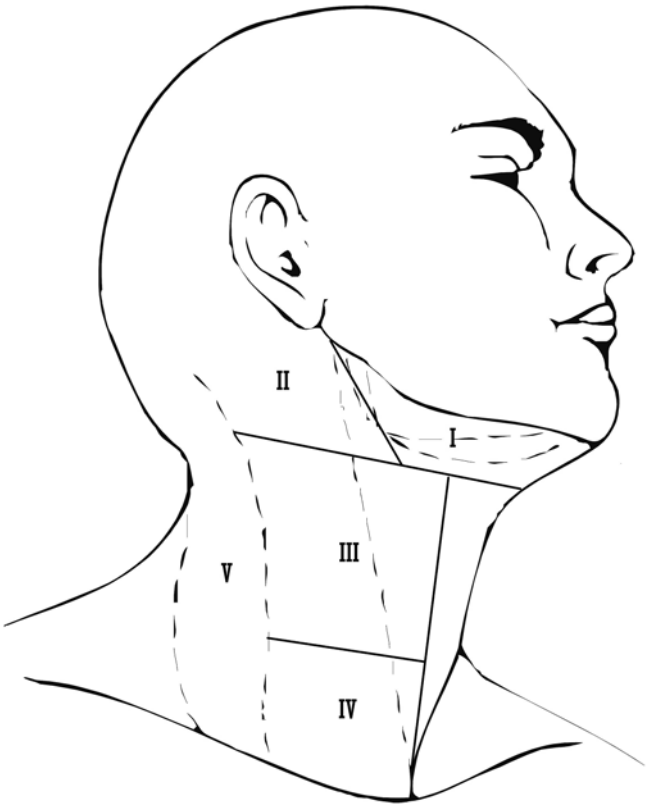

Fig. 33.1 Classification of neck node levels [Courtesy of Prof. dr. Remco de Bree]

Table 33.2 Classification of cervical lymph node metastases

N stage	
N0	No lymph node metastasis
N1	One lymph node metastasis < 3 cm
N2a	One lymph node metastasis ≥ 3 cm
N2b	Multiple ipsilateral lymph node metastases
N2c	Multiple bilateral or contralateral lymph node metastases
N3	Lymph node metastasis ≥ 6 cm

Cervical lymphadenectomy, i.e. neck dissection, has for a long time been the principal treatment for nodal metastases from head and neck cancer. Currently, with advances in non-surgical management of head and neck squamous cell carcinoma, the role of surgery is changing. This has led to an altered approach to patients with nodal disease when treated by chemoradiation. Indeed, several aspects of the management of clinically detectable and occult neck disease in patients have become controversial [5].

Treatment of the neck, i.e. surgical (neck dissection with or without postoperative (chemo)radiotherapy) or non-surgical (irradiation with or without chemotherapy), is usually dependent on the treatment modality for the primary tumour. Contrary to such accepted principles, however, in some circumstances, there may be an indication to treat the neck surgically, leaving the primary tumour for subsequent (chemo)radiotherapy. In patients with advanced lymph node metastases and a primary tumour that can be treated well with non-surgical means, the justification for such an approach is to minimise morbidity [6]. A different strategy is (chemo)radiotherapy to the primary site and neck followed by a planned neck dissection in case one judges the chances for neck cure limited [7]. Both strategies may yield acceptable locoregional control and survival rates.

A number of strategies towards management of the neck in patients with head and neck squamous cell carcinoma currently exist. Whereas diagnostic workup is discussed in other chapters, herein we discuss the different treatment options and strategies for the different stages of the neck.

33.1 Surgical Treatment

Neck dissection has proven to be an important procedure in the treatment of head and neck cancer. The neck dissection procedures performed today are the result of many years of refinements and modifications of the first description in the English language by Crile in 1906 [8]. The described procedure is a systematic en bloc dissection of the lymphatic tissue of the lateral neck and is presently known as the radical neck dissection (RND). In an effort to reduce the morbidity of the classic RND, various modifications have been proposed that preserve non-lymphatic structures that are normally sacrificed during this procedure but still remove all of the lymphatic tissue excised in RND. In these modified radical neck dissections (MRND), the spinal accessory nerve, the internal jugular vein and/or the sternocleidomastoid muscle are preserved. Due to better insights into lymph drainage pathways and the assumption of predictable patterns based on the location of the primary tumour, further modifications were developed such as the selective neck dissection (SND). In these techniques, only those lymph node groups that have the highest risk of containing metastases are removed. The main goal of these modifications is minimising morbidity without diminishing tumour control in the neck. Due to the variety of surgical techniques, the American Academy of Otolaryngology-Head and Neck Surgery standardised the nomenclature of the different types of neck dissections in 1991. An update was published in 2002 [2, 9]. The update of 2002 brought further consensus in the description of the modified and selective neck dissections. In modified neck dissections, the structures preserved are named, and in selective neck dissections, the dissected levels or sublevels are specified between brackets (Table 33.3).

Recently further refinements in the selection of lymph nodes, which should be included in a selective neck dissection, have been made. There is discussion about the inclusion of sublevel IA (submental regions), sublevel IIB

Table 33.3 Neck dissection classification

Type of neck dissection	Dissected levels	Sacrificed structures	Preserved structures
Radical	I–V	Spinal accessory nerve, internal jugular vein and sternocleidomastoid muscle	
Modified radical	I–V		Spinal accessory nerve, internal jugular vein and/or sternocleidomastoid muscle
Selective	Denote the (sub)levels removed		Spinal accessory nerve, internal jugular vein and sternocleidomastoid muscle
Extended	I–V	Additional structures	

(submuscular recess) and level IV in selective neck dissection in patients with certain primary tumour sites, particularly when the neck is clinically negative. Sublevel IA is rarely involved in patients with tumours other than the lip and oral cavity. The overall incidence of metastatic disease in level IIb in the context of a clinically negative neck from any site is 2.0 %. Most authors agree that dissection of sublevel IIB is not necessary in oral and laryngeal cancer, while it should be included in selective neck dissection in oropharyngeal cancer [10, 11]. Some studies suggest not to include level IV in patients with supraglottic laryngeal cancer and a clinically negative neck [12]. In a clinically negative neck, level V harbours rarely lymph node metastasis and does not have to be included in neck dissection for mucosal HNSCC. A novel approach may be the sentinel node-guided superselective neck dissection. In this approach only the lymphatic structures (e.g. one level) surrounding the sentinel node, which is identified by scintigraphy or peroperative gamma probe, are dissected [13].

Besides a therapeutic procedure, a neck dissection could also be considered as staging procedure. Neck dissections may, indeed, provide valuable additional information that helps in counselling the patients and planning adjuvant treatment, e.g. postoperative radiotherapy with or without chemotherapy.

The neck nodes may be fixed to adjacent structures, but are still resectable if the adjacent structures are dispensable such as the jugular vein, the sternocleidomastoid muscle and the skin. Although the prognosis may be poor, these neck node metastases are considered operable if vertebrae, brachial plexus and common or internal carotid artery are not involved. Sacrificing both internal jugular veins harbours the risk of increased intracranial pressure with eventual blindness and therefore has to be avoided [14]. Although the carotid artery is resectable with either ligation or replacement with a graft, most surgeons consider neck masses that involve the common or internal carotid artery as unresectable, particularly because of its association with very poor prognosis: 2-year disease-free survival of 22 % after carotid resection [15]. The most important criteria for vascular invasion are compression and deformation of the artery and partial fat or fascia deletion between the tumour and the artery on computed tomography (CT) [16]. Yousem et al. [17] found that the single criterion of involvement of 270° or more of the circumference of the carotid artery on MRI was accurate in predicting the surgeon's inability to peel the tumour off the carotid artery in all investigated 29 patients with clinical suspicion of carotid artery encasement (Fig. 33.2). Lodder et al. observed a false-negative rate of only 1.4 % when a combination of all aforementioned criteria is used. However, the interobserver variation was high [18].

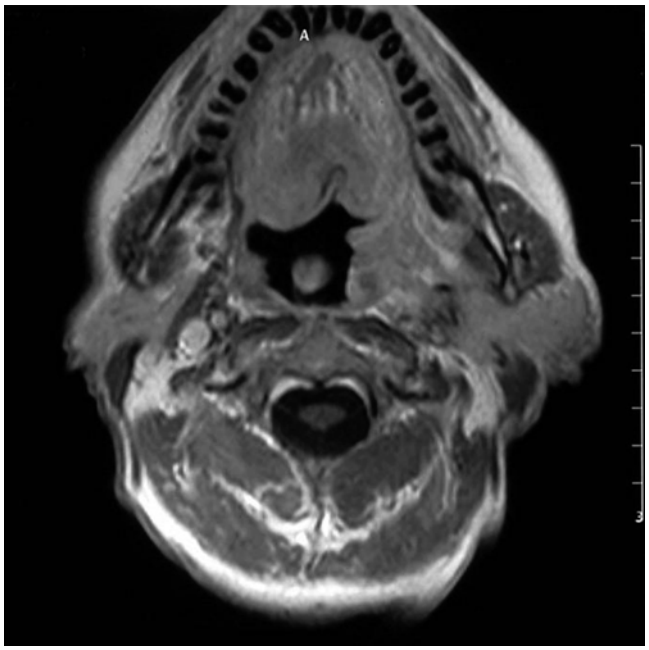

Fig. 33.2 MRI of a patient with a T3N3 oropharyngeal carcinoma and encasement of the carotid artery

33.2 Paratracheal Lymph Node Metastases

Paratracheal lymph node metastases carry a high risk for subsequent metastases to the mediastinum and to distant sites [19]. Paratracheal lymph node metastases also have been linked to stomal recurrence after total laryngectomy [19, 20]. Plaat et al. [21] evaluated the prognostic significance of paratracheal lymph node metastases with respect to tumour recurrence and survival in a group of patients with laryngeal or hypopharyngeal carcinoma treated with total laryngectomy. The presence of paratracheal lymph node metastases with

extranodal growth appeared to be most predicting factor of overall survival (OS) [21]. The reported incidence of paratracheal metastases varies according to primary site (larynx, hypopharynx and proximal oesophagus), stage and extension of the primary tumour from 3 to 26 % [20, 22, 23]. Unfortunately, the indications for elective paratracheal dissection during laryngectomy are not well defined. As the reported incidence of paratracheal metastases is low in supraglottic and glottic carcinomas without subglottic extension, paratracheal lymph node dissections are not routinely performed for these tumours. Because of the high incidence of paratracheal metastases, paratracheal lymph node dissections are recommended in patients with hypopharyngeal and oesophageal cancer and laryngeal tumours with subglottic extension beyond 1 cm caudally from the glottis [24].

33.3 Adjuvant Treatment

Although there are no prospective randomised studies that tested surgery alone versus surgery followed by adjuvant radiotherapy or chemoradiation, it is generally acknowledged that patients with HNSCC with multiple metastatic lymph nodes or lymph node metastases with extranodal spread (ENS) benefit from adjuvant treatment. The pertained benefit of adjuvant treatment is mainly based on retrospective analyses, historical comparisons and matched-pair analyses [25–32]. Adjuvant treatment is given in particular to reduce the risk of (locoregional) failure. In general, indications for adjuvant treatment included advanced T stage (especially cartilage and bone invasion), perineural invasion, vasoinvasive growth, close or positive surgical margins, multiple lymph node metastases and ENS. If adjuvant treatment is indicated by the primary tumour, this treatment is usually also given on the neck [33].

Langendijk et al. [34] performed a recursive partitioning analysis (RPA) to define risk groups of patients with HNSCC treated with surgery and postoperative radiotherapy. Patients classified as intermediate risk had one or more of the aforementioned classical indications but had free surgical margins (≥5 mm) and no ENS. Those with T1, T2 and T4 tumours with close or positive surgical margins and/or one lymph node metastasis with extranodal spread were classified as high risk, while T3 tumours with close or positive margins, multiple lymph node metastases with extranodal spread and/or N3 neck disease were classified as very high risk. This RPA classification system allowed for a distinct stratification of patients with different outcomes with regard to locoregional tumour control after surgery and postoperative radiotherapy alone, which was 92 %, 78 % and 58 % in class I, II and III patients, respectively. The overall survival was 67 %, 50 % and 37 % in classes I, II and III, respectively. The RPA classification system was a strong prognosticator for other endpoints as well, including disease-free survival and the occurrence of distant metastases, and has been validated among different study populations [35, 36].

Since the results of surgery and postoperative radiotherapy alone have been unsatisfactory in particular among high and very high-risk patients, the added value of concomitant chemotherapy to postoperative radiotherapy has also been investigated in a number of randomised trials. In the EORTC (#22931) trial, 334 patients treated with primary surgery for HNSCC of the oral cavity, oropharynx, larynx and hypopharynx were randomly assigned to receive either radiotherapy alone (66 Gy in 33 fractions) or chemoradiation with the same radiation schedule combined with cisplatin 100 mg/m^2 every 3 weeks [37]. The progression-free survival, which was the primary endpoint, was 23 months in the radiotherapy group compared to 55 months in the chemoradiation group ($p=0.02$), which also translated into a significant improvement of the 5-year overall survival after chemoradiotherapy compared to after postoperative radiotherapy alone (53 % vs. 40 %, $p=0.02$). Grade III/IV mucositis was more frequently observed in the chemoradiation arm of the study (41 % vs. 21 %, $p=0.001$). Severe late effects (≥grade III) were not statistically different [27]. In the RTOG (#9501) trial, 449 patients with high-risk HNSCC were randomly assigned after primary surgery to receive either radiotherapy alone (66 Gy in 33 fractions) or chemoradiation with the same radiation schedule combined with cisplatin 100 mg/m^2 every 3 weeks [38]. A significant improvement was observed in disease-free survival, which was 20 months in the radiotherapy group and 28 months in the chemoradiation group ($p=0.04$), which resulted in a non-significant improvement of the 5-year overall survival in the chemoradiotherapy group (44 % vs. 37 %, $p=0.19$). Grade III/IV mucositis was more frequently observed in the chemoradiation arm of the study (30 % vs. 18 %, $p=0.003$). Severe late effects (≥grade III) were observed in 17 % in the radiotherapy arm and 21 % in the chemoradiation arm of the study, but this difference did not reach the level of statistical significance ($p=0.3$) [38]. Recently, the long-term results of this study were published. After a median follow-up of 9.4 years for surviving patients, no significant differences were observed in the analysis of all randomised eligible patients with regard to neither locoregional failure rate, disease-free survival nor overall survival. However, analysis of the subgroup of patients who had either microscopically involved resection margins or extracapsular spread of disease showed improved locoregional control and disease-free survival with the addition of concurrent chemotherapy to postoperative radiotherapy. The remaining subgroup of patients with only 2 or more lymph nodes did not benefit from the addition of CT to RT [39].

Similar results were found in a third large randomised trial conducted by a German Group (ARO) that have not been presented in a full paper yet. In this study, 440 high-risk

patients were randomly assigned to receive either 64 Gy conventionally fractionated radiotherapy alone or to the same radiotherapy in combination with two cycles of concurrent chemotherapy (cisplatin 20 mg/m^2 + 600 mg/m^2 5FU CI; d1–5 + 29–33). Also in this study, a significant improvement of locoregional control and overall survival was observed. In a meta-analysis of the EORTC and the RTOG trial, a statistically significant survival benefit of chemoradiation was observed in overall survival, but this difference was confined to the subset of patients with ENS and/or close surgical margins (<5 mm) (Fig. 33.3), i.e. the RPA class II and III patients (high- and very high-) risk patients [40]. However, HNSCC with other risk factors like perineural disease, vascular embolism and >2 involved lymph nodes did not benefit from chemoradiation (RPA class I: intermediate-risk patients) [29]. The RPA classification system can thus be used to assess standard treatment strategies for HNSCC in the postoperative setting. In general, in case of intermediate-risk RPA class (RPA class I), conventional postoperative radiotherapy alone is indicated, while postoperative chemoradiation is indicated in case of the high- or very high-risk RPA classes.

Recently, the results of a meta-analysis showed a significant improvement of survival after altered fractionation radiotherapy in the primary setting. The results suggested that the most benefit could be obtained by using hyperfractionated schedules. The benefit of altered fractionation in the postoperative setting is less clear. Ang et al. [41] reported on the results of a phase III study, in which patients following surgery were randomly assigned to receive conventionally fractionated postoperative radiotherapy (63 Gy in 7 weeks) versus accelerated radiation (63 Gy in 5 weeks). In that study, locoregional control (LRC) after 5 years improved from approximately 62 % with conventional fractionation to 76 % with accelerated fractionation which was also translated in higher rates in OS that improved from 30 % to 48 % after 5 years. However, these differences were not statistically significant possibly due to the relatively low number of patients included in that study. The 5-year LRC and OS rates among patients with intermediate risk (comparable with RPA class I) in that study were approximately 93 % and 68 % [41]. In another relatively small randomised study, shortening of the overall treatment time of postoperative radiotherapy by accelerated hyperfractionation provided a significant improvement of LRC without significantly improving the OS only in fast-growing tumours [42]. It has to be stressed that the results of shortening the overall treatment of radiation are likely to be influenced by the interval between surgery and the start of radiation treatment [41, 42].

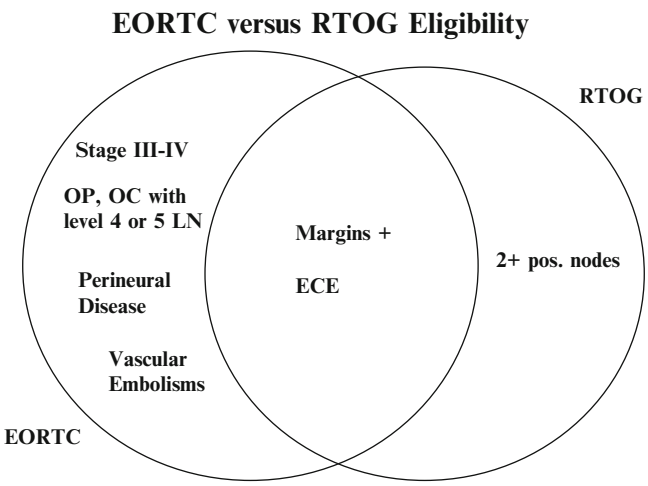

Fig. 33.3 Criteria for postoperative chemoradiation from RTOG and EORTC studies [Based on data from Ref. 29]

The total treatment package is defined as the period from the day of surgery to the last day of radiation and can be divided in the interval between surgery and radiotherapy and the total treatment time of radiation itself. In a number of studies [41, 43–46], the prognostic significance of the interval between surgery and radiotherapy was investigated (Table 33.4).

In most studies, the univariate analysis showed that the interval between surgery and radiotherapy was significantly associated with LRC. However, this was confirmed in the multivariate analysis in just one study [44]. In another study the interval was only associated with locoregional control and survival among patients who had been treated with conventionally fractionated radiation and not in those treated according to the accelerated fractionation schedule [41].

If single lymph node metastases without ENS are identified, adjuvant radiotherapy is usually not recommended. Controversy exists in what to do in this latter situation when found in a selective neck dissection: wait and see, adjuvant radiotherapy on the whole neck or complete the neck dissection. In most occasions, adjuvant radiotherapy will be given, increasing the morbidity to an extent probably higher than a modified radical neck dissection [33]. Postoperative reirradiation in patients with recurrent or new primary in a previously irradiated area is expected to increase locoregional control at the expense of higher toxicity and probably without survival advantage [47].

33.4 Non-surgical Treatment

Primary radiotherapy alone can be considered in case of non-bulky nodal disease. In a retrospective study, regional control of nodal metastases among patients with HNSCC treated with radiotherapy alone was over 90 % after 2 years in case of small nodal volumes (<3 cm), no presence of radiological central necrosis and no presence of radiological extranodal spread [48]. Elective neck irradiation for cN0 or pN0 disease resulted in excellent regional control rates of 90–97 % [49].

Table 33.4 Overview of studies regarding the prognostic significance of the interval between surgery and (postoperative) radiotherapy

Study	Design	Dose	Interval surgery—radiotherapy	Number of patients	5-year results		Comments
					Locoregional control	Overall survival	
Ang et al. [30]	Retrospective analysis from a prospective phase II study	63 Gy	0–31 days > 31 days	76 75	80 %; 72 % 65 %; 48 % $p=0.34$; 0.33	51 %; 47 % 41 %; 20 % $p=0.50$; 0.01	No randomisation for interval No multivariate analysis
Bastit et al. [32]	Retrospective multivariate	45–74 Gy	0–30 days >30 days	219 201	78 % 73 % ns	35 % 28 % ns	Multivariate analysis: no effect
Muriel et al. [33]	Retrospective multivariate	50–75 Gy	0–50 days >50 days	Total 214	83 % 68 % $p=0.02$	NA	Interval independent prognostic factor for locoregional control
Parsons et al. [34]	Retrospective univariate	55–73 Gy	0–50 days >50 days	76 39	79 % 59 % $p=0.02$	NA	
Schiff et al. [35]	Retrospective univariate	32–76 Gy	0–6 weeks >6 weeks	61 50	88 % 73 % $p=0.11$	NA	

In these cases, a planned neck dissection appears not to be indicated. However, in case of a larger volumes, central necrosis and/or radiological sign of extranodal spread, the risk on regional recurrence turned out to be unacceptably high [48, 50]. In these cases, chemoradiation and/or planned neck dissection is indicated as the application of accelerated radiotherapy does not result in better regional control [51].

Treatment of bulky neck disease with radiation alone offers poor regional control. Modern definitive chemoradiation of N3 neck disease results in a 2-year locoregional control of 88 % [52], 3-year regional control rate of 69 % without planned neck dissection [53] and 2-year regional relapse-free survival with neck dissection of 96 % [54].

The majority of patients who present with metastasis in the neck of unknown primary tumour have advanced regional disease. Whereas the standard treatment for those patients has been (modified) radical neck dissection followed by radiation therapy, there is now an increasing trend to treat these patients with chemoradiation followed by neck dissection when residual disease is present [55].

The decision to perform a neck dissection following (chemo)radiation is clear when patients have proven residual neck disease. However, distinction between residual metastasis and chemoradiation sequelae is difficult in most cases with a residual neck mass, since post-treatment induration and fibrosis obscure accurate clinical assessment. The difficulty in evaluating for recurrence has made salvage neck surgery less effective and late recurrences in the neck rarely surgically salvageable [56]. Therefore, in some institutes, planned neck dissections after curative (chemo)radiation are performed, as a reliable assessment of the pathological status after chemoradiation is often difficult [57, 58]. A negative predictive value of CT for the detection of residual or recurrent neck metastasis of 94–97 % is reported, with a good sensitivity (75–97 %) but with a specificity ranging from 24 % to 93 % [59–61]. These studies are difficult to compare due to heterogeneity of response assessment methodology. Ojiri et al. [61] reported specific abnormal radiological measures for predicting residual tumour in metastatic nodes in patients with head and neck cancer treated with radiotherapy: If lymph nodes on CT after radiotherapy were ≤15 mm, free of significant internal focal low attenuation or calcification and without imaging evidence of ENS, the neck was positive in 1 (3.4 %) side of the 29 surgical neck specimens. Others used a cut-off size of ≤10 mm or a regression of ≥80 % of maximal initial diameter. The optimum timing of post-treatment CT is probably around 8 weeks [62]. Since in N3 neck disease better disease-free survival is observed for patients undergoing neck dissection because of partial response as compared to patients without neck dissection because of complete response based on physical examination and CT, clinical assessment with CT is likely not sufficient for evaluating tumour response [54].

Recently, some retrospective studies on the use of FDG-PET in the prediction of necessity for post-radiation therapy neck dissection have been reported [63]. To avoid futile neck dissections, a high negative predictive value is needed. Negative predictive values between 14 and 100 % are reported in these studies, probably depending on the timing of PET scanning. PET imaging obtained too soon after radiation had been associated with high rate of false-positive findings due to post-radiation soft tissue effects and false-negative findings because of the residual viable cancer cells not having sufficient time to repopulate to a level that can be detected by PET. One month after radiation, the negative predictive value was only 14 % [64]. When PET scanning was performed

4–12 weeks after chemoradiation, this figure was 73 % [65]. When the interval between PET and completion of chemoradiation was 8–12 weeks, a negative predictive value of 92 % was reported [66]. If the time interval between the end of therapy and PET scanning increases, the negative predictive value improved to 97–100 % [67–70]. Also a high sensitivity is warranted to refrain patients from neck dissection. In these studies the sensitivities from 45 to 100 % are reported, depending on timing of the scanning. The reported specificity was 65–94 %. A study of 43 HNSCC patients with N2 or N3 neck disease before chemoradiation and FDG-PET-CT 2–5 months after treatment reported a sensitivity of 88 %, a specificity of 91 %, a positive predictive value of 70 % and a negative predictive value of 97 % [71]. Moeller et al. [72] observed no advantage of PET-CT over CT alone in radiation response assessment for unselected patients with locally advanced tumours. The negative predictive values of PET-CT and CT were 96 % and 98 %, respectively. However, in the high-risk group (T3–T4, N2b–N3, HPV-negative, non-oropharyngeal primaries or significant tobacco use history), the accuracy of PET-CT appeared to be superior [72]. These studies indicate that FDG-PET can predict residual neck disease after (chemo) radiation for HNSCC reliable [73]. Although these data suggest that in patients with a negative FDG-PET scan neck dissection can be avoided, concern exists that delaying a neck dissection allows more time for both cancer progression and for radiation-induced fibrosis, which may hamper the feasibility of a neck dissection and increase surgical complications.

Diffusion-weighted MRI uses strong magnetic field gradients to make the MRI signal sensitive to the molecular motion of water and is able to characterise tissue and generate imaging contrast based on differences in diffusion motion of water protons in the tissues. In a pilot study of 26 patients, Vandecaveye et al. [74] found a sensitivity of 95 %, a specificity of 96 % and accuracy of 96 % for the detection of residual or recurrent head and neck tumours after radiotherapy with or without chemotherapy using diffusion-weighted MRI with apparent diffusion coefficient (ADC) measurements in patients with suspicion of persistent disease. When compared with CT, conventional MRI and FDG-PET, diffusion-weighted MRI yielded fewer false-positive results for persistent nodal disease [54]. In a more recently study, they showed that ADC change (between prior to and 3 weeks after treatment) was significantly lower in adenopathy with a later recurrence than in adenopathy with complete remission [74, 75] performed DW-MRI 6 weeks after end of (chemo)radiation for HNSCC and showed that post-treatment ADC of a residual mass was associated with locoregional failure with a 100 % specificity, 45 % sensitivity, 100 % positive predictive value and 63 % negative prediction value. Also in DW-MRI, timing may affect accuracy. Although these results are promising, larger studies on diffusion-weighted MRI including patients with tumours at specific sites and treatments are needed. In optimising the decision making to perform a neck dissection following chemoradiation, a combination of FDG-PET and DW-MRI may be an attractive option [76].

Because no reliable clinical parameters are available to predict pathological status after (chemo)radiation, routine planned neck dissection is performed in some institutes. The integration of planned neck dissection into the multidisciplinary management of patients with locoregionally advanced head and neck cancer treated by concomitant chemoradiotherapy is highly effective in controlling residual cervical metastatic disease [77, 78]. However, in the majority of neck dissection specimens, no vital tumour cells are found [79–84]. Moreover, neck dissection after radiation bears a significant risk of wound healing problems. To prevent wound healing problems, pedicled pectoralis major muscle flaps should be used which may further increase treatment-related morbidity. In patients treated with a combination of chemotherapy and radiotherapy, this risk of wound healing problems is even higher. Extensive fibrosis is an untoward outcome observed in many patients who undergo surgery after (chemo)radiation therapy. These late and frequently progressive soft tissue side effects are more likely to occur after chemoradiation than after radiation alone. Delayed wound healing of surgical incision and potential wound breakdown with flap necrosis and large vessel exposure may complicate surgery after chemoradiation. Complication rates for planned neck dissections after chemoradiation of 17–35 % have been reported [57, 79, 85]. Postoperative complication rates of 53 % have been reported after en bloc salvage surgery for HNSCC. The clinical stage of the recurrent tumour and the previous site treated are major factors associated with the occurrence of postoperative complications [86].

Taking into account the relatively high complication rate of planned neck dissections, the question arises if all patients actually need such an “elective” surgical treatment. If the neck was clinically staged N0 or N1 before (chemo) radiation, no planned neck dissection is needed [87, 88]. In HNSCC patients with initial N2 or N3 neck disease or residual mass in the neck after (chemo)radiation, the perplexing decision remains whether to see the patient in clinical follow-up (watch and wait), looking for eventual growth of the mass, or perform a planned neck dissection regardless of whether the neck disease seems to regress completely [56, 84]. In some institutions, routine planned neck dissections are performed for pretreatment N2–N3 disease. Other institutes recommend neck dissection only for patients with no or partial clinical or radiological response [89]. In other institutes neck dissections following chemoradiation are performed in all patients with clinically residual disease and/or N3 [90]. The advantage of limiting neck dissection to patients with residual neck disease 6–8 weeks post-treatment is that overtreatment is reduced. There is a tendency to perform neck dissections after chemoradiation only if indicated by

post-treatment diagnostic (physical examination, imaging and/or cytological) evaluation of the neck [61, 66, 91–94]. Van der Putten et al. [95] reported on 129 patients with neck recurrence out of 540 HNSCC patients who underwent neck dissection after chemoradiation. They found that 6 % might have benefited from a planned neck dissection, while this planned neck dissection would have been unnecessary in 76 % of the patients with N2–N3 disease. For patients with N0–N1 neck, the number of unnecessary neck dissections was even higher (92.8 %). Other studies found that only 4–8 % of patients with complete response after (chemo)radiation would have benefited from planned neck dissection. In 47 % of patients with clinically partial response, the neck dissection specimen did not contain viable tumour cells. Because only very few patients with complete response in the neck develop regional relapse, a watch and careful observational strategy has an acceptable outcome and a planned neck dissection strategy results in a considerable overtreatment [53, 54, 96, 97]. Due to improvements in imaging techniques and criteria, routine planned neck dissection will probably be performed less often in the near future and the yield of neck dissection will be improved. Since a better response rate is observed in non-smokers with HPV-positive tumours, it should be appealing to include HPV status in decision making on the treatment of the neck after (chemo)radiation.

In the event of neck failure after (chemo)radiation, salvage surgery is indicated. Neck dissection as salvage procedure is also employed when initial response of tumour to non-surgical treatment is only partial. In patient treated with local recurrence after primary radiation for N+ disease, a 22 % risk of occult metastasis was reported. This figure was higher for patients with persistent compared to recurrent local disease or advanced recurrent T stage [98]. Similar to what has been discussed for the planned neck dissection, wound healing after salvage surgery may be problematic as well. As the possibilities of postoperative re-irradiation are often limited, in particular when the interval is short, it is essential to carry out adequate dissection in order to remove all residual or recurrent cervical lymph nodes harbouring malignancies while at the same time minimising morbidity to the surgical procedure [99].

If the decision to perform a neck dissection following radiation or chemoradiation has been made, the next dilemma is determined by the extent of the neck dissection that needs to be performed. The potential scope of lymph node removal ranges from excision of the affected nodal level, to selective neck dissection, to (modified) radical neck dissection [100]. Based on the assumption that any occult disease present before treatment will be sterilised by (chemo) radiation in low-risk levels, a (modified) radical neck dissection is probably not always warranted. Some studies have confirmed the feasibility and safety of planned post-chemoradiation selective neck dissections [101, 102]. Robbins et al. [100] examined the histopathological results of 84 neck dissections performed because of residual mass after chemoradiation in 240 patients with advanced-stage head and neck carcinoma. In 34 (40 %) of the neck dissection specimens, residual tumour was found, of which 41 % was confined to 1 level, 35 % had positive nodes in 2 levels and 24 % had positive nodal disease in 3 or more levels. In the selected group of patients who underwent selective or superselective (2 or fewer levels) neck dissections, regional disease as the first site of failure was only 5 % and 0 %, respectively. In a more recent study, 30 patients underwent 35 superselective neck dissections after chemoradiation. Although 8 patients developed local or distant recurrence, none of these patients had isolated neck recurrence [103]. They concluded that (super)selective neck dissections seems to be an effective procedure with potentially better preservation of function and less morbidity for patients with residual lymph adenopathy confined to 1 neck level after chemoradiation [100, 103]. The combination of primary location and CT findings can reliably identify low-risk levels that not require dissection [104]. The use of intraoperative frozen section in the post-chemoradiation setting is probably not reliable and can therefore not be used to assess the extent of salvage neck dissection.

33.5 The Patient Presenting with N0 Disease

The management of the clinically negative (N0) neck is a controversial issue. There is general agreement that elective treatment of the neck is indicated when there is a high likelihood of occult, clinically undetectable, lymph node metastases and when the neck needs to be entered for surgical treatment of the primary tumour (excision and/or reconstruction) or when the patient will be unavailable for regular follow-up. If the primary tumour is treated by irradiation, the adjacent lymph nodes are generally treated as well partly due to technical reasons.

Since lymph node metastases of T1 and T2 glottic laryngeal carcinoma are rare, the regional lymphatics are usually not treated electively. On the other hand, even in small oropharyngeal, hypopharyngeal and supraglottic tumours, the risk of occult metastases is high and the lymph node levels at risk are treated electively. Since most of these tumours are treated by irradiation, the radiation field must be extended to include the neck. When there is intermediate likelihood of occult lymph node metastases, the choice is between elective treatment and watchful waiting. This question certainly arises in the smaller (T1 and T2) carcinomas of the oral cavity and oropharynx, because these usually can be excised adequately by the transoral route, and the neck is not entered surgically.

The rationale for elective treatment is based on the following premises. First, occult metastases will inevitably develop into clinically manifest disease. Secondly, despite regular follow-up, some patients will develop extensive or even inoperable disease in the neck with a wait-and-see policy. Finally, untreated disease in the neck may give rise to distant metastases, while the lymph node metastasis is growing to a clinically detectable size. The arguments against elective treatment of the neck are as follows. Firstly, a large proportion of patients are subjected to treatment that they do not require. Secondly, such treatment may remove or destroy a barrier to cancer spread in case of local recurrence or second primary tumour. Finally, elective treatment of the neck is associated with morbidity, i.e. shoulder morbidity.

A number of mostly retrospective studies have shown a better regional control by elective neck dissection or irradiation as compared to observation in oral cancer patients [105–111]. The results of surgery after 'watchful waiting' (observation) are generally poor and often more extensive than elective treatment [105, 106, 112, 113]. However, most studies did not show improved survival for elective treatment of the neck [29, 107, 114–118]. D'Cruz et al. [119] compared the results of 159 patients with T1–2 N0 oral tongue carcinoma who underwent an elective neck dissection with 190 patients who had wait and watch follow-up of the neck for these tumours. The estimated 5-year disease-specific survival was 71 % and 68 % for these groups, respectively. Only a few studies found a survival benefit of elective neck dissection [107, 111]. In one study an improved survival was found for elective neck dissection only in T2 oral tongue carcinoma [105]. It may be possible that the survival advantage offered by elective treatment is small and that the sample size of most studies does not afford sufficient power to adequately demonstrate this difference [117]. It seems likely, however, that if elective treatment of the neck is to improve survival, it will most benefit those patients with a high risk of occult metastasis. Weiss et al. (1994) [120] reported on a decision analysis based on the diagnostic techniques and the expert opinions in those days. Since then it is generally accepted that the neck should be treated if the risk of lymph node metastases is greater than 20 %. It is remarkable that this risk percentage is still accepted despite technical improvements in the last decades. In these days an acceptable risk of not treating occult metastases is probably much lower. The risk of occult metastases is dependent on site, stage and other tumour characteristics. Histopathological features such as differentiation (in the deep portion), (invasive) growth pattern, thickness, depth of muscle invasion, vasoinvasive growth (angiolymphatic invasion), perineural invasion and degree of inflammatory reaction surrounding the tumour may have some relevance in predicting nodal disease [119, 121–125]. In the near future it may be anticipated that molecular biological diagnostic techniques will be able to predict the presence of (occult) lymph node metastases more reliable [126].

If a clinically negative neck is not treated electively, close follow-up with or without diagnostic techniques, e.g. ultrasound-guided fine-needle aspiration cytology, is an option in carefully selected patients to detect occult metastases in an early stage [127–129]. In such strategies futile elective neck dissections can be avoided in the majority of patients, and neck disease control and survival seem not to be compromised. However, in the few patients who need a (salvage) neck dissection for delayed metastases, treatment of the neck will probably be more extensive, e.g. modified radical neck dissection with or without radiotherapy, than if they had undergone elective treatment [129].

If it is decided to treat the clinically N0 neck surgically, several types of operation are available: selective and (modified) radical neck dissections. Rarely adjuvant radiotherapy is indicated. The reported regional recurrence rate after elective neck dissection is between 5 and 12 % [29, 105–118]. Elective radiation to a dose of 5000 cGy yields a control rate of the neck exceeding 90 % [130].

In the management of the clinically N0 neck, it is important to realise that the definition of the N0 neck is not uniform since different diagnostic techniques have been used in different studies. The risk of occult metastases is also dependent on the diagnostic techniques used. Modern imaging techniques, like computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and ultrasound (US), are more reliable than palpation. The capability of all of these techniques to detect small tumour deposits (micrometastases) is limited [131]. US-guided fine-needle aspiration cytology (USgFNAC) proved to be superior to the other current imaging techniques [132]. In the clinical negative neck, FDG-PET was not superior to conventional imaging techniques [133]. In an attempt to select the lymph nodes potentially containing metastases more reliably, the sentinel lymph node (SN) concept was introduced. Whereas conventional USgFNAC uses the abovementioned criteria, the SN concept is fundamentally based on the theory of orderly spread of tumour cells within the lymphatic system. The first lymph node in a regional lymphatic basin that receives lymphatic flow from a tumour is considered to be the SN. The SN concept assumes that lymphatic metastases, if present, can always be found at least in the SN. A tumour-negative SN would thus preclude the presence of lymphatic malignant involvement elsewhere in the neck. Oral cancer is eminently suitable for sentinel node evaluation as metastasis takes place through lymphatic corridors to specific areas of the neck, depending on the site of the primary tumour [134]. A meta-analysis revealed a sensitivity of 93 % and a negative predictive value of 88–100 % for the detection of occult lymph node metastases in early oral cancer [135]. To confirm these findings, larger multicentre studies are ongoing.

In some institutes, treating most pharyngeal and laryngeal cancers endoscopically with sentinel node procedures has been performed for these sites as well [136].

33.6 The Patient Presenting with N1 Disease

In general management of N1, disease by modified radical neck dissections harbours an excellent oncological outcome. The role of selective neck dissections in N1 disease is evolving. Adjuvant (chemo)radiation may be indicated by the results of the histopathological examination of the surgical specimen.

Almost all patients presenting with N1 disease receive nodal control from (chemo)radiation, provided that the primary site is cured. In only 0–8 % of the neck dissection specimens after radiotherapy alone for N1 disease, tumour is found [88]. In 30 patients presented with N1 disease who obtained local control after hyperfractionated radiotherapy and concurrent cisplatin and 5-flurouracil chemotherapy, modified radical neck dissection showed pathological complete response in 92 % [137]. In general, patients with N1 disease do not need to undergo a neck dissection after (chemo)radiation unless there is a persistent mass in the neck. Neck dissections in patients with a residual mass in the N1 neck after (chemo) radiation yield viable tumour cells in 25 % of cases [5].

33.7 The Patient Presenting with N2–N3 Disease

In patients with N2–N3 disease, (modified) radical neck dissection with adjuvant radiotherapy resulted in 86 % 5-year neck control rate [138]. In advanced head and neck cancer, chemoradiation has been proven effective in achieving disease control at the primary site. The management of the neck in patients with N2–N3 disease who undergo non-surgical treatment for the primary tumour is debatable. Although the addition of neck dissection to radiation of N2 or N3 disease shows fewer regional recurrences, planned neck dissection following radiation for patients presented with N2–N3 lesions reveals tumour in only 20–50 % of the specimens. For patients treated with chemoradiation, this figure is even lower [56]. Such findings provide rationale for withholding neck dissection for patients staged N2 with a complete clinical response. Since the probability of complete pathological response decreases with increasing pretreatment nodal size, some authors recommend a neck dissection for N3 patients, regardless of clinical response to non-surgical therapy [88, 90, 91]. Because the salvage rate (if neck disease recurs clinically) is low, regional control is enhanced by planned neck dissection. However, an improvement in overall survival with the addition of a planned neck dissection to (chemo) radiation for N2–N3 head and neck cancer is not demonstrated consistently. The improvement of regional control by planned neck dissections must be weighed against the complications and morbidity of neck dissections after (chemo) radiation. Recent studies show that a careful observational strategy is worthwhile and safe [95]. No generally accepted guidelines are available on this difficult subject.

33.8 Recurrence in the Neck

Recurrence of cancer in the neck following appropriate treatment is a poor prognostic sign. When considering treatment for recurrent neck disease, examinations for local recurrence, distant metastases and second primary tumours have to be performed. Treatment options depend on previous treatment and extent of the recurrence in the neck. Recurrent lymph node metastasis in the field of a previous (modified) radical neck dissection is often unresectable. If surgical treatment is not possible, e.g. unresectability or severe comorbidity, radiation therapy or chemotherapy may be used with curative intent or as palliation. Re-irradiation, administered either with or without concurrent systemic therapy, is feasible and tolerable in properly selected patients [47]. Regional control could be achieved by brachytherapy in 67 % of patients with inoperable recurrent cervical lymphadenopathy [139]. Even in case of distant metastases, surgery may be considered as palliative option since uncontrolled tumour growth in the neck induces severe morbidity.

33.9 Shoulder Morbidity

It is well established that neck dissection procedures are associated with shoulder morbidity. This morbidity is characterised by shoulder pain, limitations of abduction and scapular winging. Shoulder function is an important aspect of health-related quality of life as it is related to various activities of daily living, e.g. dressing, writing, driving, lifting objects and reaching for things [140, 141]. Because of the impact of impaired shoulder function on social and leisure activities and work, several domains of quality of life may be affected [142].

Modifications of the radical neck dissection were fashioned to limit the extent and frequency of shoulder dysfunction [143]. Spinal accessory nerve-sparing neck dissections are associated with better preservation of shoulder function as compared to nerve-sacrificing neck dissections [144, 145]. Nevertheless, significant shoulder dysfunction continues to arise even when the spinal accessory nerve is spared during the neck dissection procedure [146]. To diminish shoulder morbidity, the concept of the selective neck dissection was introduced in which only the levels at risk for (occult) lymph node

metastases are dissected [147]. To minimise shoulder morbidity further, in selective (levels I–III or I–IV) neck dissections, level IIb is not always dissected to avoid traction on the spinal accessory nerve as well as devascularisation in patients with certain primary tumour sites and clinically negative neck.

Also after non-surgical treatment of the neck, shoulder morbidity is often present but to a lesser extent compared to surgical treatment. Radiotherapy adds no morbidity to neck dissection, and chemotherapy does not add extra morbidity to primary radiation [148].

Shoulder morbidity may be improved by physiotherapy and exercising programmes. Physiotherapy has an important role in promoting function, improving scapular stability and reducing pain by maintaining length of muscles, range of movement and preventing frozen shoulder symptoms [142]. In the postoperative care, a specific rehabilitation programme may be prescribed.

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Postoperative Management of High-Risk Resectable Head and Neck Cancer

34

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Abstract

Primary surgery is often a treatment modality used in the management of head and neck cancer. For patients with high-risk disease, surgery alone is insufficient, thus mandating a risk-adapted approach to determine which patients benefit most from the addition of adjuvant therapies. Typically, patients with advanced T stage, surgical margin involvement, perineural invasion, lymph node involvement, extracapsular spread, or bone involvement warrant the addition of postoperative radiotherapy. Randomized trials have also identified a select group of patients for whom the addition of chemotherapy concurrent with postoperative radiotherapy has been shown to improve outcomes. Specifically, patients with resected disease whose final pathology demonstrates the presence of extracapsular spread or surgical margin involvement should be treated with adjuvant, platinum-based chemoradiation. Targeted therapies in the adjuvant setting have achieved mixed success and remain under active investigation. The identification of more efficacious and less toxic adjuvant therapies is paramount to maximizing oncologic outcome and quality of life.

Keywords

Head and neck cancer • Surgery • Radiation therapy • Chemotherapy • Chemoradiotherapy • Adjuvant • Postoperative • High risk

34.1 Introduction

The management of patients with head and neck cancer (HNC) is complex and requires a multidisciplinary approach, with treatment decisions primarily dictated by disease site, stage, and adverse pathologic features. Traditionally, early-stage (I–II) HNC without pathologic high-risk features has been treated with single-modality surgery or radiation, whereas early-stage (with pathologic high-risk features) and advanced-stage, non-metastatic (III–IV) HNC generally requires multimodality therapy to maximize oncologic outcome. The observation that appropriate surgical resection as a single modality for treatment of locally advanced disease resulted in unacceptably high relapse rates prompted the addition of postoperative radiation (PORT) for most patients with resectable stage III–IV disease to maximize local control and cure rates. Despite relatively aggressive bimodality treatment, such an approach still left room for improvement, consequently resulting in the addition of adjuvant chemotherapy in selected patients. Herein, we will discuss how risk is defined as well as the evidence-based data to support the role of adjuvant radiation therapy with or without concurrent chemotherapy in patients with resectable disease who remain at high risk of relapse following definitive surgical intervention.

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34.2 Role for Postoperative Radiotherapy

The combination of surgery and radiotherapy (RT) for advanced HNC developed empirically due to poor locoregional control rates with either modality alone. The concept of integrated treatment rather than the use of a single modality

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with subsequent salvage therapy at time of recurrence was described as early as 1957 and further supported by data published in 1970 [1, 2]. Trials throughout the 1960s and 1970s examined the dose of radiation used, with convincing evidence emerging to support the efficacy of adjuvant RT [3–8]. Specifically, the Radiation Therapy Oncology Group (RTOG) 7303 prospective randomized trial initiated in 1973 demonstrated the statistically significant superiority of postoperative (versus preoperative) RT in achieving optimal locoregional control [8, 9]. Three hundred twenty patients with advanced (T2–4, any N), operable head and neck squamous cell carcinoma (HNSCC) of the oral cavity, oropharynx, larynx, or hypopharynx were randomized to receive 50 gray (Gy) preoperatively versus 60 Gy postoperatively. With follow-up ranging 9–15 years, the 10-year locoregional control rate was significantly improved in the PORT group (70 % vs. 58 %, $p=0.04$). There was no difference in absolute survival ($p=0.15$), which was attributable to deaths from the development of distant metastases and second primaries. While this study could not discriminate between the effects of timing versus the higher RT dose given postoperatively, concerns about inducing higher complication rates with the administration of 60 Gy in the preoperative setting effectively established the use of 60 Gy postoperatively as the gold standard for high-risk disease. The 1970s and 1980s ushered in a number of surgical series attempting to identify various clinicopathologic features associated with risk of recurrence, including primary site, surgical margin status, perineural invasion, involvement and location of nodes, and extracapsular extension (ECE) [10–14].

Building on this mounting body of evidence, the first prospective phase III randomized trial to determine the optimal dose of PORT was published in 1993 by Peters et al. at the University of Texas MD Anderson Cancer Center (MDACC) [15]. This trial had three aims: to evaluate clinicopathologic criteria defining subsets of patients at higher or lower risk of recurrence, to determine the optimal radiation dose for both high- and low-risk categories, and to examine the dose–response relationship for normal tissue injury with PORT. Patients were initially stratified by primary site of disease and then assigned to risk categories with a separate point system for both the primary site and neck. Patients were categorized as higher or lower risk, with each risk category further being randomized to one of two treatment arms that differed only in the radiation dose given to the sites of maximum risk. Various putative prognostic factors were examined, including oral site primary, close or positive margins, nerve invasion, at least two or more positive nodes, largest node at least 3 cm, presence of ECE, Zubrod score of 2 or greater, and delay in RT start by more than 6 weeks. Extracapsular spread was the only independently significant prognostic factor ($p=0.04$), with the presence of at least two positive nodes trending toward worse locoregional recurrence ($p=0.08$). Not surprisingly, the coexistence of clusters of two or more of these putative adverse prognostic factors did correlate with risk of recurrence; patients without ECE but having at least four other adverse factors had similar poor outcomes as those with ECE.

This risk assessment method was subsequently tested in a follow-up phase III randomized trial published by Ang et al. in 2001, in which the results yielded prospective validation that risk assessment by clusters of clinicopathologic features does differentiate the need for and dose of PORT [16]. Patients were categorized into one of three risk categories (low, intermediate, high) based on the presence or absence of certain risk features, including oral cavity primary site, microscopic positive margins, perineural invasion, a lymph node greater than 3 cm, at least two positive nodes, more than one nodal group involved, and ECE. Low-risk patients had none of the above risk features and were treated with surgery alone, yielding 5-year actuarial locoregional control (LRC) and overall survival (OS) rates of 90 % and 83 %, respectively. Consequently, the addition of more therapy for these patients is unlikely to improve outcome. Patients were classified as intermediate risk if they had one adverse risk feature (other than ECE); these patients uniformly received 57.6 Gy in 32 fractions (1.8 Gy per fraction) over 6.5 weeks. Their 5-year actuarial LRC and OS rates were 94 % and 66 %, respectively. Although these patients presumably had more aggressive tumor phenotypes than the low-risk group, they achieved comparable locoregional control rates, likely due to the addition of PORT. The considerably worse overall survival, however, suggests that PORT as utilized in this study could not fully compensate for more aggressive phenotypes, thus corroborating the risk assessment method's ability to differentiate between levels of risk. Patients with high-risk disease (ECE or at least two adverse features) had 5-year actuarial LRC and OS rates of 68 % and 42 %, respectively, despite receiving a higher dose of PORT (63 Gy). This latter finding also provides confirmation that extracapsular spread or clusters of ≥2 adverse risk factors portend a higher risk of locoregional recurrence despite the higher PORT dose.

A combined post hoc analysis of two RTOG trials (8503 and 8824) was subsequently undertaken to determine the importance of pathologic features on identifying subgroups of patients at highest risk of locoregional relapse despite appropriate surgical resection and PORT [17]. RTOG 8503 was a prospectively randomized, intergroup phase III trial of patients with advanced, operable HNSCC (oral cavity, oropharynx, larynx, hypopharynx) who were randomized to receive PORT or sequential chemotherapy (cisplatin 100 mg/m^2 on day 1 and continuous infusion 5-fluorouracil 1000 mg/m^2 on days 1–5 of a 21-day cycle for a total of three cycles) followed by PORT [18]. For the first analysis, patients were retrospectively assigned into various risk groups based on presumed progressive risk, not the original stratification

Table 34.1 Simplified scheme of risk by author [and reference]; see text for details

	Ang [16]	RTOG 8503 [18]	Rosenthal et al. [19][a]	Le Tourneau et al. [20]	Langendijk et al. [21]
≥2 involved nodes	I	I	H	H	–
Extracapsular extension	H	I	H	H	I
Involved margin	I	H	H	–	I
N3 disease	–	–	–	H	H
Node ≥3 cm	I	–	I	–	–
Oral cavity primary	I	–	–	–	–
Perineural invasion	I	–	I	–	–
Perivascular invasion	–	–	I	–	–
T4 disease	–	–	I	H	–
Tumor volume	–	–	–	H	–
>1 nodal group involved	I	–	–	–	–

If more than one intermediate-risk feature is present, consider the tumor high risk
I intermediate risk, *H* high risk
[a]Additional intermediate-risk factors included primary invasion of cartilage, bone, or soft tissue and need for emergent tracheostomy
[Used with permission from Springer Science: Adapted from original tables by Dr. Jay S. Cooper featured in the 1st edition of Head and Neck Cancer: Multimodality Management]

criteria used for the trial. Group 1 had less than two involved nodes, no ECE, and negative surgical margins. Group 2 had at least two positive nodes or ECE but negative surgical margins. Group 3 had microscopically involved surgical margins. Based on these risk stratifications, 5-year LRC was 83 %, 70 %, and 38 % in groups 1, 2, and 3, respectively. Similarly, OS also differed among the groups, with 5-year OS rates of 53 %, 32 %, and 26 % in groups 1, 2, and 3, respectively.

In addition to the MDACC risk assessment methods, other models have also been employed to capture risk (Table 34.1). In RTOG 8503, patients treated with surgery followed by RT alone were retrospectively grouped based on presumed markers of risk [18]. Group 1 patients had less than two involved nodes, no ECE, and negative margins. Group 2 had at least two positive nodes and/or ECE and negative margins. Group 3 had positive margins. At 5 years, the LRC was 83 %, 70 %, and 38 % in groups 1, 2, and 3, respectively. Similarly, 5-year OS rates were 53 %, 32 %, and 26 % in groups 1, 2, and 3, respectively.

Retrospective evaluation of institutional databases has also been conducted [19, 20]. Rosenthal et al. evaluated 208 consecutive patients with HNSCC treated at the University of Pennsylvania with surgery followed by PORT between 1992 and 1997 [19]. Patients were high risk if they had at least two positive nodes, ECE, and/or microscopically involved margins (<5 mm). Intermediate-risk factors included T4 disease, at least a 3 cm node, perineural or perivascular invasion, primary invasion of cartilage, bone or soft tissue, or need for emergent tracheostomy. Two-year LRC and OS rates correlated favorably with level of risk, with LRC rates of 91 % vs. 74 % (intermediate vs. high risk) and OS rates of 86 % vs. 60 % (intermediate vs. high risk). Le Tourneau et al. evaluated 621 consecutive patients with HNSCC resected at Sainte-Barbe Clinic in Strasbourg, France, between 1990 and 1997 [20]. They concluded that tumor volume, pathologic T and N stage, number of involved lymph nodes, and presence of ECE were all significantly associated with survival outcome.

Finally, it is worth noting that predefined mathematical models have also been utilized to define risk, with Langendijk using recursive partitioning analysis (RPA) to evaluate 801 patients with HNSCC treated with surgery followed by PORT [21]. Three groups were identified: group 1 (intermediate risk) had no N3 involvement, negative margins (>5 mm), and no ECE; group 2 (high risk) had one node with ECE or T1, T2, and T4 tumors with close or positive margins; and group 3 (very high risk) had N3 disease, at least two nodes with ECE, and/or T3 tumor with close or positive margins. The 5-year LRC and OS rates were 92 %, 78 %, and 58 % and 67 %, 50 %, and 36 % for groups 1, 2, and 3, respectively. A prospective validation of these RPA-defined groups was subsequently performed in 780 newly diagnosed patients with 5-year LRC and OS rates closely resembling their initial analysis [22].

As described above, many trials have attempted to justify the level of treatment intensity by establishing pathologic risk groups. In general, postoperative RT is typically administered for patients with advanced T stage (T3, T4), positive surgical margins, perineural or lymphovascular invasion, lymph node involvement, ECE, and bone involvement [23].

34.3 Role for the Addition of Chemotherapy to PORT

While the addition of PORT following surgical resection was clearly advantageous to surgical resection alone, the poor outcomes of this bimodal approach combined with data demonstrating improved efficacy of chemoradiation in the

LAHNC setting [24–28] as well as activity of chemotherapy in the recurrent/metastatic setting [29–32] led to investigations of whether modulating treatment intensity with the addition of chemotherapy in the adjuvant setting would further improve outcomes.

RTOG 8503 (Intergroup 0034), as previously described, tested the efficacy of sequential chemotherapy as an adjuvant to surgery and PORT for patients with resected LAHNC [18]. Four hundred forty-two patients were categorized as low-risk or high-risk treatment volumes based on surgical margin involvement (≥5 mm), presence of ECE, and/or carcinoma in situ at the surgical margins. RT was dosed at 50–54 Gy for low-risk and 60 Gy for high-risk volumes. Patients were randomized to receive RT alone or three cycles of cisplatin/5-fluorouracil followed by RT (CT/RT). With a median follow-up of 45.7 months, 4-year locoregional failure rate was 29 % vs. 26 % for RT vs. CT/RT, 4-year disease-free survival (DFS) was 38 % vs. 46 % for RT vs. CT/RT, and 4-year actuarial survival rate was 44 % vs. 48 % for RT vs. CT/RT (none of these findings were significant). The incidence of first failure in cervical nodes was 10 % vs. 5 % for RT vs. CT/RT ($p=0.03$), and overall incidence of distant metastases was 23 % vs. 15 % for RT vs. CT/RT ($p=0.03$). Chemotherapy was generally tolerated and did not adversely impact subsequent delivery of radiotherapy.

RTOG 8824, a non-randomized, phase II, single-arm trial, was subsequently completed to evaluate the efficacy of adjuvant cisplatin concurrent with RT for patients with resected stage IV HNC or any stage HNC with microscopically involved margins [33]. Fifty-two patients were enrolled, with planned treatment including cisplatin 100 mg/m^2 on days 1, 22, and 43 of PORT (60 Gy in 30 fractions over 6 weeks). Given this was a single-arm study, the results were compared to the control arm (surgery + PORT) from RTOG 8503. To facilitate an accurate comparison, only patients with ≥2 positive nodes, ECE, or positive surgical margins were included from both trials. One hundred ninety-three patients from RTOG 8503 and 42 patients from RTOG 8824 were included in this comparative analysis. The 3-year locoregional failure rate was significantly lower with the addition of chemotherapy (20 % for RTOG 8824) versus adjuvant RT alone (36 % for RTOG 8503). The 3-year OS rate was 47 % for RTOG 8824 versus 42 % for the control arm.

Numerous additional trials testing the use of other systemic agents as well as alternative delivery schedules demonstrated some promise, but the findings were not uniformly beneficial (Table 34.2). In 2004, further support for the concurrent use of adjuvant chemotherapy and radiotherapy emerged, based on the simultaneous publications of two large, multicenter, randomized, prospective clinical trials (RTOG 9501 and European Organization for Research and Treatment of Cancer [EORTC] 22931) [34, 35]. Both trials were designed and run independently on both sides of the Atlantic, prescribed fairly similar treatments (addition of cisplatin 100 mg/m^2 on days 1, 22, and 43, with 60–66 Gy PORT in RTOG vs. 66 Gy in the EORTC trial), and sought to determine if chemotherapy added to PORT would improve outcomes in patients with high-risk HNSCC that underwent

Table 34.2 Attempts at biologically intensifying radiation therapy by study [and reference]

Study	Agent #1	Agent #2	Timing	Outcome
RTOG 8503 [18]	Cisplatin	5-FU	Sequential	No significant improvement
RTOG 8824 [33]	Cisplatin		Concurrent	Possible increase in LR control
Haffty et al. [52]	Mitomycin C		Concurrent	Possible increase in LR control
Bachaud et al. [53]	Cisplatin		Concurrent	Significant increase in LR control and OS
Smid et al. [54]	Mitomycin	Bleomycin	Concurrent	Significant increase in LR control and OS
Racadot et al. [55]	Carboplatin		Concurrent	No significant improvement
RTOG 9501 [34]	Cisplatin		Concurrent	Significant increase in LR control
EORTC 22931 [35]	Cisplatin		Concurrent	Significant increase in LR control and OS
RTOG 0234 [47]	Cisplatin or docetaxel	Cetuximab	Concurrent	Significant improvement in DFS compared to historical standard (RTOG 9501)
Harrington et al. [50]	Cisplatin	Lapatinib vs. placebo	Concurrent followed by monotherapy maintenance	No significant improvement

5-FU 5-fluorouracil, *LR* locoregional, *OS* overall survival, *DFS* disease-free survival

Table 34.3 Summary of RTOG 9501 and EORTC 22931 trials

Study features	RTOG 9501 ($n=334$)	EORTC 22931 ($n=459$, 414 analyzed)
Shared "high-risk" eligibility	Microscopically involved margins Extracapsular extension	Microscopically involved margins Extracapsular extension
Unique "high-risk" eligibility	Two or more lymph nodes involved	Oral cavity or oropharynx primaries with nodal spread to levels IV and/or V Stage III/IV Perineural invasion Vascular embolism
Primary endpoint	Locoregional disease control	Progression-free survival
Outcome (RT vs. CRT) • Locoregional failure rate • Disease-free survival rate • Overall survival rate	10-year estimate: 28.8 % vs. 22.3 %, $p=0.1$ 19.1 % vs. 20.1 %, $p=0.25$ 27 % vs. 29.1 %, $p=0.31$ [a]Unplanned subset analysis: LRF 33.1 % vs. 21 %, $p=0.02$ DFS 12.3 % vs. 18.4 %, $p=0.05$ OS 19.6 % vs. 27.1 %, $p=0.07$	5-year estimate: 31 % vs. 18 %, $p=0.007$ 36 % vs. 47 %, $p=0.04$ 40 % vs. 53 %, $p=0.02$

RT radiation alone, *CRT* radiation with chemotherapy, *LRF* locoregional failure rate, *OS* overall survival rate, *DFS* disease-free survival rate

[a]Unplanned subset analysis limited to patients with microscopically involved margins and/or extracapsular extension

macroscopically complete resections. The trials differed in their location, definition of "high-risk" features, and primary endpoints chosen (Table 34.3). While both trials included surgical margin involvement and ECE as high-risk criteria, RTOG also included patients with at least two positive lymph nodes. Additional inclusion criteria for the EORTC trial were stage (pT3–4 with any N except T3N0 larynx, pT1–2 if also N2–3, or pT1–2 N0–1 if other adverse risk factors present), oropharynx or oral cavity primaries with level IV and/or V nodal involvement, perineural invasion, and/or vascular embolisms. The primary endpoint for the RTOG trial was locoregional disease control rate, whereas the EORTC trial selected progression-free survival (PFS).

Initial results of the RTOG trial demonstrated significantly improved 3-year locoregional progression rates (22 % vs. 33 %, $p=0.01$) and DFS rates (47 % vs. 36 %, $p=0.04$) with a nonsignificant trend toward improved OS (56 % vs. 47 %, $p=0.086$) with combined chemoradiotherapy (CRT). However, the updated 5-year RTOG results demonstrated only nonsignificant trends toward improved locoregional control (79.5 % vs. 71.3 %, $p=0.086$) and DFS rates (37.4 % vs. 29.1 %, $p=0.098$). In contrast, the EORTC trial did demonstrate a significant benefit to the addition of chemotherapy to the adjuvant paradigm. With a median follow-up of 60 months, the 5-year PFS rate of 47 % vs. 36 % favored CRT over RT alone (HR 0.75, CI 0.56–0.99, $p=0.04$). Similarly, CRT performed favorably compared to RT alone with respect to OS rate (53 % vs. 40 %, HR 0.7, CI 0.52–0.95, $p=0.02$) and cumulative incidence of local or regional relapses ($p=0.007$). In both trials, adjuvant cisplatin did not influence the rate of development of distant metastases (EORTC, 25 % with RT vs. 21 % with CRT, $p=0.61$; RTOG, 23 % with RT vs. 21 % with CRT, $p=0.46$).

Given the discordance in survival outcomes as well as a desire to further refine assessment of risk levels, an unplanned, collaborative, comparative analysis pooling the data of both trials was subsequently undertaken [36]. The joint analysis included the assessment of LRC, DFS, and OS. Given the marked differences in selection criteria between the two trials, a substantially higher proportion of patients had N2–N3 disease in the RTOG trial (94 % vs. 57 % in EORTC). The EORTC trial had fewer patients with oropharyngeal primaries (30 % vs. 42 % in RTOG) but more patients with hypopharyngeal primaries (20 % vs. 10 % in RTOG). Distribution of common high-risk features for EORTC and RTOG, respectively, included 41 % vs. 49 % for ECE alone, 13 % vs. 6 % for positive margins alone, and 16 % vs. 4 % for both. Thus, 70 % of patients in EORTC and 59 % of patients in RTOG shared one or both of the common high-risk features. Chemotherapy doses were similar in both studies. Regarding RT, 13 % of patients in RTOG received 66 Gy (study allowed 60–66 Gy) compared to 91 % in EORTC. The general conclusions of this combined analysis were as follows: *ECE and/or surgical margin involvement were the only risk factors for which adjuvant chemoradiotherapy significantly improved outcomes.* There was a nonsignificant trend favoring the use of CRT in patients with stage III–IV disease, perineural invasion, vascular embolisms, and/or level IV or V nodal involvement with oral cavity or oropharyngeal tumors. Importantly, patients with the presence of two or more pathologically involved lymph nodes in the absence of ECE did not obtain benefit from the addition of chemotherapy to PORT.

In 2012, the RTOG 9501 trial group published long-term follow-up data [37]. With 410 analyzable patients and a minimum follow-up of 10 years, RT vs. CRT resulted in locoregional failure rates of 28.8 % vs. 22.3 % ($p=0.1$), DFS rates of 19.1 % vs. 20.1 % ($p=0.25$), and OS rates of 27 % vs. 29.1 % ($p=0.31$). Interestingly, an unplanned subset analysis of patients with positive surgical margins and/or ECE did demonstrate significantly improved rates of locoregional failure (33.1 % vs. 21 %, $p=0.02$) and trends toward improved DFS (12.3 % vs. 18.4 %, $p=0.05$) and OS rates (19.6 % vs. 27.1 %, $p=0.07$) in favor of the addition of chemotherapy. Importantly, for the subgroup of patients with at least two positive nodes as their only risk factor, there was a persistent lack of benefit with the addition of chemotherapy to PORT.

Just as these two trials identified which groups of patients potentially derive the greatest benefit from concurrent postoperative CRT, they also highlighted the trade-off of increased toxicity. Being mindful that only fit patients were included in both trials, the incidence of grade 3 or higher hematologic and non-hematologic adverse events (AEs) in both studies was at least doubled in the CRT arm compared to the RT alone arms. In the RTOG trial, 77 % of patients receiving CRT had grade 3 or higher AEs, versus 34 % of patients receiving RT alone, $p<0.001$. In the EORTC trial, 41 % of patients receiving CRT had grade 3 or higher AEs, versus 21 % of patients receiving RT alone, $p=0.001$. Of note, the traditional method of AE reporting used in these trials may have underestimated the true burden of toxicity as the maximum grade system did not account for how often multiple, severe toxicities were experienced by the individual patient [38]. Therefore, it is reasonable to conclude that based on the degree of toxicity experienced in both trials, the routine use of adjuvant chemotherapy concurrent with radiation should be restricted to fit patients with ECE and/or positive margins, unless it is in the context of a clinical trial.

34.4 Consideration of Targeted Therapies

There remains a need to improve outcomes, especially for patients with high-risk disease. Coupled with significant treatment-related toxicity from cytotoxic chemotherapy, exploiting the tumor's molecular phenotype through the incorporation of targeted therapies provides a rational approach to improving outcomes while minimizing toxicity. The epidermal growth factor receptor (EGFR) is one of four transmembrane receptors in the ErbB family, with the others including ErbB2/HER2/neu, ErbB3/HER3, and ErbB4/HER4 [39]. Activation of these signaling pathways has been implicated in the transcription of genes involved in cellular proliferation, invasion, metastasis, cell survival, and angiogenesis [39, 40]. EFGR is virtually overexpressed in HNC and has been linked to poor outcomes, including decreased OS, locoregional relapse, and treatment failure [41–45]. Therefore, therapies targeting EGFR represent an attractive target. Cetuximab, an IgG1 chimeric (human–murine) monoclonal antibody with high affinity to EGFR, has been the only targeted agent to obtain an FDA-approved indication when combined with definitive radiation for locally advanced HNC [46].

Cetuximab has thus been studied in the adjuvant setting in RTOG 0234, a phase II randomized trial that evaluated the efficacy of postoperative CRT with concomitant cetuximab in patients with high-risk features [47]. Two hundred thirty-eight patients with resected stage III–IV SCC of the oral cavity, oropharynx, hypopharynx, or larynx were included. Pathology had to demonstrate microscopically involved margins and/or two nodal metastases and/or ECE. All patients received 60 Gy of RT. Randomization included weekly cetuximab (400 mg/m^2 loading dose followed by 250 mg/m^2 weekly) plus weekly cisplatin 30 mg/m^2 or docetaxel 15 mg/m^2. The preliminary study results were also compared to historic data from the RTOG 9501 chemoradiation arm. With a median follow-up of 4.4 years, the cetuximab–docetaxel arm compared favorably to the cetuximab–cisplatin arm with respect to 2-year OS (79 % vs. 69 %), 2-year DFS (66 % vs. 57 %), and adherence to radiation and chemotherapy (81.5 % vs. 67.9 %). When DFS was compared to the historical control (RTOG 9501 CRT arm), the hazard ratio for cetuximab–cisplatin was 0.76 vs. control, while it was 0.69 for cetuximab–docetaxel vs. control ($p=0.012$). The improvement for cetuximab–docetaxel compared to the historic control was primarily related to improved distant control (2-year distant metastasis rate of 13 % vs. 20 % in historic control). This study demonstrated the feasibility and safety of adjuvant cetuximab–docetaxel, and this combined systemic approach is now being further investigated in a phase II/III adjuvant trial (NCT01810913). The combination of cetuximab with adjuvant radiation is also currently being studied for patients with intermediate-risk factors (NCT00956007).

Lapatinib, a reversible dual EGFR and HER2 tyrosine kinase inhibitor, has also been investigated in the adjuvant setting. This investigation was pursued despite phase II data in recurrent/metastatic HNSCC [48] demonstrating lapatinib's lack of clinical efficacy (no objective responses observed and correlative analyses in paired tumor biopsies demonstrating an absence of EGFR inhibition). In a phase II, randomized, placebo-controlled trial of lapatinib combined with definitive chemoradiation followed by maintenance monotherapy for locally advanced HNSCC [49], the complete response rate (primary endpoint) was 53 % with lapatinib versus 36 % with placebo, and p16-negative patients had longer PFS than placebo recipients. This study was deemed to be hypothesis generating only, as it was not powered to detect a statistically significant difference in the primary endpoint between treatment groups. A placebo-

controlled, phase III adjuvant trial of 688 patients with resected stage II–IVA HNSCC with surgical margins ≤5 mm and/or ECE was randomized to receive adjuvant chemoradiation with lapatinib versus placebo [50]. Chemotherapy consisted of cisplatin 100 mg/m^2 on days 1, 22, and 43 of RT. RT was administered to a dose of 66 Gy (2 Gy per fraction). Placebo or lapatinib 1500 mg daily was given for 1 week prior to adjuvant CRT, throughout CRT, and up to 12 months as maintenance monotherapy. The addition of lapatinib did not extend DFS (primary endpoint) compared to placebo. Based on the negative phase III results, use of lapatinib is not recommended. Interestingly, there is still an active phase II trial incorporating lapatinib into induction chemotherapy and concurrent adjuvant CRT for high-risk patients following transoral resection (NCT01612351).

34.5 Additional Treatment Considerations

In addition to selecting the appropriate adjuvant therapies, one needs also to be mindful of other factors which may influence outcome, including timing of therapy. For patients who undergo surgery followed by PORT alone, surgery and radiation must be considered as a treatment package, with the goal of completing the treatment package within the shortest feasible time frame. Rosenthal et al. demonstrated the importance of "package time" (time from surgery to completion of PORT) in a retrospective analysis in which they arbitrarily selected a cut point of 100 days [19]. Based on worse 2-year LRC and OS rates in patients with longer package times, the authors concluded that "every effort should be made to keep the time from surgery to the completion of postoperative RT to <100 days."

Ang et al. prospectively evaluated the impact of package time in the previously described phase III trial, in which the high-risk group of patients was randomized to receive identical doses of PORT albeit at different durations [16]. Seventy-five patients received 63 Gy in 35 fractions delivered once daily over 7 weeks, while 76 additional patients received 63 Gy in 35 fractions accelerated into 5 weeks (daily fractions for first 3 weeks, followed by twice-daily fractions for last 2 weeks). There was a nonsignificant trend toward improved LRC and OS rates when PORT was delivered in 5 rather than 7 weeks. For patients receiving PORT over 5 weeks, there was no difference in outcome based on timing of radiation (starting sooner versus later). However, for patients receiving PORT over 7 weeks, a prolonged interval between surgery and PORT resulted in significantly lower LRC ($p=0.03$) and survival ($p=0.01$) rates. Cumulative duration of the treatment package also significantly impacted LRC and OS outcomes. Patients who were able to receive the entire treatment package in less than 11 weeks had higher 5-year actuarial LRC rates (76 %) than patients with treatment package durations of 11–13 weeks (62 %) or >13 weeks (38 %), $p=0.002$. The corresponding survival rates were 48 %, 27 %, and 25 %, respectively ($p=0.03$). These findings suggest that the accelerated 5-week regimen could potentially compensate, to some extent, for the greater risk inherent in prolonged package times by shortening the package time by 2 weeks.

One confounding variable to the above analyses is that some patients may have tumors requiring more complex surgeries, resulting in protracted recoveries that lead to unavoidable delays initiating PORT. Secondly, the impact of package time is not presently known when PORT is delivered with concurrent chemotherapy. Based on the premise that locoregional failure after surgery and PORT is due to residual tumor cells that were not fully eradicated by either treatment modality, RTOG explored whether the addition of chemotherapy initiated shortly after surgery and continuing until the start of PORT could influence outcome (RTOG 0024) [51]. Seventy patients with resected stage III–IV HNSCC who had positive margins, ECE, or multiple positive nodes were included in this phase II trial. Patients received paclitaxel 80 mg/m^2 weekly during postoperative weeks 2–4 (prior to PORT). PORT was initiated 4–5 weeks after surgery, for a total of 60 Gy over 6 weeks. Paclitaxel 20 mg/m^2 and cisplatin 20 mg/m^2 were administered once weekly during the last 3 weeks of PORT. Treatment safety and tolerability were the study endpoints and were compared to a historical standard (concurrent cisplatin 100 mg/m^2 every 3-week arm of RTOG 9501). Safety and tolerability were comparable to RTOG 9501, and risk-adjusted rates of LRC, DFS, and OS exceeded outcomes in RTOG 9501. Being mindful of the concerns and limitations related to comparisons of phase II and III trials, the concept of redistributing therapy to the early postoperative period in an attempt to undermine early tumor cell repopulation is intriguing nonetheless. At present, every effort should be made to complete adjuvant therapy (radiation with or without chemotherapy) as timely as possible after patients have adequately recovered from surgery.

34.6 Conclusions

Patients with advanced HNSCC require multimodal treatment for optimal oncologic efficacy. Following surgical resection, adverse pathologic features dictate the need for adjuvant therapies. High-risk pathologic features including advanced T stage (T3, T4), positive surgical margins, perineural or lymphovascular invasion, lymph node involvement, ECE, or bone involvement warrant the addition of postoperative radiation. ECE and/or positive margins are the only two risk factors for which there is established benefit to administering chemotherapy concurrent with adjuvant radiation.

Chemotherapy has not demonstrated additional benefit for patients with multiple positive nodes in the absence of ECE or surgical margin involvement and thus should not be routinely offered in this setting. When adjuvant chemoradiation is offered, chemotherapy should be platinum based, and appropriate supportive care is necessary to minimize treatment-related toxicity. Adjuvant therapies should always be completed in a timely fashion to maximize benefit. Finally, continued efforts at testing other combinations of cytotoxic chemotherapy and/or targeted agents in combination with postoperative radiotherapy are critically important to further improve efficacy while reducing toxicity.

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Multidisciplinary Approach of Unresectable Head and Neck Cancer

35

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Abstract

The management of locally advanced head and neck cancer has seen the emergence of different combined modality therapies in recent years and new types of treatments, such as chemoradiation, new induction chemotherapy schemes, and salvage surgery.

Keywords

Unresectable head and neck cancer • Induction chemotherapy • Chemoradiation • Taxanes

35.1 Introduction

Head and neck cancer (HNC) is usually a wide number of tumors from different areas of the neck and the face (e.g., pharynx, larynx, lips, nasal cavity, etc.) with the same general approach and management, but, in same cases, the natural history of these tumors is completely heterogeneous, and the treatment could have a wide range of possibilities. However, locally advanced disease of HNC has similar clinical characteristics, especially in the definition and treatment [1].

Most of HNC are squamous cell carcinoma (SCC) originating from the epithelium of the mucosal lining of the upper aerodigestive tract and adenocarcinomas from secretory glands. Carcinomas in the head and neck spread readily to the lymph nodes of the neck; when it does, this is usually the first manifestation of the disease at the time of presentation. The local tumor extension, the number and the size of affected nodes, is used to classify the stage of the disease. Using this terminology (T stage, N stage), the carcinoma is divided in early stage disease and locally advanced or very locally advanced disease [1]. Distant disease is an uncommon debut in this group of tumors; however, when patients with locally advanced disease undergo extension test before local treatment, up to 30–40 % of them may have distant metastases [2].

The management of locally advanced head and neck cancer (LAHNC) must start with establishing a correct tumor classification; using different image techniques such as CT scan and PET-TAC, these techniques permit a clear understanding of the extension of the disease. Nowadays with clinical evaluation and diagnostic images, it is possible to classify the LAHNC in two very different groups: resectable and unresectable tumors.

This classification allows differentiating two different diseases that need specific treatments and have different prognoses.

35.2 Unresectable Locally Advanced Head and Neck Cancer

35.2.1 Definition

The American Joint Commission on Cancer (AJCC) has recently revised its TNM classification to clearly separate T4 disease into two categories: resectable or T4a and unresectable or T4b. The following is the official definition of unresectable or T4b disease per AJCC [3]:

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1. Oral cavity: Tumor invades the masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery. The lesion must be so extensive that a functional reconstruction is not possible.
2. Oropharynx: Tumor invades the lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases the carotid artery.
3. Hypopharynx: Tumor invades the prevertebral fascia, encases the carotid artery, or involves mediastinal structures.
4. Larynx: Tumor invades the prevertebral space, encases the carotid artery, or involves mediastinal structures.

The following criteria are also important for establishing resectable or unresectable disease:

1. For vascular encasement, involvement of 270° or more of the circumference of the carotid artery is accurate in predicting the surgeons' inability to peel the tumor off of the carotid artery in 100 % of the cases [4, 5]. This criterion is often used to determine whether a tumor is unresectable. MR is the preferred imaging modality.
2. Involvement of the prevertebral fascia means the fixation of the tumor to the prevertebral musculature. The presence of a high-signal-intensity fat stripe on sagittal or axial T1-weighted scans by MRI shows the absence of infiltration of the prevertebral musculature with an accuracy of 91 % [6].
3. Mediastinal invasion, which is more typical in infrahyoid tumors, is the infiltration of the mediastinal fat, vascular invasion of the supra-aortic vessels, or infiltration of the trachea and esophagus [5].

The following are the criteria used to determine inoperability on a patient:

1. Technical unresectability as previously detailed for T4b disease
2. Low surgical curability such as seen in many patients with T4a disease and large and fixed neck adenopathy
3. Medical contraindication to surgery

Recently, AJCC replaced the terms resectable and unresectable with moderately advanced and very advanced. The advanced stage disease classification regroups in as group IV disease, subdividing the group as follows: for all sites into moderately advanced locoregional disease (stage IVa), very advanced local/regional disease (stage IVb), and distant metastatic disease (stage IVc) [7].

The following are the official definitions of "very advanced local disease":

1. Lip and oral cavity: Tumor invades the masticator space, pterygoid plates, or skull base and/or encases internal carotid artery disease.
2. Nasopharynx: Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, and orbit or with extension to the infratemporal fossa/masticator space.
3. Oropharynx: Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases the carotid artery.
4. Hypopharynx: Tumor invades the prevertebral fascia, encases the carotid artery, or involves mediastinal structures.
5. Larynx: Tumor invades the prevertebral space, encases the artery, or involves mediastinal structures.

Some of these criteria have been classically considered "unresectable disease" as vascular encasement and invasion, prevertebral space invasion, and invasion of mediastinal structures.

35.2.2 Masticator Space

It includes the muscle of mastication, medial and lateral pterygoid, masseter and temporalis, and the ramus of the mandible and the third division of the V cranial nerve as it passes through foramen ovale [7]. The masticator space is defined as a synonym of infratemporal fossa "extension of tumor beyond the anterior surface of the lateral pterygoid muscle, or lateral extension beyond the posterolateral wall of the maxillary antrum, and the pterygomaxillary fissure," but it should be noted that this definition does not include the medial and lateral pterygoid muscle.

35.2.3 Vascular Encasement

In LAHNC extracapsular spread of tumor from neck nodes is one of the most significant prognostic factors for poor outcome.

Encasement of the ICA, as a sign of extracapsular extension, implies a poor prognosis and is often a contraindication for surgical treatment. In this case, survival is less than 15 months [8].

One of the most useful criteria is probably the involvement of more than 270° of circumferential of the ICA. Yousem et al. [5] demonstrated on MRI a high sensitivity and specificity, 100 % and 88 %, respectively. Pons et al. proposed 5 different imaging signs in the evaluation of carotid artery invasion by cervical lymph nodes. No correlation with preoperative findings was shown measuring the size of the adenopathy and intensity of the contact. Therefore, they concluded that in the combination of deformation of the carotid artery, encasement of more than 180° of the carotid perimeter and segmental obliteration of the fat between the

adenopathy and the ICA was highly predictive of invasion ($p < 0.05$). Lodder et al. found that preoperative assessment of encasement of the ICA using MRI and/or CT was missed in only 1.5 %. However, the criteria used in the literature show a high interobserver variation [9–11].

According to the literature, the combination of radiological criteria seems to be more useful for the assessment of carotid artery invasion. The criteria that the radiologist should report are:

1. Encasement of the artery >270°
2. Obliteration of the fat between the lymph node/primary tumor and the carotid artery
3. Deformation of the carotid artery
4. Length of contact with tumor

35.2.4 Involvement of the Prevertebral Fascia

Prevertebral space is situated between the prevertebral fascia anteriorly and the vertebral bodies posteriorly. It contains the prevertebral muscles and fat. From the anterior to the prevertebral fascia, there is the retropharyngeal space (RPS), which is delineated anteriorly by the buccopharyngeal fascia. RPS is subdivided by the alar fascia, a part of the deep layer of the deep cervical fascia, into the danger space posteriorly and the true RPS anteriorly. Hematogenous dissemination may occur as the tumor, once it extends to the prevertebral space, can penetrate into vertebral and prevertebral veins or prevertebral lymphs. The presence of prevertebral space invasion in hypopharyngeal and laryngeal cancer is considered as very locally advanced stage and is classified as T4b. According to Lee et al. [10, 12], patients with nasopharyngeal cancer (NPC) and prevertebral space involvement have more recurrence and a poorer survival rate and are associated with an increased risk for distant metastasis. A complete resection of tumor when longus colli/capitis muscle complex is involved is technically difficult and does not improve long-term survival rates. Therefore, the assessment of prevertebral extension becomes relevant as an independent prognostic factor for NPC recurrence [6].

Neoplastic fixation to the prevertebral fascia is inaccessible to clinical inspection; thereby, preoperative imaging is essential. Loevner et al. [13] evaluated 4 criteria for prevertebral fixation assessment with MRI: ipsilateral muscle concavity, irregular muscular border at the tumor–muscle interface, muscle T2 hyperintensity, and muscle enhancement. They found low specificity (range, 14–43 %) and low accuracy (range, 53–60 %). The most accurate criterion (60 %) was the enhancement of the muscle (positive predictive value, 58 %).

CT has a lower accuracy in predicting prevertebral muscle involvement. Nowadays, there are no accurate radiological criteria defined in the literature for prevertebral space involvement. Even if they are not validated, radiologist should watch out for the following:

- Indistinguishable intensity between tumor and muscle
- Asymmetry in signal intensity
- Disruption of the prevertebral fascia, particularly if found in two orthogonal views
- Muscle T2 hyperintensity and enhancement

The presence of retropharyngeal fat stripe between tumor and the prevertebral fascia on unenhanced sagittal or axial T1-weighted scans should be considered as a sign of resectable disease as it reliably predicts the absence of fixation to the prevertebral fascia (negative predictive value of 97.5 %) [14]. In conclusion, the most useful radiological tool seems to be the preservation of the retropharyngeal fat plane on MRI for detection of the absence of prevertebral space involvement.

35.2.5 Mediastinal Invasion

Mediastinal invasion includes supra-aortic vessel encasement and tracheal and esophageal invasion. This is much more frequent in infrahyoid cancers, as laryngeal, thyroid, or even hypopharynx carcinomas. When it presents, it classifies as T4b in the hypopharynx and larynx. In thyroid cancer, involvement of the trachea, esophagus, or even recurrent laryngeal nerve should be classified as T4a. Mediastinal vessel encasement is classified as T4b. For anaplastic carcinomas, any extrathyroid extension is classified as T4b.

The extrathyroid invasion should be suspected if:

- Thyroid carcinoma has a poor definition on MRI (81 % accuracy, 71 % sensitivity, and 82 % specificity).
- Effect of fatty tissue in tracheoesophageal groove on CT is present (as a sign of recurrent laryngeal nerve invasion).

The radiological criteria used in the literature for tracheal involvement are:

- Tumor surrounding >180° of tracheal circumference on MRI
- The presence of a focal bulging, irregularity, or thickening in the mucosal lumen on MRI
- Soft tissue signal in the tracheal cartilage with synchronous enhancement with thyroid cancers on MRI

The combination of any of these three criteria showed the greatest accuracy for predicting tracheal invasion (90 %), with 100 % sensitivity and 84 % specificity.

The criteria used for esophageal involvement are:

- Outer layer invasion on MRI (isointense to hypointense areas on unenhanced T1W images and isointense to hyperintense areas to the outer layer on T2W images)
- Contrast-enhanced T1W images of invaded areas
- Synchronous enhancement with the mass [15–17]

35.3 Treatment Options in LAHNC

35.3.1 Concurrent Chemoradiotherapy

The use of concurrent chemoradiotherapy is considered by many to represent a standard of care in the management of patients with locally advanced and unresectable disease (Table 35.1). Studies have shown that combining chemotherapy with radiation improves local control and survival. Bolus of cisplatin at 100 mg/m^2 every 3 weeks is the drug of choice for patients with a good performance status [18].

The American Head and Neck Intergroup conducted a phase III randomized trial to study the benefit of adding chemotherapy to radiation in patients with unresectable squamous cell carcinoma of the head and neck [18]. Patients were randomly assigned between arm A, single daily fractionated radiation (70 Gy at 2 Gy/day); arm B, identical radiation therapy with concurrent bolus cisplatin at 100 mg/m^2, given on days 1, 22, and 43; and arm C, a split course of single daily fractionated radiation and three cycles of concurrent infusional FU and bolus cisplatin chemotherapy, 30 Gy given within the first cycle and 30–40 Gy given within the third cycle. Surgical resection was encouraged if possible after the second chemotherapy cycle on arm C and, if necessary, as salvage therapy on all three treatment arms. The extent of midcourse surgery for arm C patients was defined on the basis of the residual disease present, not the original tumor. Two hundred and ninety-five patients were included in this trial. Median age was 56 and half of the patients had oropharynx primary. With a median follow-up of 41 months, the 3-year overall survival for patients enrolled in arm A is 23 %, compared with 37 % for arm B ($p=0.014$) and 27 % for arm C ($p=$not significant). Chemotherapy did not affect the likelihood of distant recurrence when compared with radiation therapy alone. Distant metastases were the first site of recurrence in 17.9 % of arm A patients, 21.8 % of arm B patients, and 19.1 % of arm C patients; the differences were statistically insignificant. When surgical results were analyzed, little difference in the rate of surgical resection was observed among the three treatment arms. Ultimately, 21 % of all patients underwent surgery; neck dissection alone was performed in 56 % of the surgical cases. Grade 3 or worse toxicity occurred in 52 % of patients enrolled in arm A, compared with 89 % enrolled in arm B ($p<0.0001$) and 77 % enrolled in arm C ($p<0.001$). Major toxicities encountered were mucositis and feeding tube dependency; toxicity was worse in arm B. The authors concluded that the addition of concurrent high-dose, single-agent cisplatin to conventional single daily fractionated radiation significantly improves survival, although it also increases toxicity.

Weekly low-dose cisplatin has been tried, and it does not appear to be as beneficial as high-dose cisplatin with one study showing it to be equivalent to XRT alone [19].

Given the toxicity of high-dose cisplatin, other regimens have been explored. Weekly carboplatin and paclitaxel are another regimen that can be used for those patients who cannot tolerate high-dose cisplatin, and phase II data suggest that the treatment can be effective. This regimen was explored in a single institution study with 55 patients [20]. Fifty-two patients (95 %) had stage IV and 51 (93 %) had technically unresectable disease; 62 % had an oropharyngeal primary site. Grade 3 or 4 mucositis occurred in 30 % of patients. Forty of 50 assessable patients (80 %) had an objective response, with a complete response rate of 52 %. With a median follow-up of 69 months for surviving patients, the 5-year progression-free survival was 36 %, and the 5-year overall survival was 35 %. Another study from the University of Maryland group explored the same regimen of carboplatin/paclitaxel and standard daily radiation [21]. Sixty-two patients were treated with 70.2 Gy of RT at 1.8 Gy/fraction/day to the primary site. Weekly chemotherapy was given during RT consisting of paclitaxel (45 mg/m^2/week) and carboplatin (100 mg/m^2/week). All patients presented with locally advanced disease; 77 % had T4 disease and 21 % had T3 disease. Fifty-eight percent had N2b–N3 disease. 98 % of patients completed the prescribed therapy. A clinical complete response at the primary site was obtained in 82 %, with a total (primary site and neck) complete response rate of 75 %.

Table 35.1 Summary of clinical trials in unresectable head and neck cancer

	Type	Number	Treatment	Chemotherapy used	OS (%)
Intergroup study	Phase III	295	RT/CRT/split	Bolus cisplatin (with 5-FU for split regimen)	23/37/27
Agarwala et al.	Phase II	55	CRT	Weekly carboplatin and paclitaxel	35
University of Maryland	Phase II	62	CRT	Weekly carboplatin/paclitaxel	48
Medina et al.	Phase II	94	CRT	Weekly cisplatin	41
ECOG	Phase II	60	CRT	Cisplatin q 3 weeks and cetuximab weekly	67

RT radiotherapy, *CRT* chemoradiotherapy

The median survival for the entire cohort is 33 months. Response to therapy and status of the neck at presentation were the only prognostic factors found to influence survival. The median survival for patients who attained a CR is 49 months versus 9 months in those who did not attain a CR. The 2- and 3-year overall survival for complete responders is 79 and 61 %. The regimen was well tolerated with over 90 % of patients completing the prescribed therapy. With 48 % 3-year overall survival for the entire group, this regimen is an acceptable choice for this group of patients with a historically poor prognosis.

Given the poor outcome encountered in patients with unresectable disease, other radiation modalities have been tried. Concomitant boost radiation, in which a second daily radiation treatment is applied, can result in decreased tumor repopulation, a major factor in local/regional failure. A phase II study exploring weekly cisplatin with concomitant boost radiation has been recently reported [22]. In this study, a total of 94 patients (median age, 58 years) with cancers of the oropharynx, larynx, hypopharynx, and oral cavity were included. Patients received radiotherapy with a concomitant boost scheme (1.8 Gy on days 1–40 and 1.5 Gy boost on days 25–40 with a total dose of 72 Gy) and concurrent cisplatin, 40 mg/m^2 weekly, for the first 4 weeks only. Most patients (95 %) received both radiation and chemotherapy according to protocol. Toxicity was manageable. With a median follow-up of 41 months, median overall survival and time to progression were 27 and 25 months, respectively. The estimated overall survival at 4 years was 41 %.

The poor results encountered with standard chemotherapy regimens have also prompted studies of novel agents. EGFR inhibitors appear to be the most promising class of drugs [23]. Recently, investigators from the Eastern Cooperative Oncology Group (ECOG) reported their first study of CRT with cetuximab in unresectable head and neck cancer [24]. In this study, patients with unresectable, newly diagnosed head and neck cancer received cetuximab, an EGFR inhibitor, 400 mg/m^2 on day 1 and then 250 mg/m^2 weekly, in combination with definitive radiation therapy (70 Gy/2 Gy/day × 7 weeks) starting day 15, and cisplatin 75 mg/m^2 every 3 weeks. In the absence of disease progression or untoward toxicity, patients could continue cetuximab weekly for up to 1 year. In this trial, 60 patients were treated; median age was 56 and 98 % were stage IV. Most common primary sites included the base of the tongue (34 %), tonsil (21 %), and other oropharynges (13 %). One-year survival is 76 % and projected 2-year survival is 67 %. Median survival is 33 months. Unique toxicities include acneiform rash and an increase in severe mucositis. These early results are promising and do represent a significant improvement over cisplatin/radiation regimens. Further trials with this regimen are underway.

35.3.2 Sequential Treatment

As mentioned above, with CRT or radiation treatment alone, locoregional control (LRC) and survival rates in patients with unresectable LAHNC are quite poor. The use of new induction chemotherapy regimens with taxanes added to platinum–5-FU (PF) results in a high response rate and better survival compared to the traditional PF schedule. Taxane-based chemotherapy was not analyzed in the MACH meta-analysis, where patients included received different modality treatments with induction chemotherapy and CRT, and stratification according to resectable or unresectable tumors did not take place [25]. There are many studies that have examined the addition of taxanes to PF, and these combinations do represent a significant improvement over PF in terms of efficacy and toxicity (Table 35.2).

The safety and efficacy of docetaxel with PF (TPF) as induction chemotherapy for patients with SCCHN were evaluated in a multicenter, open-label, randomized trial (Tax 323) [26]. In this European study, 358 patients with SCCHN with previously untreated inoperable locally advanced stages III and IV, and good performance status, received either docetaxel 75 mg/m^2 followed by cisplatin 75 mg/m^2 on day 1, followed by 5-FU 750 mg/m^2/day as a continuous intravenous infusion on days 1–5 (TPF), or cisplatin 100 mg/m^2 on day 1, followed by 5-FU 1000 mg/m^2/day as continuous intravenous infusion. These regimens were administered every 3 weeks for four cycles. From 4 to 7 weeks after chemotherapy, patients whose disease had not progressed

Table 35.2 Summary of phase III induction chemotherapy trials in unresectable head and neck cancer

Study	Regimen	Number	End point	Results
TAX 324	TPF vs. PF followed CRT	501	Overall survival (months)	71 vs. 30 ($p=0.006$)
TAX 323	TPF vs. PF followed CRT or RT	358	Progression-free survival (months)	11.0 vs. 8.2 ($p=0.007$)
Spanish Intergoup	PF or TPF followed CRT vs. CRT	439	Time to treatment failure (months)	Induction chemotherapy plus CRT = 12.5 (median) vs. CRT = 5 (median) $p=0.0001$
Spanish Intergroup	PCF vs. PF followed CR	382	Complete response (CR)	33 vs. 14 % ($p=0.001$)

TPF docetaxel, cisplatin, and 5-FU; *PF* cisplatin and 5-FU; *PCF* paclitaxel, cisplatin, and 5-FU; *CRT* chemoradiotherapy

received radiotherapy. Radiation was delivered either with a conventional or an accelerated/hyperfractionated regimen (i.e., more than one fraction per day). Surgical resection was allowed following chemotherapy, before or after radiotherapy. The trial's primary end point was progression-free survival (PFS) that was defined as the time from randomization to disease progression or death from any cause, whichever occurred first. Median PFS was significantly longer in the TPF arm (11.4 months) than in the PF arm (8.3 months). Median overall survival was significantly longer in the TPF arm (18.6 months) than in the PF arm (14.2 months). The FDA approved this regimen for patients with inoperable SCCHN on October 17, 2006.

Tax 324 [27] took a different approach from TAX 323. Patients included in this study had both operable and inoperable disease. The clinical observations of the last three decades that concurrent chemoradiotherapy is crucial in SCCHN were taken into account when this study was designed, and instead of giving radiation therapy only after IC, all patients received concurrent chemoradiotherapy. The goal is to combine both models of therapy in one study: IC and concurrent chemoradiotherapy.

This is an international multicenter, open-label, randomized phase III trial. In this study, 501 patients with previously untreated locally advanced SCCHN, and good performance status, received either docetaxel 75 mg/m^2 followed by cisplatin 100 mg/m^2 on day 1, followed by 5-FU 1000 mg/m^2/day as a continuous intravenous infusion on days 1–4 (TPF), or cisplatin 100 mg/m^2 on day 1, followed by 5-FU 1000 mg/m^2/day as a continuous infusion on days 1–5 (PF). These regimens were administered every 3 weeks for three cycles. All patients in both treatment arms who did not have progressive disease following induction chemotherapy (close to 80 %) received 7 weeks of CRT. During radiotherapy, carboplatin, area under the curve (AUC) of 1.5, was administered weekly as a 1-h infusion for a maximum of seven doses. Surgery could be considered at anytime following the completion of CRT. The majority of patients had locally advanced stage IV disease (84 %). Overall survival was significantly prolonged with TPF compared to PF regimen (log-rank test, $p=0.0058$). The median survival was 70.6 months in the TPF group compared to 30.1 months in the PF group.

There is an increase in the incidence of neutropenia and febrile neutropenia with TPF and more stomatitis/diarrhea with PF likely reflecting the higher dose of 5-FU dose used.

In TAX 324, close to 70 % of patients completed the concurrent chemoradiotherapy regimen as defined per protocol. The major reasons for not completing CRT are disease progression and adverse events. Two treatment-related deaths related to induction chemotherapy occurred in TAX 324.

In TAX 323, close to 70 % of patients completed radiotherapy per protocol, with disease progression as the main reason for not completing the protocol. Five treatment-related deaths related to induction chemotherapy occurred in this study.

The Spanish group examined the addition of paclitaxel to PF in a randomized phase III study [28]. The primary objective is to compare the activity and toxicity of the two induction chemotherapy treatments of paclitaxel, cisplatin, and FU (PPF) versus standard cisplatin and FU (PF), both followed by CRT, in locally advanced and unresectable head and neck cancer. Both regimens were administered for three cycles every 21 days. Patients with complete response (CR) or partial response of greater than 80 % in primary tumor received additional CRT (cisplatin 100 mg/m^2 on days 1, 22, and 43 plus 70 Gy). A total of 382 eligible patients were randomly assigned to PF ($n=193$) or PPF ($n=189$). The CR rate was 14 % in the PF arm versus 33 % in the PPF arm ($p<0.001$). Median time to treatment failure (TTF) was 12 months in the PF arm compared with 20 months in the PPF arm ($p=0.006$). PPF patients had a trend to longer overall survival that was not statistically significant. This difference was more evident in patients with unresectable disease. PF patients had a higher occurrence of grade 2–4 mucositis than PPF patients (53 vs. 16 %, respectively; $p<0.001$). However, the induction chemotherapy plus CRT approach was limited to a select group of patients because of the significant toxicity produced by such treatment. Six cycles of cisplatin (induction plus chemoradiation) are possible only in patients with excellent performance status, adequate organ function, and intensive medical support. This significantly limits the use of this regimen.

Finally, the same Spanish group recently presented the data of a randomized phase III trial [29], where induction chemotherapy (with TPF or PF) plus CRT was compared with standard CRT as frontline treatment in patients with unresectable locally advanced head and neck cancer. The primary end point of this study was TTF for induction versus no induction chemotherapy; secondary end points included LRC. In evaluable patients, the median TTF was 12.5 months with induction plus CRT versus 4.9 months with CRT alone ($p<0.001$). LRC was 60 % with induction chemotherapy plus CRT versus 44.5 % with CRT alone ($p=0.003$).

However, in this trial, when patients were analyzed by intention to treat, there were no differences between both arms. The difference was observed per protocol population; due to the approach using 3 cycles of induction chemotherapy and 3 cycles of cisplatin and radiotherapy, it was possible in selected patient populations; for this reason, this trial was negative in the different end point.

Today we know that only a low percentage of patients with very locally advanced have a good ECOG for this type of clinical trial, where the majority of patients due to comorbidity and high volume of local disease, in general, are not candidate for sequential treatment.

In ASCO 2014 (Chicago), Italian Head and Neck Cancer Group presented the first randomized phase III trial with positive results for induction CT prior to chemoradiotherapy (Fig. 35.1). In this study, patients with LAHNC were

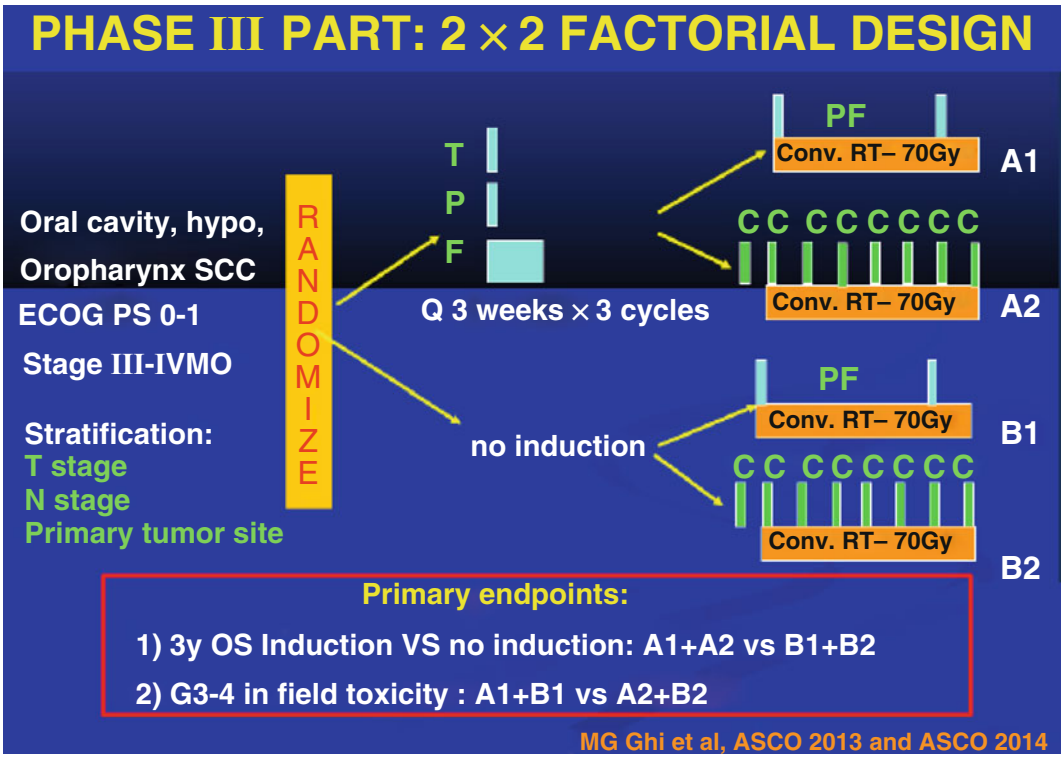

Fig. 35.1 Design of phase III trial, Italian group

randomized between induction CT with TPF followed by CRT and BioRT vs. CRT as frontline treatment. This trial included 420 patients, 210 per arm. The complete response in the group with induction CT was of 43 % vs. 28 % of patients treated with CRT alone ($p=0.0023$), the median of PFS was 29, 7 months, vs. 18, 5 months (HR 0.73, $p=0.0155$), and the median overall survival was 53, 7 months (ICT), vs. 30, 3 months (CRT) (with HR 0.72, $p=0.025$). This trial has demonstrated the benefits of ICT in selected populations of patients, with respect to complete response, disease-free survival and overall survival [30].

Spanish Head and Neck Cancer Group done a new phase III trial in patients with LAHNC very advanced disease. In this study with 530 patients, they received (all patients) ICT with TPF, and then patients with at least 2 cycles were randomized between CRT with classical cisplatin and BioRT as Bonner scheme. The end point of this trial is it demonstrates that BioRT is similar to CRT and less toxic. Final results will be reported in few time.

35.3.3 Discussion

The management of patients with LAHNC requires a multidisciplinary evaluation. Differentiation between resectable and unresectable disease is important and carries significant prognostic implications. Patients with unresectable head and neck cancer have a worse prognosis, and novel therapies are needed for this patient population. A multidisciplinary approach for these patients is crucial and helps with staging, treatment decision, and management of the acute and long-term complication of therapy. A better definition for unresectable disease is needed.

Currently, there are two acceptable standards for these patients: concurrent chemoradiotherapy and induction chemotherapy followed by CRT. Each approach has its own advantages and disadvantages. We would recommend induction chemotherapy for the following patients:

1. Symptomatic patients in need for immediate therapy or patients with impending local problems such as locally advanced larynx cancer where airway compromise is imminent
2. Patients with high risk of distant metastasis such as nodal disease N2b, N2c, and N3 patients
3. Patients with possible or proven distant metastasis at presentation

For these patients, induction chemotherapy with TPF is our choice for therapy followed by concurrent chemoradiotherapy with weekly carboplatin and radiation based on the results of TAX 324. All other patients with unresectable disease can be treated with concurrent chemoradiotherapy upfront with either bolus cisplatin every 3 weeks or weekly carboplatin/paclitaxel.

4. In selected patient populations, induction chemotherapy plus CRT offers benefit in survival; mature results of new studies are necessary.

Given the overall poor outcome for these patients, novel approaches are urgently needed. Two approaches that have shown early promising results are accelerated radiotherapy and the addition of novel targeted agents. Early results appear to show some improvement over standard therapy, and further studies are ongoing to define the optimal strategy for these patients.

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Management of Salivary Gland Cancer

36

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Abstract

Carcinomas of the salivary glands are uncommon representing only 2–6.5 % of all head and neck cancers and less than 1 % of all cancers. About 85 % of salivary gland tumors arise in the parotid glands, and approximately 75 % of these are benign, while about 75 % of tumors arising from minor salivary glands are malignant. The latest WHO histological classification (2005) includes both benign and more than 20 different types of malignant tumors. The morphological diversity between different tumor types and sometimes within the same tumor mass along with the relative rarity of some tumors can make diagnosis difficult and needs a skilled pathologist.

The American Joint Cancer Committee's (AJCC) tumor, node, and metastasis (TNM) system has defined a staging system for major salivary gland malignancies. Tumors from the minor salivary gland scattered throughout all the head and neck mucosa are staged according to the AJCC system for the more common squamocellular cancer arising in the same location.

Surgery of primary tumor, whenever possible, is the treatment of choice both for major and minor salivary gland tumors. A clinically positive neck requires a neck dissection along with the resection of the primary tumor. The treatment of cN0 neck in patients with malignant salivary gland tumors is a matter of debate. High-grade tumors, high primary T stage, and facial nerve paralysis are associated with high incidence of neck node metastasis.

Adjuvant radiotherapy improves locoregional control following surgery. Despite the absence of randomized trials, postoperative radiotherapy is recommended in high-grade tumors, advanced-stage tumor (T4), "close" (≤5 mm) or microscopically positive surgical margins, and neck node metastases. The use of concomitant chemoradiotherapy in high-risk cases is still investigational.

Radiotherapy can be the best treatment option in case of "technically" unresectable or "medically" inoperable tumor. Heavy-particle radiotherapy (i.e., proton therapy, carbon ion therapy) seems to exert a higher activity in adenoid cystic cancer.

Chemotherapy is delivered in case of relapsed and/or metastatic disease with a palliative aim. There is neither standard chemotherapy regimen nor data on whether polychemotherapy is more active than monochemotherapy. Although, a cisplatinum-based chemotherapy is considered the best choice. New treatment approaches, such as hormonal deprivation treatment or tyrosine-kinase inhibitors, are under evaluation.

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Salivary gland cancer • Surgery • Radiotherapy • Chemotherapy • Target therapy

36.1 Epidemiology

Malignant tumors of salivary glands are uncommon: the world annual incidence rates are comprised between <2 and <0.05 per 100,000 [1]. In the United States, incidence rates showed a significant increase in the period during 1974–1999, accounting for 6.3 %, compared to 8.1 %, of all head and neck cancers in 1998–1999 ($p=0.002$) [2]. In Europe in the period 1995–2002, the annual crude incidence rate for major salivary glands and salivary gland-type tumors was 13.1 per million with a prevalence at the beginning of 2003 of 65,000 cases. The incidence of disease is age related with an increase after 65 years old; although very rare, few cases have been reported also in children, in adolescents, and in young adults. Males are more affected than females [3]. The causes of salivary gland tumors are still to be further investigated. Diet may effectively prevent salivary gland cancer, by increasing fruit and vegetable consumption, in particular those rich in vitamin C, and by limiting cholesterol intake [4, 5]. Irradiation may also favor the onset of malignant salivary gland tumors [6]. Many studies have indicated a possible association with a history of prior cancers, especially those caused by ultraviolet radiation, immunosuppression, and Epstein–Barr virus [7–10]. Workers employed in rubber manufacturing companies and in hairdresser's shops and beauty shops, as well as those exposed to nickel compounds, showed an increased risk to develop salivary glands carcinomas [11–13]. Chronic inflammation of salivary glands is not clearly defined as a risk factor. Younger age, female sex, and married status are associated with a better outcome [14]. In Europe, based on 5-year relative survival rates, the prognosis for epithelial tumor of major salivary glands reaches 66 % [3].

36.2 Anatomy

Salivary glands are exocrine organs responsible for the production and secretion of saliva. They comprise the three-paired major salivary glands—the parotid, submandibular, and sublingual—and the minor salivary glands. The head and neck contain about 450–750 minor salivary glands. They are widely distributed throughout the mouth and oropharynx, and similar glands are present in the upper respiratory and sinonasal tracts and the paranasal sinuses. These latter are morphologically and functionally similar to many of the oral minor salivary glands, but effectively they are not salivary glands since they do not contribute to saliva. However, they are often comprised in papers on salivary glands carcinomas as in this text, because some histotypes are similar or identical to tumors of the salivary glands.

36.3 Histology

Salivary gland tumors are classified according to the latest WHO's histological classification published in 2005 [14, 15]. More than 20 different malignant histotypes are included in this classification, characterized by a range of various biological behaviors. Salivary gland cancers can be divided into histotypes originating from the intercalated ducts (including adenoid cystic carcinoma and adenocarcinoma, NOS) and those of the secretory duct origin, as mucoepidermoid carcinoma (MEC) and salivary duct cancer (SDC). MEC, adenoid cystic carcinoma (ACC), and adenocarcinoma, NOS, are the most represented salivary gland cancer histotypes, although their frequency varies according to the site of origin (major versus minor salivary glands). In this classification, only MEC is graded by a point score system, as low-grade type (well differentiated), intermediate-grade type, or high-grade type (poorly differentiated). Differences in tumor grade have been also suggested for adenocarcinoma NOS, SDC, and acinic cell carcinoma. In these cases, prognosis correlates with grading: high-grade tumors are associated with a poor prognosis, whereas the prognosis of low-grade tumors is much more favorable [15]. The wide spectrum of morphological diversity among different tumor types and sometimes within the same tumor mass, together with the presence of hybrid tumors, may sometimes require a skilled pathologist to make the diagnosis (Table 36.1).

36.4 Molecular Alterations

In the last few years, several oncogenic aberrations have been described in SGCs.

The genome of ACC, in particular, has been recently analyzed by sequencing [16, 17]. Genomic alterations are uncommon in ACC, where *MYB–NFIB* gene fusion is the most relevant oncogenic event. Other mutations have been described in the NOTCH pathway (13 %) and in the FGF-IGF-PI3K signaling pathway (30 %). MYB activation is present in at least 80 % of ACC, while it is not found in the other histotypes [18], suggesting that MYB is a molecular hallmark of ACC. *MYB–NFIB* fusion is derived from the t(6;9) translocation,

Table 36.1 WHO's histological classification and risk stratification

Low risk	High risk
Acinic cell carcinoma	Sebaceous carcinoma and lymphadenocarcinoma
Low-grade mucoepidermoid carcinoma[a]	High-grade mucoepidermoid carcinoma[a]
Epithelial–myoepithelial carcinoma	Adenoid cystic carcinoma§
Polymorphous low-grade adenocarcinoma	Mucinous adenocarcinoma
Clear cell carcinoma	Squamous cell carcinoma
Basal cell adenocarcinoma	Small cell carcinoma
Low-grade salivary duct carcinoma (low-grade cribriform cystadenocarcinoma)	Large cell carcinoma
Myoepithelial carcinoma	Lymphoepithelial carcinoma
Oncocytic carcinoma	Metastasizing pleomorphic adenoma
Carcinoma ex pleomorphic adenoma (intracapsular/minimally invasive or with low-grade histology)	Carcinoma ex pleomorphic adenoma (widely invasive or high-grade histology)
Sialoblastoma	Carcinosarcoma
Adenocarcinoma, NOS, and cystadenocarcinoma, low grade[a]	Adenocarcinoma and cystadenocarcinoma, NOS, high grade[a]

[a]Risk category assignment is controversial for intermediate grade. For mucoepidermoid carcinoma, it depends on the grade scheme used; in case of adenocarcinoma, NOS, it has been suggested to place the intermediate grade in the high-risk group, although data are few; for ACC§, only the solid variant is considered as a high-grade pattern

[Modified from Seethala RR. *An Update on Grading of Salivary Gland Carcinomas*. Head Neck Pathol. 2009;3(1):69–77. With permission from Springer Science]

involving the *MYB* oncogene and the transcription factor gene *NFIB*. The oncoprotein derived from the *MYB–NFIB* fusion activates the transcription of genes involved in oncogenic transformation of cells. Other than by gene fusion, MYB can be activated more uncommonly by copy number gain or insertion of the 3′-part of *NFIB* near the *MYB* locus. MYB could be useful as a diagnostic tool in doubtful ACC cases as well as a potential new target for novel therapies. More recently, preclinical data showed that TrkC/NTRK3 signaling pathway is activated in ACC [19]. Mutations in the RAS pathway (*BRAF* and *HRAS*) have been reported as well [20], representing along with the Trk pathway [21] new potential therapeutic targets. Wild-type c-kit is overexpressed in about 80 % of ACC; c-kit has been investigated in the past as a therapeutic target with no significant results [22, 23].

Another fusion gene was described in MEC. This is a tumor-specific translocation t(11,19) which involves the *MALM2* and the *CRTC1* genes [18, 24] and acts disrupting a NOTCH signaling pathway [25]. This translocation is almost limited to low- and to intermediate-grade MEC with a good prognosis. Although high-grade MEC might harbor the fusion gene, most of them are generally fusion negative.

New rearrangements regarding the gene *EWSR1* have been described in a subset of hyalinizing clear cell carcinoma. Rearrangements of *EWS1* gene have been reported also in soft-tissue myoepithelial tumor (SMET) where different genes can be pattern of rearrangements, resulting in several fusion transcripts (i.e., *EWSR1-ZNF444*, *EWSR1-PBX1*, or *EWSR1-POU5F1*). Only the *EWSR1-ATF1* fusion product has been described in hyalinizing clear cell carcinoma, becoming a useful diagnostic hallmark of this rare subtype [26].

In the last years, a new distinctive pathological entity has been described: the mammary analogue secretory carcinoma (MASC). This tumor presents several histological and immunohistochemical characteristics in common with the secretory carcinoma of the breast, including a chromosomal translocation t(12,15) (p13;q25) which leads to a fusion gene between the ETV6 gene on chromosome 12 and the NTRK3 gene on chromosome 15 [27, 28]. The biological consequence of the translocation is the fusion of the transcriptional regulator (ETV6) with membrane receptor kinase (NTRK3) that activates kinase through ligand-independent dimerization and thus promotes cell proliferation and survival. The *ETV6-NTRK3* fusion gene has not been demonstrated in any other salivary gland tumors, although it has been reported in different malignant tumors as congenital fibrosarcoma, congenital cellular mesoblastic nephroma, and acute myeloid leukemia.

The main histopathological characteristic of SDC is the overexpression of androgen receptor (AR) in at least 70 % of the cases. *AR* activation is not sustained by gene amplification; the gene copy number gain, alternative *AR* isoform (AR-V7/AR3) equal to those reported in hormone-resistant prostate cancer, and AR mutations have been identified [29]. *HER2* overexpression is reported in more than 50 % of the cases coupled with *HER2* amplification in 57–73 % of cases [30, 31]. Mutation in *PIK3CA* (20–33 %) and deletions of *PTEN* (50–59 %) have been described in HER2-negative SDCs [32–34]. *BRAF*-activating mutations have been reported in 7 % of the cases [35]. No rearrangement has been reported in SDC.

36.5 TNM Classification and Stage Grouping

Tables 36.2 and 36.3 show the TNM classification and stage grouping of salivary glands tumors according to the latest AJCC/UICC classification [36].

36.6 Clinical Presentation

36.6.1 Major Salivary Gland Tumors

Malignant neoplasms in these sites usually appear clinically indistinguishable from benign tumors. Consequently, every painless swelling of a salivary gland must be suspected, especially in the absence of further signs of inflammation. Pain is not typical; it could be reported as intermittent in over a third of patients. Malignant tumors account for 15–32 % in the parotid gland, 41–45 % in the submandibular gland, and 70–90 % in the sublingual gland. Malignant salivary tumors show a range of biological behaviors. In approximately 40 % of cases, these tumors are indolent (especially in patients under the age of 40 years) and present as slow-growing lumps, and if long lasting, they may be associated with pain or early nerve involvement. In about 40 % of cases, moreover, such tumors are also aggressive (especially in elderly patients); facial palsy may be a presenting sign; and soon an evolving mass is evident. Malignant neoplasms of the salivary glands are characterized by rapid growth rate, pain, facial nerve involvement, and cervical lymph nodes. Nodal metastases seem to depend on the histological type and grading more than the primary tumor site (Table 36.4). A rapid growth and sometimes ulceration of a long-stay parotid mass is seen in one-third of patients suffering from carcinoma ex pleomorphic adenoma. Facial nerve palsy, either complete or partial, always indicates a locally infiltrating cancer of the parotid. Soft palatal fullness may also be present, in case of tumors invading the parapharyngeal space. Trismus, fixation of the tumor to the overlying skin, ulceration, and fistulas are signs of very advanced-stage disease.

Table 36.2 Major salivary glands: definitions of TNM

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less in greatest dimension without extraparenchymal extension[a]
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension[a]
T3	Tumor more than 4 cm and/or tumor having extraparenchymal extension[a]
T4a	Tumor invades the skin, mandible, ear canal, and/or facial nerve
T4b	Tumor invades the skull base and/or pterygoid plates and/or encases the carotid artery
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis as specified in N2a, 2b, and 2c below
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, not more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, not more than 6 cm in greatest dimension
N3	Metastasis in a lymph node, more than 6 cm in greatest dimension
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

[a]Extraparenchymal extension is a clinical or macroscopic evidence of invasion of a soft tissues or nerve, except those listed under T4a and 4b. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes

[Reprinted from Compton CC, Byrd DR, Garcia-Aguilar J, et al. Lip and Oral Cavity. In: Compton CC, Byrd DR, Garcia-Aguilar J, et al. (eds). *AJCC Cancer Staging Atlas: A Companion to the Seventh Editions of the AJCC Cancer Staging Manual and Handbook*. New York, NY: Springer Science; 2012:41–53. With permission from Springer Science]

Table 36.3 Major salivary glands: anatomic stage/prognostic groups

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IV A	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IV B	T4b	Any N	M0
	Any T	N3	M0
Stage IV C	Any T	Any N	M1

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36.7 Minor Salivary Gland Tumors

A greater proportion of malignancies occurs in the minor salivary glands than in the major counterpart. The incidence of malignancy depends on the site of occurrence, and signs and symptoms depend on tumor size and position and may

Table 36.4 Occurrence of cervical lymphadenopathies in malignant tumors of the salivary glands

	Nodal metastases	References
Site of primary		
Parotid gland	12–25 %	[37–40]
Submandibular gland	15–42 %	[37, 41, 42]
Minor salivary gland	8–18 %	[37, 43–45]
Histotype—grade		
Mucoepidermoid carcinoma—low grade	3–8 %	[46–48]
Mucoepidermoid carcinoma—high grade	50–70 %	[46–48]
Acinic cell carcinoma	1–47 %	[49–53]
Acinic cell carcinoma—high grade	56 %	[54]
Adenoid cystic carcinoma	12–38 %	[53, 55, 56]
Salivary duct carcinoma	43–58 %	[57, 58]
Salivary duct carcinoma—low grade	0	[59]

vary according to the tumor location. Survival rates for palate tumors are similar to those related to submandibular carcinomas, i.e., 40–60 %. Incidence increases up to 90 % from the tongue to the floor of the mouth and sublingual glands. The upper lip is affected twice as much by malignancies compared with the lower lip, i.e., 60 % vs. 30 %, respectively. In over 50 % of cases, minor salivary gland tumors are intraoral: a painless submucosal swelling is usually present, sometimes accompanied by ulceration of the overlying mucosa. A painless lump may indicate tumors arising in the oropharyngeal area. In case of nasopharyngeal or the nasal cavity infiltration, facial pain, nasal obstruction, or bleeding may be present. Tumors occurring in the larynx or trachea may cause hoarseness, voice change, or dyspnea.

36.8 Diagnosis

Physical examination represents the most important diagnostic tool for major salivary gland carcinomas. As approximately 80 % of salivary gland tumors arise in the parotid and approximately 75 % of them are benign, an initial differential diagnosis should be performed between cancer and other benign diseases, such as cysts, inflammatory status, and lymph node hyperplasia. In case of a suspected malignant lesion, a pathological diagnosis must be considered. Ultrasonography (US) is a highly sensitive (approximately 100 %—similar to CT scan) and low-cost modality. This is always recommended as a preoperative examination, since approximately 90 % of tumors arise in the superficial lobe of the parotid gland. US is the most indicated tool to differentiate intraglandular from extraglandular lesions, although it is not feasible to visualize the deeper parotid lobe. MRI has a sensitivity of 87 % with a specificity of 94 %, and it is particularly useful in visualizing the tumor interface and surrounding tissues for a correct surgical planning, especially in case of larger tumors (more than 4 cm), tumors arising in deep structures, and/or involving them. Among the advantages of MRI, in comparison with CT, the elimination of dental artifacts and the ability to distinguish between a tumor and obstructed secretions should be mentioned. Since the full extent of minor salivary gland cancers arise in oral and nasal cavity, paranasal sinuses cannot be defined by clinical examination; MRI is, instead, recommended. In particular, MRI with contrast-enhanced and with fat-suppressed T1-weighted images results useful in case of perineural invasion.

18F-FDG-PET/CT is not employed for staging at diagnosis in case of low-grade histotypes. It could be useful in intermediate- and high-grade tumor for surgical planning [60, 61]. 18F-FDG-PET/CT has a high negative predictive value to detect distant metastasis [62], although routinely PET/CT use in advanced disease is not recommended, above all in low-grade histotypes.

Methionine PET/CT seems to be useful in predicting therapeutic efficacy of carbon ion therapy in ACC [63].

Histological diagnosis is indicated in those cases when an evidence of malignancy has been assessed and demolitive surgery, such as neck dissection and total parotidectomy, is needed. Fine-needle aspiration biopsy (FNAB) is the preferred method to obtain a pathological diagnosis from a salivary gland lesion [64]. More controversial are those cases in which an indolent cancer masquerades as a benign tumor. The clinician's experience can distinguish between the two in 90 % of cases [65], while fine-needle aspiration cytology (FNAC) may further support the best treatment choice. Inadequate sampling may lead to false-negative diagnoses, which is the most frequent error. In case of a periglandular nodule, FNAC is feasible to distinguish a primary salivary tumor from a pathological lymph node. A proper diagnosis allows avoiding unnecessary surgery [66]. Tumor with cystic degeneration, which is relatively frequent in mucoepidermoid carcinomas, may be recognized by repeating aspirations. Intraparotid cystic lesion should be considered in differential diagnosis with lymph node from squamocellular head and neck cancer.

Open biopsy should be avoided because of the risk of seeding. In case small masses in minor salivary glands (palate, tongue) should be proved malignant, punch biopsy (dermatological punch) may be preferable to direct excision, unless the latter provides adequate margins. Frozen section diagnosis is still an issue of debate. False-positive rates account for 1.1 %, while false-negative rates are 2.6 %. Accuracy is better for benign tumors than for malignant

lesions (98.7 % vs. 85.9 %). If malignancy is not confirmed by FNAC, frozen section examination should always be performed. Frozen section examination, including periglandular lymph nodes, is often performed in view of an immediate neck dissection. The difficulty to differentiate among various histotypes represents the major limit of this procedure.

36.9 Natural History and Prognosis

The initial spread of a major salivary gland tumors is local invasion. Parotid tumors present fixation to surrounding structures in about 20 % of cases [67], skin invasion in 10 % of cases [37], and facial nerve involvement in 25 % of cases [67, 68].

Neck lymph node metastases are more common in the submandibular gland than in the parotid gland, about 40 % versus 25 % [37, 69]. The frequency of neck nodes seems to be dependent on T stage, site of origin, and histological type.

Distant metastases at presentation are rare. At 10 years they account for about 30–40 % mainly depending on the histological type (adenoid cystic, squamous cell, undifferentiated, and salivary duct carcinoma). The lung and bone are the most common sites of distant metastases [37].

Survival is related to tumor stage, histological type (Table 36.5), grading, facial nerve paralysis, extrasalivary gland tumor extension, and cervical node involvement. All these predictors may influence treatment outcome [70–72]. Besides the abovementioned predictors of survival, patient's age and positive surgical margins are the most important factors predicting locoregional control in parotid gland cancer [73, 74]. Perineural invasion and solid histological features are additional prognostic factors in adenoid cystic carcinomas [75]. Margin status, angiolymphatic invasion, tumor necrosis, and myoepithelial anaplasia are the major predicting factors of recurrence in epithelial–myoepithelial carcinomas [76].

Table 36.5 Survival rates of the most common major salivary gland malignancies

Histology	5-year survival
Polymorphous low-grade adenocarcinoma	95–100 %
Acinic cell carcinoma	75–96 %
Mucoepidermoid carcinoma—LG	75–89 %
Myoepithelial carcinoma	67 %
Mucoepidermoid carcinoma—HG	23–50 %
Adenoid cystic carcinoma	35–70 %–(10-year DFS 10–20 %)
Carcinoma ex pleomorphic adenoma	40 %–(30–96 % correlated with histology)
Salivary duct carcinoma—HG	4-year DFS 20–35 %

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Patients with mucoepidermoid carcinoma of the parotid gland have a better prognosis than those with submandibular gland tumors [77, 78], but these figures were not confirmed for other histotypes. No data suggesting different prognosis between major and minor salivary gland tumors are available.

The site of occurrence is an effective predicting factor of prognosis in the small subset of minor salivary glands cancers [79].

36.10 Treatment

36.10.1 Surgery

36.10.1.1 Major Salivary Glands

Salivary gland cancer patients should receive an individualized treatment, more than any other cancer patients. For this reason, experienced clinicians are particularly important. Both benign and malignant salivary gland neoplasms may be approached by the similar surgical techniques and strategies. In general, tumor must be resected, together with right normal tissue margins surrounding the neoplasm. Treatment plan may be influenced by tumor location, extension, and histology.

In parotid neoplasms, the diagnostic procedure of choice is superficial parotidectomy with formal facial nerve dissection and preservation, which is also the treatment of choice for many malignant tumors of the superficial gland lobe. Enucleation may, instead, increase the risk of recurrence and facial nerve dysfunction. Local excision should only be performed in tumors arising in the tail of the gland (i.e., Warthin tumors). Partial superficial parotidectomy, as described by Leverstein, proved a safe and effective procedure in the treatment of benign tumors [80]. In the presence of a large tumor extension into the parapharyngeal space, superficial lobectomy is needed for the surgical exposure of the deep lobe, and it may be achieved also by cervical approach, which may be accompanied by submandibular gland displacement and/or mandibulotomy.

A cervical approach may be adopted to remove a deep parotid benign tumor, by avoiding superficial parotidectomy. In this case, the formal exposition of the seventh nerve is not always necessary, but it should be pointed out that the nerve is still vulnerable. When approaching through the superficial lobe, whenever feasible, this tissue should be preserved, reflected anteriorly, and finally replaced to minimize cosmetic damage.

Histological confirmation, also by means of intraoperative frozen sections, should be obtained before any deliberate surgical injury of the seventh nerve.

Partial or complete sacrifice of the facial nerve occurred in up to 40 % of the patients treated for a parotid malignancy [71, 81, 82]. Tumor eradication must be balanced against facial nerve preservation. When the patient has a normal

facial function preoperatively, the nerve preservation should always be attempted, particularly when dealing with benign neoplasms. In selected cases, the tumor may be peeled off of the nerve. In case the tumor should be adherent or is infiltrating other structures and the nerve encased (preoperative facial palsy, skin involvement), radical parotidectomy including the facial nerve is the treatment of choice. The intraoperative use of integrity nerve monitoring device seems always appropriate, particularly in the case of a recurrent tumor in which the scar could make difficult the surgical identification of the nerve. Immediate nerve grafting (e.g., thoracodorsal nerve grafting) should be performed in patients under 65 years. Older patients should, instead, be submitted to rehabilitative local procedures. Extraparotid tumor extensions may need skin excision, mandibulectomy, or partial resection of maxilla and temporal bone.

For either benign or small submandibular tumors, well confined to the parenchyma and of low-grade histology, excision of the whole gland alone is indicated. An adequate resection should, instead, be performed in every other case, including the bed of the gland and any adjacent structure in contact with it, up to a real supraomohyoid selective dissection (removal of level I, II, and III lymph nodes). This procedure allows to obtain the tissue needed for diagnosis and also remove the primary echelon lymph nodes at risk for metastasis [41].

The risk of lymph node metastasis from parotid cancer is generally low [53], and it increases in high-grade and advanced T-stage tumors, as well as in the presence of extracapsular extension or facial paralysis, regardless of histology [39, 70, 83, 84]. In these cases, a selective prophylactic neck dissection, including levels IB, II, and III, may be appropriate. The same procedure may also be offered to selected cases, in which lymphadenectomy may facilitate primary resection. Nodal involvement requires conventional neck dissection including levels IB, II, III, IV, and VA.

Selective prophylactic neck dissection should include levels I, II, and III in the rare cancer of sublingual glands.

36.10.1.2 Minor Salivary Glands

A very high number of minor salivary glands are scattered throughout the head and neck. Most of them are located in the oral cavity. Surgery is the recommended treatment for patients with resectable tumors. The treatment of these tumors is usually similar to the one adopted for squamous cell carcinomas arising in the same sites. However, special considerations should be addressed when the tumor arises in the hard palate. In this site the small amount of soft tissue between the tumor and bone implies that every effort should be carried out to evaluate the possible bone/periosteal invasion. Bone resection is questionable in the case of benign or low-grade tumors without detectable bone involvement. Wide resection including the bone should be reserved for infiltrating and high-grade tumors. Surgical resection with close margins should be considered for adjuvant treatment. Low rates of cervical lymph node metastases have been reported [37, 45, 79]. Therefore, elective neck dissection seems not to be of much benefit for patients with small and low-grade minor salivary gland tumors. In general, if the primary tumor is accessed through the neck, then some form of neck dissection should follow.

36.10.2 Radiotherapy

36.10.2.1 Benign Tumors

Pleomorphic adenoma, a mixed benign tumor, is the most frequent, accounting for about 60 % of all epithelial tumors with an incidence of 2.4–3.05 per 100,000 [12]. It occurs in young people, mainly in the fifth decade with a slight predominance among females. In 80 % of cases it arises from the parotid gland, and the standard therapy is represented by conservative parotidectomy. This tumor tends to recur, sometimes as a malignant lesion. Some authors reported recurrence rates of 3.4 % at 5 years, 2.5–6.8 % at 10 years, and 5 % at 20 years. The risk of relapse seems to be higher in multinodular disease. The role of postoperative radiotherapy (RT) is still debated not only because of efficacy concerns but also for issues on treatment-related morbidity. Nevertheless, most authors advocated RT in cases of unclear resection margins, intraoperative spillage of tumor, multinodular recurrences, or multiple recurrences, to achieve better locoregional control.

Generally, RT has not been considered as a treatment modality for the first recurrence in relatively young patients because of the major risk of radio-induced malignancy, which may occur from 20 to 30 years after treatment [85–88].

The target volume is represented by the parotid area irradiated with a total dose of 50–60 Gy with conventional fractionation (2 Gy fraction per day/5 days a weeks/5–6 weeks).

36.11 Malignant Tumors

36.11.1 Postoperative Radiotherapy

Indications to postoperative RT are generally the same for carcinoma arising from both major and minor salivary glands. In contrast, some peculiar aspects characterized ACC vs. no ACC tumors with regard to target volumes.

36.11.2 ACC

The addition of RT to surgery has been reported to improve local control (LC) rates compared to surgical resection alone in all ACC sites. With combined modalities, 5- and 10-year

LC rates were 88–95 % and 84–91 %, respectively [87, 89–92]. Postoperative RT is essentially recommended in all patients or at least suggested in presence of various adverse parameters such as advanced tumor stages (e.g., T4), positive or close surgical margins, perineural invasion, and bone involvement [87, 90, 91, 93–95]. In the study by Chen et al. from UCSF on 140 ACC patients, the omission of adjuvant RT was an independent predictor of local recurrence [87]. Some studies questioned the utility of postoperative RT due to the lack of significant advantage on overall survival (OS) for the high rate of distant metastases and the relatively high probability of long-term survival after salvage therapy [96–98]. Adjuvant RT could be omitted for patients with a grade 1 pT1N0 lesion resected with wide negative margins and no perineural invasion [90].

Radiotherapy target volumes (clinical target volumes—CTVs) will be customized based on the disease extent before surgery and on pathological findings. The postoperative tumor bed must include the parapharyngeal space and temporal fossa in parotid gland tumor and surrounding structures in case of a submandibular gland tumor. A bolus over the scar region is indicated in the case of skin invasion and/or for very superficial localized tumors of the parotid or submandibular gland. In case of perineural invasion, besides the tumor bed, RT volumes should cover the pathway of the cranial nerve up to the skull base. Moreover, no consensus exists on which neurologic anatomical structures should be included within the RT field. Some authors treat electively the skull base only when a named nerve is involved; other authors include it routinely even when a microscopic perineural involvement is reported. To target the base of the skull, at-risk areas are delineated from the involved region to the inferior aspect of the cranial cavity (e.g., clivus and surrounding neural foramina), following the relevant cranial nerve pathways depending on site of disease [87, 91]. In cN0 patients, neck dissection is generally not necessary. However, in case of ACC involving sites with a rich lymphatic drainage, e.g., the base of the tongue, palate, nasopharynx, floor of the mouth, and submandibular gland, the neck has to be treated in every case. If neck surgery is not planned, elective neck irradiation must be considered, and it should include at least the first echelon nodes [87, 89–91].

With regard to radiation dose with conventional X-ray RT, a dose–response relationship might exist for head and neck ACC. Local control was significantly improved with doses to tumor bed/original tumor volume of 60 Gy with standard fractionation (1.8–2 Gy per fraction). A minimum dose of 66 Gy was recommended in case of positive multiple margins or extensive soft-tissue involvement with conventional fractionation. Doses at least of 56–63 Gy should be administered to the skull base if consistently included [87, 91, 93, 94, 99]. Elective nodal volume should receive a dose of 45–50 Gy with standard fractionation.

Due to very complex-shaped tumors and numerous radiosensitive structures in the head and neck region, as doses range between 60 and 70 Gy, high conformal radiotherapy techniques such as intensity-modulated radiation therapy (IMRT) are strongly recommended. In a retrospective outcome analysis of 35 salivary gland carcinoma patients who have undergone postoperative IMRT with or without concurrent chemotherapy, half of whom had ACC, RT was well tolerated with a high LC rate [100]. The potential risk of radiation-induced injury resulting from high-dose postoperative radiotherapy could be reduced by using IMRT techniques in case of minor salivary gland tumors of the paranasal sinuses as well as for the hearing loss after radiotherapy for parotid gland tumors. Figure 36.1 shows the postoperative RT dose distribution on CT axial images in a case of ACC of the parotid gland.

High-Grade Salivary Gland Tumors (High-Grade MEC, Salivary Duct Carcinoma, Carcinoma Ex Pleomorphic Adenoma, and Adenocarcinoma)

It is pivotal to underline that the majority of published series include a wide range of histologies, including both ACC and high-grade tumors. The limited data available support contention that postoperative RT increases both LC and survival for patients with high-grade tumor with advanced-stage disease. Besides advanced T stage, additional high-risk features of failure include close or positive margins, bone erosion, and neural/perineural spread [98, 101–104]. In a study of the Dutch Head and Neck Oncology Cooperative Group on 498 patients, postoperative RT improved significantly the 10-year LC compared with surgery alone in T3–4 tumors (84 % vs. 18 %), in patients with close margins (95 % vs. 55 %), in case of incomplete resection (82 % vs. 44 %), in case of bone invasion (86 % vs. 54 %), and in the presence of perineural invasion (88 % vs. 60 %). Moreover, nodal involvement is an independent predictor of locoregional failure after surgery alone. Postoperative RT significantly improved locoregional control versus surgery alone in the case of pN(+) (86 % vs. 62 %) [105]. Small primary lesions (pT1) completely excised are at very low risk of failure after surgery alone and could not benefit from adjuvant RT [106].

As for ACC, CTV delineation depends on disease extent and pathologic findings after surgery; in any cases it is mandatory to cover the whole surgical bed. Ipsilateral neck node levels I to V should be included in case of pathologically positive nodes. It is generally recommended to cover electively ipsilateral node levels I to III due to a 20–30 % risk of subclinical nodal

(continued)

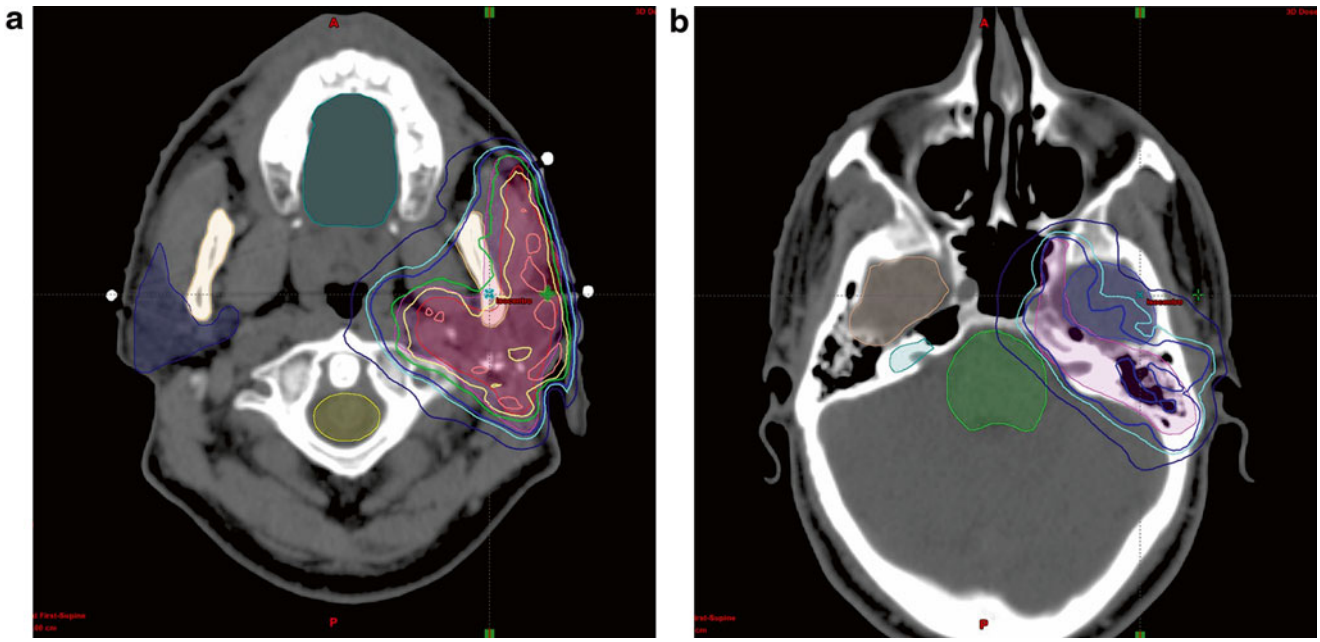

Fig. 36.1 Patient with ACC of the left parotid gland underwent superficial parotidectomy with facial nerve preservation (pathological stage T1, close margins, and microscopic perineural invasion) and postoperative intensity-modulated radiotherapy. Prescribed total doses were 69.96 Gy and 60 Gy in 30 fractions to the high-risk volume and "neural volume," respectively. (**a**) Computed tomography simulation axial image (level of the second cervical vertebrae) showing the high-risk volume including the parotid surgical bed (*red line*), organs at risk and radiation doses: 45 Gy (*dark-blue line*), 56.43 Gy (*cyan line*), 59.4 Gy (*blue line*), 66.46 Gy (*green line*), 69.96 Gy (*yellow line*), and 73.46 Gy (*orange line*). (**b**) Computed tomography simulation axial image (level of internal acoustic meatus) showing the "neural volume" covering facial nerves, the stylomastoid foramen, and the internal acoustic meatus and auriculotemporal nerve up to the forame ovale and RT doses (the same as in (**a**))

(continued)

disease in cN0 cases. Some authors would not recommend elective nodal irradiation for early T stage of the oral cavity [105, 107]. In case of perineural invasion, in particular if macroscopic, cranial nerve pathways up to the base of the skull must be included in the target volume [105]. No significant dose–response relationship has been shown in most studies. However, the total dose is generally adjusted to the resection margin status [105]. A trend toward greater LC has been observed for a dose of at least 60 Gy with standard fractionation [107, 108]. In case of incomplete resection, a dose ≥ 65 Gy is recommended (for gross residual disease a dose of 70 Gy) [105]. General guidelines in head and neck oncology for elective and curative dose to neck nodes are also applicable to salivary glands tumors.

As for ACC, RT should be preferably administered by the IMRT technique to reduce the risk of radio-induced side effects.

36.11.3 Primary Radiotherapy

Patients with resectable early-stage lesions generally receive surgery, whereas patients with advanced lesions tend to be treated with RT alone. A subset of patients with early-stage disease may receive primary radiotherapy, depending on the locations of the tumor, on the histology, and on the philosophy and expertise of the attending physicians [90].

Patients with locoregional unresectable disease are usually treated with RT alone. In these cases, CTV is generally defined as the gross tumor volume (GTV), i.e., the macroscopic disease plus a 5-mm basic margin for all histologies and sites. The base of the skull and the lymph nodes are considered as the target volume according to the same criteria defined in a postoperative setting, although primary disease control is the first object of the cure.

Patients with an unresectable disease treated with photon-based conventional RT have a long-term locoregional control rates lower than 50 % and 20 % for ACC and non-ACC tumors, respectively [90, 109–111].

Radiotherapy with neutrons has shown a higher locoregional control (but not survival) than photon-based conventional RT. In the RTOG-MRC study (Radiation Therapy Oncology Group in the United States and the Medical

Research Council in Great Britain), 32 patients were randomized to be treated by neutrons (no. = 17 patients, total dose of 70 Gy) or photon therapy (no. = 15 patients, total dose of 50 Gy with a total dose to macroscopic disease of 55 Gy equivalent): a significant improvement of locoregional control at 2 years was found with neutron in comparison with photon (67 % vs. 17 %) [112]. A borderline impact on survival without statistical significance was reported in a subsequent paper [113]. The authors reported a higher late morbidity with neutron defined as "severe" due to an inability of the neutrons to focus the beams precisely to the tumor, as also reported in other studies of single institutions [114, 115]. Due to a doubtful benefit over photons in terms of therapeutic index, to the several biases and weaknesses of the single randomized trial and the lack of comparison with modern photon RT, including IMRT, neutrons are not used in clinical practice. On the other hand, IMRT techniques with doses ≥70 Gy, in patients with unresectable salivary gland tumors compared with neutron therapy, showed a comparable disease control with fewer late complications [116]. More recently, proton therapy and carbon ion (heavy particles) therapy have been studied for salivary gland tumors, in particular for ACC. In a study by Pommier, 23 patients with newly diagnosed ACC with skull base extension were treated with combined proton and photon RT at the total dose of 75.9 Gy equivalent with 5-year DFS and OS rates of 56 % and 77 %, respectively [117]. More recently, a phase II trial showed the therapeutic effectiveness of carbon ion therapy with 65 Gy equivalent in 26 fractions with 5-year LC and OS of 73 % and 68 %, respectively [118].

Charged particles produce a more conformal dose distribution with respect to photon RT due to their superior ballistic properties. Although there are similar physical properties of protons and carbon ions, these latter seem to have more biological advantages compared with protons. However, no significant differences between these two radiotherapy modalities in terms of LC and OS were found in ACC. In any case, 5-year LC rates for T4 and inoperable cases were 66 % and 68 %, respectively, better than photon RT alone, suggesting that particle therapy should become a standard treatment for such cases [119]. Carbon ions are also used in combination with photon IMRT in advanced-stage ACC with satisfactory LC and consistently moderate toxicity [120].

36.11.4 Re-irradiation

There are little data on retreatment of malignant salivary gland tumors and indications for a re-irradiation derive from other head and neck tumor recurrences [121, 122].

The best treatment for resectable recurrence is surgery. However, ACC often presents disease recurrence with skull base invasion and perineural spread preventing a complete resection in most of the cases.

Re-irradiation should be done with highly conformal techniques such as IMRT or stereotactic RT with a sufficiently high dose to the gross tumor volume (at least 60 Gy with conventional fractionation), including only the visible local relapse with a small safety margins [123].

Recently, re-irradiation with carbon ion has been used in 58 consecutive ACC recurrent patients. Despite the high doses applied, moderate side effects and encouraging response rates were observed, even in heavily pretreated patients [124].

36.12 Chemotherapy and Other Therapies

Chemotherapy is employed almost exclusively with a palliative aim. Different chemotherapy regimens have been tested, although no randomized studies have been conducted to date to define the best therapeutic choice in this setting. A platinum-based chemotherapy seems to be associated with the best response rate, both as a monotherapy and as a combined regimen with doxorubicin in most of cases, although it is still not clear whether a combination chemotherapy has any advantage over a single-agent chemotherapy (Table 36.6). In ACC some chemotherapeutic regimens such as mitoxantrone, vinorelbine, and epirubicin seem to be a reasonable and less toxic alternative to cisplatin as monotherapy [125], while paclitaxel could have a rationale use in adenocarcinoma, NOS [126]. The choice of the best chemotherapy regimen and whether polychemotherapy rather than monotherapy should be used considering the histotype to cure and the potentially high rate of toxicities expected in case of polychemotherapy are all still issues of debate. No benefit, in terms of survival, has been observed in patients responding to chemotherapy over non-responding. For this reason, chemotherapy should be reserved to symptomatic patients and/or those with a rapid progressive disease. A watchful waiting is, instead, preferable, in cases of indolent disease or for patients with just a few symptoms (Table 36.7).

Tailored therapies have been also investigated in case of advanced disease.

Several phase II trials with new agents have been conducted in the last years (Table 36.8); results have been disappointing in most of the cases. One long-lasting partial response was reported with trastuzumab in a case of HER2 3+ mucoepidermoid cancer [127], while no activity has been recorded for imatinib, gefitinib, cetuximab, lapatinib, and sunitinib (Table 36.8). Rare objective responses to imatinib were recorded favoring in case of strong c-kit immunostaining [137]. Some activity with antiangiogenic agents (e.g., sorafenib, dovitinib, axitinib) has been reported in ACC, although MEC seems to get the highest benefit from this class of agent [133] (Table 36.8).

Table 36.6 Chemotherapy regimens and clinical activity

Treatment	Adenoid cystic Response rate %	Adenoid cystic Response rate %	Mucoepidermoid cancer Response rate %	Mucoepidermoid cancer Response rate %	Adenocarcinoma Response rate %	Adenocarcinoma Response rate %
Cisplatin	R	15	R	20	NR	0
Paclitaxel	NR	0	R	25	R	24
Vinorelbine	R	15	–	–	R	40
Epirubicin	R	10	–	–	–	–
Mitoxantrone	R	10	–	–	–	–
Methotrexate	–	–	R[a]	40	–	–
CAP (various) or CAP-5FU	R	28	R	83	R	62
Anthracycline/cisplatin ± 5FU	R	32	R	25	R	57
Cisplatin/vinorelbine	R	44	–	–	R	20
Carboplatin/paclitaxel	R	20	–	–	R[a]	100
Cyclophosphamide/doxorubicin	R	3	NR	0	R[a]	100
Gemcitabine	NR	0	–	–	–	–

R objective response, *NR* no response, *CAP* cyclophosphamide/doxorubicin/cisplatin, *5FU* 5 fluorouracil

[a]Data derived from case reports/retrospective series rather than prospectively performed clinical trials

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Table 36.7 Frequency of expression of biological targets in salivary gland cancer

Histotype	c-kit %	EGFR %	HER2 %	Androgen receptor %	Estrogen receptor %	Estrogen receptor alpha %	Estrogen receptor beta %	Progesterone receptor %
Adenoid cystic carcinoma	78–92	36–85	2–36	0	<10	75	17	<10
Mucoepidermoid carcinoma	0–40	53–100	0–38	0	<10	Not investigated	Not investigated	<10
Adenocarcinoma	9	59	14–21	21	<10	Not investigated	Not investigated	<10
Salivary duct cancer	0–8	9–41	44–83	43–100	<10	Not investigated	73	0

[Adapted from Guzzo M, Locati LD, Prott FJ, et al. Major and minor salivary gland tumors. Crit Rev Oncol Hematol. 2010;74:134–48. Review. With permission from Elsevier]

Table 36.8 Phase II study with targeted drugs

Drug	Target	Histology	Response rate (%)
Imatinib [22]	c-kit	16 ACC	0
Trastuzumab [127]	HER2	2 ACC/12 non-ACC	0/7
Gefitinib [128]	EGFR	19 ACC/9 non-ACC	0
Lapatinib [129]	HER2/EGFR	19 ACC/17 non-ACC	0
Cetuximab [130]	EGFR	23 ACC/7 non-ACC	0
Sunitinib [131]	VEGFR/c-kit	11 ACC	0
Sorafenib [132]	VEGFR/*BRAF*	23 ACC	11
Sorafenib [133]	VEGFR/*BRAF*	19 ACC/18 non-ACC	11/22
Dovitinib [134]	FGFR	21 ACC	10
Axitinib [135]	VEGFR-1, VEGFR-2, VEGFR-3	33 ACC	9
Vorinostat [136]	Histone deacetylase inhibitor	30 ACC	1/30
Dasatinib NCT00859937	Bcr-Abl and Src inhibitor	Ongoing	
Pazopanib NCT02393820	VEGFR-1, VEGFR-2, VEGFR-3	Ongoing	

Androgen receptor is a pathogenetic factor in SDC and representing a valid therapeutic target. Androgen deprivation therapy (ADT) is active in AR-positive SDC and adenocarcinoma, NOS [138, 139]. An international randomized phase II trial has been designed to elucidate whether ADT is superior to chemotherapy in relapsed/metastatic patients in those histotypes with AR expression. The employment of target therapies is currently recommended only within clinical trials.

36.13 Conclusions

Surgery is currently the cornerstone of benign and malignant salivary gland tumor management. Radiation therapy is reserved in postoperative setting in malignant tumors according to the pathological report (e.g., positive surgical margins, high-grade histotype) and, seldomly, in benign tumors. Radiotherapy alone must be recommended to unresectable neoplasms or to metastatic patients with a palliative aim. Promising results are coming from heavy ion particles in selected cases. Chemotherapy has a palliative role; clinical trials with emerging tailored therapies are ongoing.

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Primary Mucosal Melanomas of the Head and Neck

37

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Abstract

Mucosal melanomas of the head and neck are a rare disease of dismal prognosis. They account for less than 1 % of all cancers, less than 4 % of all melanomas, and more than half of all mucosal melanomas. Five-year survival is about 20–30 %, mainly because of deaths from distant metastases. Mucosal melanomas of the head and neck deserve central pathology reviews and case discussions within multidisciplinary rare disease networks, aware of all the diagnostic and therapeutic challenges. Early diagnosis followed by surgical excision remains the mainstay of treatment, and postoperative radiation therapy is often recommended. Current controversies include the role of minimal invasive endoscopic approaches, their challenges in terms of margin assessment, and radiation therapy dose. As for the modalities of radiation therapy, the current level of evidence pleads in favor of optimized tridimensional conventionally fractionated radiation therapy. However, technological advances suggest that carbon therapy might be preferred to proton therapy because of an expected better biological efficacy and charged particle therapy (proton or carbon therapy) to photon-based irradiation because of dose distributions and safer ability toward hypofractionation. The domain of medical oncology and genetic research may provide further clues, especially in light of benefits noted of KIT inhibitors and the proportion of mucosal melanomas with this genetic aberration. Adequate methodology needs to be developed for rare diseases with specific therapeutic challenges, and patient associations, patient-reported outcomes, and quality-adjusted life-years (QALY) should be part of the assessment of the treatment modalities.

Keywords

Melanoma • Mucosal melanoma • Head and neck • Sinonasal • Oral cavity • Prognosis • Treatment

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37.1 Introduction

37.1.1 Epidemiology and Clinical Presentation

The first case of mucosal melanoma published was reported in 1856. Since then, mucosal melanomas are increasingly reported. However, while cutaneous melanomas represent about 90 % of all melanomas, mucosal melanomas remain an uncommon condition. Mucosal melanomas occur more commonly in the head and neck than in other regions of the body. Primary mucosal melanomas of the head and neck account for 0.03 % of all cancers, less than 4 % of all melanomas, and 55 % of all mucosal melanomas. Melanocytes develop from the neuroectoderm. As of their embryological origin, mucosal melanomas are more common in ectodermally derived mucosal tissues, such as the nasopharynx, larynx, tracheobronchial tree, and esophagus, than in non-ectodermally derived tissues. Nasal and sinonasal mucosal melanomas represent 61 % of cases and oral cavity melanomas 13 %, with a smaller incidence of pharyngeal and laryngeal cases. Within the nasal cavity, the anterior portion of the nasal septum is the most commonly involved, followed by the middle turbinate, and then the inferior turbinate. Mucosal melanoma is very rare in the superior turbinate, the olfactory region, and the ethmoid sinus. Within the oral cavity, the palate and alveolar gingiva are the most common sites, followed by the lower and upper labial mucosa, buccal mucosa, and tongue. Very rarely, mucosal melanoma can be found in the pharynx, larynx (then dominated by supraglottic region), or upper esophagus.

It is notable that sinonasal and oral cavity mucosal melanomas exhibit distinct behaviors, as illustrated by their different presentations (melanosis, Fig. 37.1a, b) and propensities to metastasize to regional lymph nodes.

Several major epidemiologic and etiologic differences exist between mucosal melanomas and their cutaneous counterpart. Mucosal melanomas present one decade later on average than melanoma of cutaneous origin. Mean age at diagnosis varies between 65 and 71 years old among studies (55–87) [1]. Mucosal melanomas account for 1.3 % of melanomas in whites, whereas 11.8 % of all melanomas in blacks are mucosal. Except for the oral mucosal site, there is no evidence for a racial predilection of mucosal melanoma. Oral melanoma can occur in any racial and ethnic group, but the highest incidence appears to be in Japanese patients. Sex ratio data are not consistent across studies, but when sinonasal and oral cavity mucosal melanomas are considered, distribution among the sexes appears to be roughly equivalent.

The incidence of cutaneous melanoma has increased dramatically worldwide over the last half century, which has largely been attributed to increased sun exposure. Since mucosal melanomas arise on surfaces which are not exposed to sun, this risk factor is unlikely involved in the development of mucosal melanomas of the head and neck. However, the incidence of mucosal melanomas has also increased. As viral infections have been increasingly associated with some cancers, human papilloma, herpes, and two polyomavirus named after the initials of patients in whom they were discovered (BK, JC) have been investigated as causal risk factors. Yet studies have not shown any relationship between such viruses and mucosal melanomas [2]. In contrast, exposure to formaldehyde has been reported as potential risk factor because of an excess of mucosal melanoma patients in workers having prolonged occupational exposure to this chemical [3]. Tobacco has also been reported as a potential risk factor in the development of oral mucosal melanomas because hyperproduction of melanocytes in the oral mucosa has been associated with cigarette smoking and particularly in pigmented oral lesions [2]. In oral mucosal melanomas, oral melanosis may precede mucosal melanoma. As such, the occurrence of oral mucosal melanoma is the primary reason why all focally pigmented lesions and most diffusely pigmented lesions require a biopsy for diagnosis and should be considered a risk factor that warrants surveillance.

Mucosal melanomas often present at an advanced stage, although there are notable differences depending on tumor site. In primary oral mucosal melanomas, the most commonly

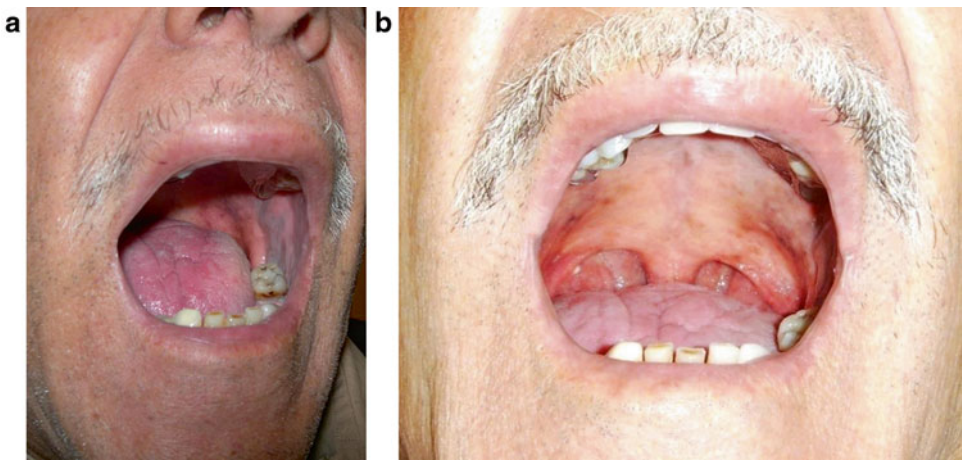

Fig. 37.1 (**a**, **b**) Oral melanosis in a 74-year-old patient with stage I level I mucosal melanoma of the nasal cavity. NED 4 years following diagnosis

affected sites include the hard palate and maxillary gingiva. Oral melanoma can present as an asymptomatic macule, plaque, or mass. It can be well-circumscribed or irregular, focally or diffusely pigmented, and even amelanotic (lacking pigment). Occasionally, tumors exhibit multifocal pigmentation due to the presence of melanotic and amelanotic areas within the same lesion. Diffuse but contiguous mucosal pigmentation should elicit more concern for a possible melanoma than diffuse but noncontiguous pigmentation. Other possible nonspecific symptoms include ulceration, pain, paresthesia or anesthesia, tooth mobility or spontaneous exfoliation, root resorption, and/or bone loss. In sinonasal mucosal melanomas, the presenting symptoms may consist of chronic unilateral discharge, nasal ulcer, nasal obstruction, intermittent epistaxis, and/or anterior cephalalgias. Facial swelling, pigmentation, cranial nerve impairment, ulceration, and bleeding may be present at diagnosis.

Determining whether a mucosal melanoma is a primary or metastatic lesion is often extremely difficult, because cutaneous melanoma may metastasize widely, including to the mucous membranes. Important features in distinguishing a primary from a metastatic lesion are site of involvement, presence or absence of pigment, overlying mucosal ulceration, extension along salivary gland ducts, and vascular and perineural invasion. Since the differential diagnosis may be rather extensive, biopsy of any persistent solitary pigmented lesion is essentially mandatory. Once diagnosed, a clinical challenge is to determine if the lesion represents a primary malignancy or represents a metastasis from a distant site. A reliable definition of the tumor's primary anatomic site is critical for tumor staging and therapeutic decision-making. Patients with disease involving a mucosal surface with a history of cutaneous or ocular melanoma or nevi that have regressed should be assessed to possibly have metastatic melanoma rather than primary mucosal melanoma.

In the case of a cervical node from an unknown primary T0N+M0, a thorough diagnostic workup should be performed. Recently, distinct molecular features were found in mucosal melanomas that could help differentiate them from their cutaneous counterpart in addition to making therapeutic decisions (see molecular findings below).

Due to their location and vascularization, mucosal melanomas represent a therapeutic challenge and are associated with a high morbidity and mortality rate.

37.1.2 Pathology

37.1.2.1 Gross Findings

Gross appearance of the tumor is often variable, including macular, nodular, and ulcerated morphologies. Tumors arising in the nasopharynx are most commonly friable and polypoid in character. The clinical color of oral melanomas varies and includes black, gray, purple, red, and white. Some lesions are uniform in color, whereas others exhibit marked variations. Grossly noticeable pigmentation occurs in approximately 75 % of oral melanomas but in only 50 % of sinonasal melanomas [3–5]. Sinonasal mucosal melanoma of the head and neck often presents as a polypoid, ulcerated, infiltrative mass. Necrosis and bleeding are common. Mean size and thickness at diagnosis are 2.4 cm and 1 cm, respectively. Mucosal melanosis has been reported to be frequently encountered adjacent to oral melanoma and may exist for a considerable period of time before diagnosis. In Japan, almost two thirds of oral melanomas are reported to be associated with melanosis; however, a preexisting pigmented lesion is not usually associated with mucosal melanomas in white patients. One suggestion is that melanosis represents the radial phase of the growth of the tumor and precedes the vertical component by years. In contrast to cutaneous melanoma, the presentation of those involving head and neck mucosal surfaces is typically at a more aggressive vertical growth phase with invasion of the underlying submucosa. As a result of the advanced stage at discovery, most do not have an associated radial growth (superficial spreading) phase.

37.1.2.2 Microscopic Features

Cellular proliferation is composed of sheets of poorly cohesive cells, separated by hemorrhage and rearranged with necrosis. These cells do not exhibit a particular architecture. Cells are large and irregular, with large nuclei and prominent nucleoli and with scant to abundant often eosinophilic cytoplasm (Fig. 37.2a). Cytonuclear atypia is obvious and mitoses abundant. Loading melanin pigment is variable within tumor cells and/or macrophages, and diagnostic can be very difficult in nonpigmented mucosal melanomas. The stromal component is scant and an inflammatory reaction is rare. Areas of degeneration were often noted between vessels giving to the proliferation a perithelial aspect (Fig. 37.2b). Oral mucosal melanomas are usually characterized by malignant melanocytes that are often observed within the connective tissue. Extension of the malignant cells into the epithelium (pagetoid spread) may also be seen (Fig. 37.2c). Association with an intra-epithelial component, particularly seen in oral cavity lesions, is suggestive of the diagnosis. Unlike cutaneous melanomas for which a number of histologic parameters, including a measure of tumor thickness, can be used to reliably predict prognosis, no such parameters reliably exist for oral melanoma. Mucosal melanomas are polymorphic [3, 6] in their tissue architecture and cytology.

As a consequence, misdiagnoses are frequent [7]. Architectural patterns can be solid, epithelioid (Fig. 37.2d), fusiform and storiform, perivascular or more rarely papillary, or desmoplastic.

Cytology aspects can show epithelioid, fusiform, plasmacytoid, small round blue, rhabdoid, and giant or undifferentiated cells or there may be a mixed dominant cytologic pattern (Fig. 37.2e–i). A strictly epithelioid pattern on cytology has been associated with a poorer prognosis [1].

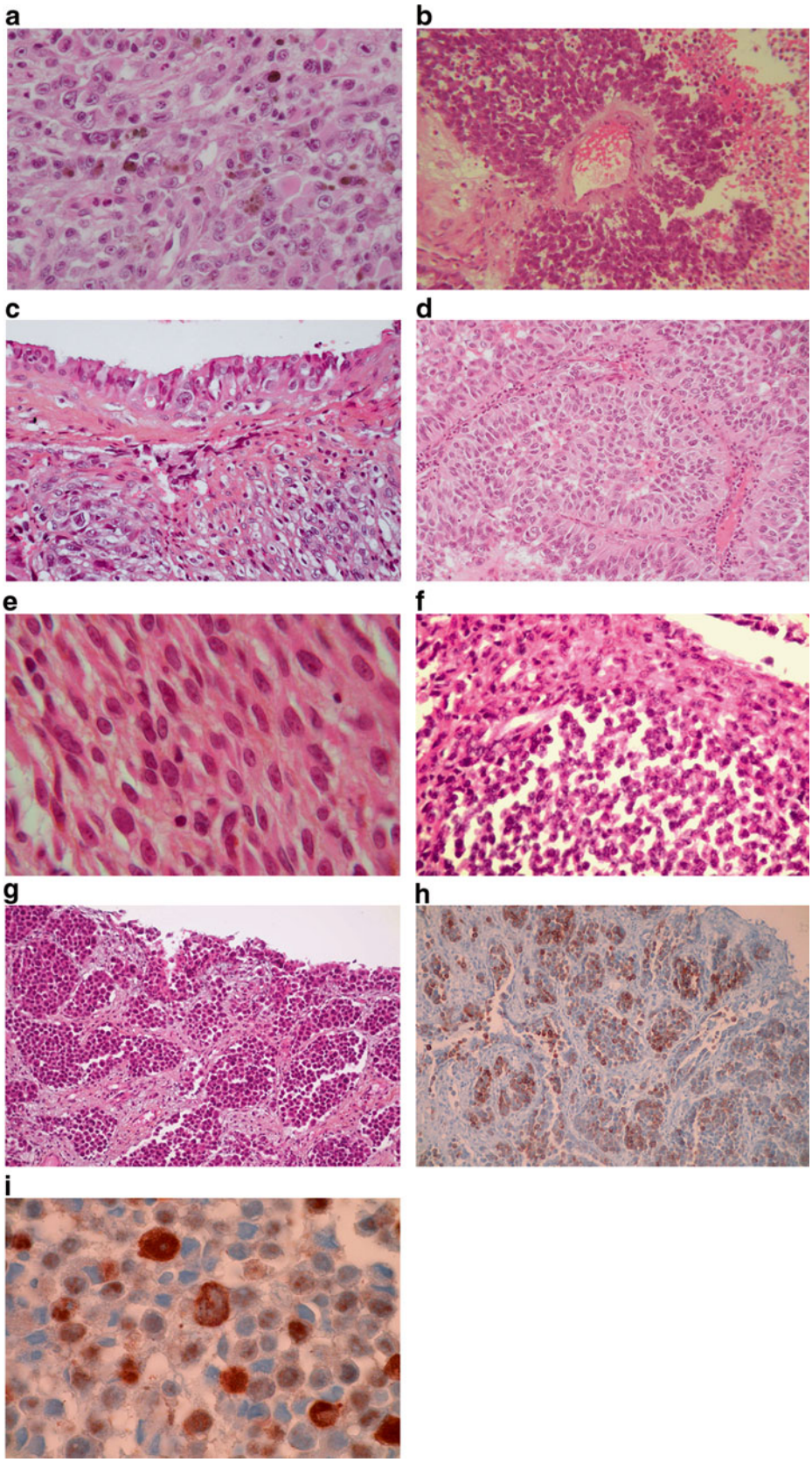

Fig. 37.2 (**a**) Mucosal malignant melanoma. Tumor cells vary in size and shape. Prominent nucleoli. Melanin pigment is seen. (**b**) Mucosal malignant melanoma. Characteristic peritheliomatous growth. (**c**) Malignant mucosal melanoma showing pagetoid component. (**d**) Mucosal malignant melanoma with epithelioid pattern. Alveolar arrangement, no melanin production in this case. (**e**) Spindle cell primary mucosal malignant melanoma lacking melanin pigment. (**f**) Mucosal malignant melanoma. Small blue cell pattern mimicking a lymphoma. (**g**) Mucosal malignant melanoma mimicking an olfactory neuroblastoma or a small cell neuroendocrine carcinoma. (**h**) Mucosal malignant melanoma. Same case as in the figure (**g**) shows HMB45 reactivity. (**i**) Mucosal malignant melanoma. Nuclear immunohistochemical reactivity with S100 protein

37.1.2.3 Immunohistochemical Findings

Tissue sections from formalin-fixed, paraffin-embedded blocks are used for immunohistochemical staining. It is necessary to apply a broad panel of antibodies, in one or more steps, when evaluating sinonasal tract tumors to make an accurate diagnosis. Mucosal melanomas shows positivity for S100 protein (polyclonal) (Fig. 37.2i), HMB45, tyrosinase (clone T311), Melan A (clone A103), and MITF (microphthalmia transcription factor, clone C5+D5, nuclear staining) [8]. Most cases are diagnosed using a panel of three markers (S100, HMB45, Melan A). Protein S100 is the most sensitive while the others are more specific. Mucosal melanomas are most commonly negative for cytokeratins, lymphoid markers (CD45, CD3, CD20), and neuroendocrine markers (chromogranin, synaptophysin, CD56). Of note, however, some mucosal melanomas can exhibit an aberrant phenotype with expression of some cytokeratins, EMA, ACE, AML, desmin, CD68, neuroendocrine markers, and calponin [7].

37.1.2.4 Molecular Findings

Recent studies have shown that mucosal melanomas are a molecularly heterogeneous disease [9, 10]. The frequency of mutations in sinonasal mucosal melanomas has not been well characterized compared with cutaneous melanomas. For example, whereas activating mutations of the BRAF oncogene, in particular the BRAF V600E mutation, have been found in up to 50–60 % of melanomas arising in cutaneous areas, they are less common in mucosal melanomas. *NRAS* mutations seem to be relatively more frequent, found at codons G12 and G13, so perhaps somewhat different from NRAS mutation found in other melanomas which typically affect codon 61 [11].

c-KIT is a key regulator of growth, differentiation, migration, and proliferation of melanocytes. It has been shown to recruit and activate a number of intracellular signaling pathways implicated in tumor progression, such as the phosphoinositide 3-kinase/AKT, Src, mitogen-activated protein kinase, Janus kinase, signal transducers and activators of transcription, and phospholipase-C-g pathways. *c-KIT* is involved in early steps of carcinogenesis. Recently, gain-of-function *KIT* mutations (in particular K642E, L576P, D816H, and V559A), gene amplifications, and overexpression of c-KIT, a receptor tyrosine kinase, were reported in 15 (39 %) of 38 mucosal melanomas [12]. Other studies have reported high rates of c-KIT expression in oral mucosal melanomas, with part of the tumors harboring activating mutations [13]. c-KIT expression has been observed to be present in atypical melanocytes, more so than in the invasive component [13]. This observation warrants extreme caution in the analysis of c-KIT expression as a marker to guide therapy. Also, this may suggest that the c-KIT expression rate might be indeed lower than expected and that staining should be interpreted only with respect to its expression in invasive components. *KIT* mutations are heterogeneous at the molecular level in mucosal melanomas and can reflect genetic mutations as well as amplifications. The frequency of *KIT* mutations in mucosal melanomas varies among different anatomic locations. c-KIT is variably expressed in sinonasal mucosal melanoma, but activating *KIT* mutations rarely present in vulvar melanoma [9, 14]. That said, even among sinonasal series, the results differ [15].

Cyclin D1 is frequently expressed in immunohistochemistry without any clear correlation with gene amplification (CCND1), leaving open the question of whether there are opportunities to target the CDK4 (cyclin-dependent kinase 4) pathway [10]. Comparative genomic hybridization in some mucosal melanomas has shown distinct patterns of chromosomal aberrations such as gains of 1q, 6p, and 8q [16]. Recently, gain-of-function mutations (in particular K642E, L576P, D816H, and V559A), gene amplifications, and overexpression of c-KIT, a receptor tyrosine kinase, were reported in 15 (39 %) of 38 mucosal melanomas [12]. Other studies have reported high rates of c-KIT expression in oral mucosal melanomas, with part of the tumors harboring activating mutations.

Recent genomic data suggest that mucosal melanoma is a separate entity from cutaneous melanoma and that prognostic and therapeutic information available for cutaneous melanoma is not necessarily applicable to its mucosal counterpart. Further, it should be noted that data do not seem fully mature and are conflicting both between subsites of oral/sinonasal mucosal melanomas and even within a given subsite. Better understanding of tumor heterogeneity, standardization in methodology (including FISH, microarrays tissue sections using split-signal FISH DNA probes, PCR and DNA sequencing, mutation analysis, molecular and phenotypic correlations), as well as more mature data will probably help resolve this issue in the coming years.

37.1.3 Differential Diagnoses

Owing to their various morphological patterns, differential diagnoses are numerous and misdiagnoses are more common in particular for amelanotic and ulcerated presentations. Misdiagnoses may be limited by the use of larger and specific sets of immunostains and better knowledge of immunostaining profiles. Epithelioid mucosal melanomas can be misdiagnosed as sinonasal undifferentiated carcinomas (SNUC), nasopharyngeal carcinomas, poorly differentiated squamous cell carcinomas, large cell neuroendocrine carcinomas, and large cell anaplastic lymphomas. Sarcomas, malignant peripheral nerve sheath tumor (MPNST), synovial sarcoma, and fusiform cell carcinomas are in the differential of fusiform cell mucosal melanomas. Olfactory neuroblastomas, Ewing sarcomas/primitive neuroectodermal tumors

(PNET), lymphomas, plasmacytomas, alveolar rhabdomyosarcomas, and small cell neuroendocrine carcinomas should be considered if one is contemplating a diagnosis of a small round cell mucosal melanoma. A separate entity, represented by pediatric melanotic neuroectodermal tumors, is a very rare and benign tumor of children in their first years of life. Mucosal melanomas in children display much less aggressive character than do similar lesions in adult patients, suggesting that these lesions represent a different phenotype than that encountered in adult patients.

37.1.4 Staging Systems

Different systems are being used to stage mucosal melanomas. The Ballantyne system only distinguished disease stage by its location rather than its volume. Disease confined to the primary site regardless of extent is stage I, disease spread to regional nodes stage II, and distant metastatic disease, stage III [17]. This system failed to accurately predict outcomes among stage I mucosal melanomas. A proposal for microstaging localized, stage I (lymph node-negative) primary mucosal melanomas, now called the Prasad's staging system, was consequently made [18]. The histology of 61 head and neck mucosal melanomas was reviewed by two pathologists blinded to patient outcomes. The invasion was evaluated as Level I, melanoma in situ (without invasion or with microinvasion only); Level II, invasion into the lamina propria only; and Level III, invasion into deep tissue (e.g., skeletal muscle, bone, or cartilage). Prasad's classification was a significant and independent predictor of survival in the subset of Ballantyne stage I mucosal melanomas. Pseudopapillary and sarcomatoid tumor architecture when tumor cells clustered around blood vessels resembling papillae, or when they resembled high-grade pleomorphic sarcoma, respectively, was correlated with worse disease-specific survival [18]. Unfortunately, Prasad's classification may be difficult to apply in non-tertiary care centers where rare diseases with challenging diagnoses and distinct staging systems are often misdiagnosed. Alternate staging systems were consequently designed to better predict outcomes and guide treatment. The AJCC TNM 2009 staging system for melanomas of the head and neck shown in Table 37.1 is not specific to mucosal presentations.

One alternate system used in routine practice is the more common TNM system for carcinomas of the head and neck, in which mucosal melanomas are similarly to their squamous counterparts based on the site of origin. A paper recently addressed the performances of the Ballantyne staging system modified by Prasad (Ballantyne/Prasad staging system), the American Joint Committee on Cancer (AJCC) TNM classification for mucosal melanomas (mmTNM), and the 2009 AJCC TNM classification for carcinomas of the nasal cavity and sinuses (carTNM) in 35 sinonasal mucosal melanoma patients, whose outcomes were compared retrospectively using the three systems [17]. The carTNM staging system better correlated to outcomes for patients with mucosal melanomas of the sinonasal tract. This work excluded oral cavity patients, who, as shown above, have distinct behavior.

37.1.5 Diagnostic Workup

The 2012 NCCN guidelines v1 states that a biopsy must be performed to make a diagnosis of mucosal melanoma, and pathology analyses include appropriate staining HMB-45, S-100, and Melan A. Mirror and fiber-optic examination should be performed as clinically indicated.

CT and/or MRI are indicated to determine anatomic extent of disease, particularly for sinus disease (Fig. 37.3). Because the appearance of melanoma on computed tomography (CT) scanning is not specific (homogeneously enhancing mass), some authors suggest the use of magnetic resonance imaging (MRI) for its diagnosis. Melanin has paramagnetic properties that can affect signal and produce a characteristic intensity pattern on MRI. The appearance is hyperintense on T1-weighted sequences and hypointense on T2-weighted sequences [19]. This is presumably related to chelated metal ions or free radicals known to exist in melanin. Although specific, this imaging pattern is not found in all mucosal melanomas, particularly amelanotic melanomas. Another MRI study

Table 37.1 7th edition of the AJCC TNM 2009 staging system for melanomas of the head and neck

Tumor			
T3	Epithelium/submucosa (mucosal disease)		
T4a	Deep soft tissue, cartilage, bone or overlying skin		
T4b	Brain, dura, skull base, lower cranial nerves, masticator space, carotid artery, prevertebral space, mediastinal structures, cartilage, skeletal muscle, or bone		
Staging group	Tumor	Node	Metastases
III	T3	N0	
IVA	T4a	N0	
IVB	T3–T4a/T4b	N1/Any N	
IVC	Any T	Any N	M1

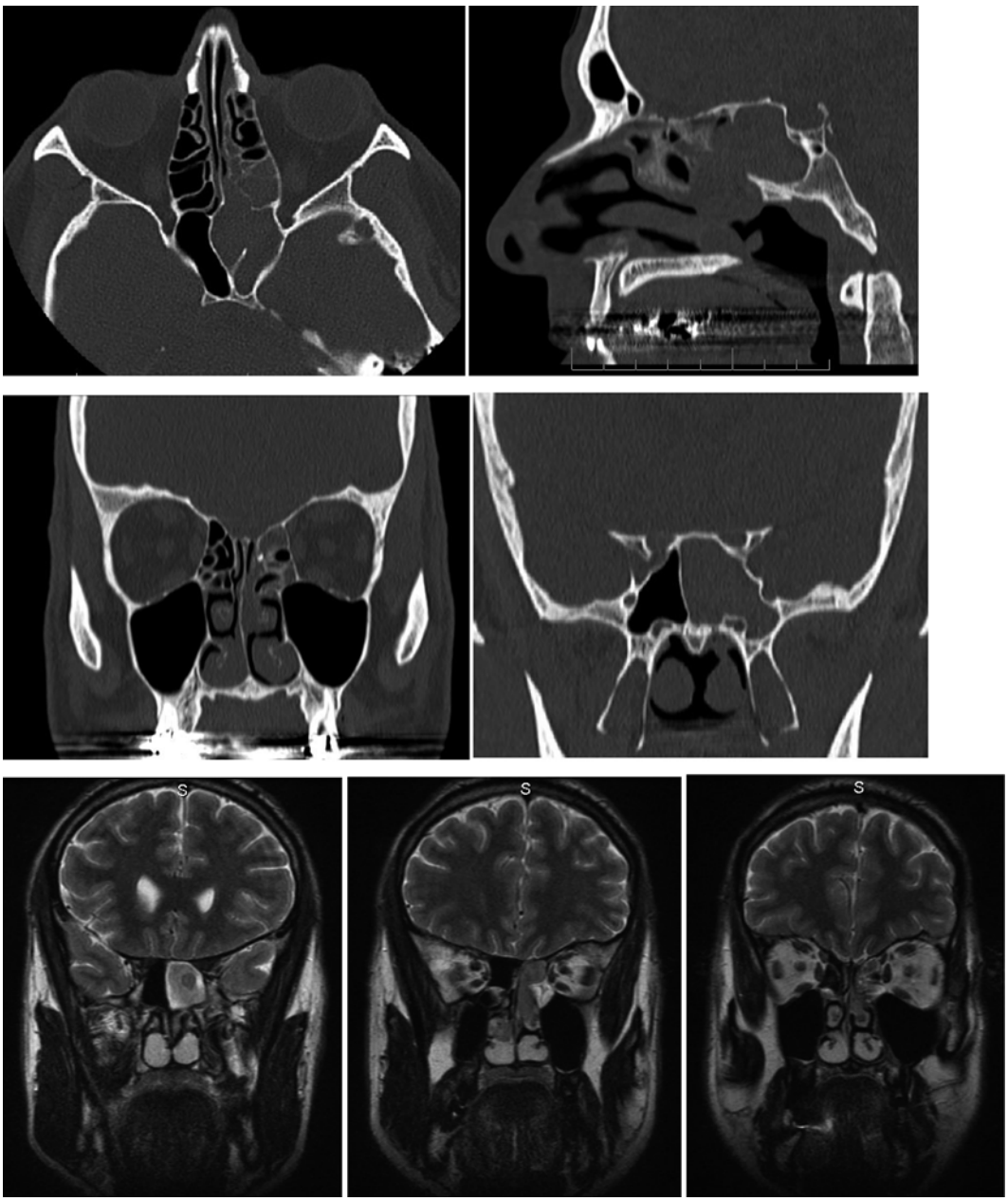

Fig. 37.3 A 50-year-old male patient with sinonasal mucosal melanoma (axial, coronal, and frontal CT scan and frontal MRI views showing the mass). DOD 2 years after diagnosis

investigated the role of the apparent diffusion coefficient (ADC) before carbon therapy to predict prognosis. ADC did not predict local control, but minimum ADC was a significant prognostic factor of distant metastasis-free survival and overall survival [20]. Other functional imaging modalities might also warrant investigations. For example, patients with mucosal malignant melanoma of the head and neck may benefit from 3′-deoxy-3′-[(18)F]fluorothymidine (FLT) and [(11)C]methionine positron emission tomography/computed tomography (PET/CT) imaging to predict their outcomes of carbon therapy [21]. [(11)C]methionine positron emission tomography/computed tomography (PET/CT) might also be of interest. Additionally, chest imaging is indicated, and PET/CT may be recommended to rule out distant metastases, given the high metastatic rate of mucosal melanomas.

37.1.6 Treatment

The 2012 National Comprehensive Cancer Network (NCCN) guidelines identify two distinct therapeutic strategies depending on sinus/nasal cavity or oral cavity, oropharynx, larynx,

and hypopharynx primary site. There are no randomized trials studying treatment modalities such as surgery, radiotherapy, or chemo-/immunotherapy specifically in mucosal melanomas. Similar to cutaneous melanomas, surgical resection is generally warranted for effective local control.

37.1.6.1 Surgery

Primary Site

Surgical resection with clear margins remains the treatment of choice, whenever feasible, with postoperative radiotherapy usually associated.

When primary tumor resection is planned, en bloc resection of the primary tumor should be attempted whenever feasible. This has historically been achieved with a double neurosurgical/head and neck surgical team approach for tumors invading the lamina criblae. However, such assessment should be tempered by the fact that endoscopic surgery does not always allow en bloc resection and yet provides seemingly comparable results in preliminary/historical studies. When perineural invasion is suspected or ascertained, proximal and distal sections should be carefully assessed clinically and pathologically using frozen section. Bone reconstruction should not be a limitation as far as functional reconstructive surgery is possible. For maxillary sinus tumors, the Ohngren's line runs from the medial canthus of the eye to the angle of the mandible. Tumors anterior to this line involve the maxillary infrastructure, while posterior ones involve the suprastructure. Surgical radicality can be assessed based on those criteria. The gold standard for sinonasal malignancies is open surgery by lateral rhinotomy, midfacial degloving, or craniofacial resection (combined sub-frontal and transfacial approach used when the skull base is involved) [22].

Considered that surgery should be performed whenever the disease is judged resectable, assessment of resectability [23] relies on proper assessment of a head and neck surgical oncologist before treatment to determine disease extent, assess the risk of morbi-mortality, assess current functional status, and evaluate for potential surgical salvage if initial treatment is nonsurgical. When a decision is made, multidisciplinary team validation should be obtained with respect to all patient treatment options including maximization of survival, organ preservation, and function sparing. Surgery planning should include assessment of the capability to obtain safe margins and reconstruct the operated area with anticipation of comprehensive rehabilitation with adequate dental, nutritional, and health behavior evaluation and intervention.

Unresectability criteria include T4b cancer (i.e., unresectable based on technical ability to obtain clear margins), involvement of the pterygoid muscles particularly when associated with severe trismus, pterygopalatine fossa involvement with cranial neuropathy, gross extension of tumor into the skull base (e.g., erosion of the pterygoid plates or sphenoid bone, widening of the foramen ovale), involvement of the brain parenchyma, deep extension into the eustachian tube and lateral nasopharyngeal walls, invasion (radiographical encasement defined as tumor surrounding the carotid artery 270°) of the common or internal carotid artery, direct extension of neck disease to involve the skin, direct extension to mediastinal structures, prevertebral fascia, or cervical vertebrae and/or presence of subdermal metastases (because they are considered as distant metastases).

Open approach is usually associated with non-negligible morbidity, especially when craniofacial resection is performed. On a 1193 patients' multicentric cohort, Gany et al. reported a postoperative complications' rate of 36.3 % (with 16.2 % of neurological complications) with 5 % of perioperative mortality [23].

In the past decade, endoscopic endonasal surgery has been become a critical therapeutic option for the management of sinonasal and skull base pathologies, even in oncology. Indeed, this mini-invasive technique provides a more accurate view of the anatomic structures and tumor extensions. The use of powered instruments (such as high-speed drills) may allow wide resections such as performed by open approach. Moreover, the reduced morbidity of this technique is linked with decreased surgical time and hospital stay, less discomfort, and improved cosmetic outcome [22].

Clear margins are difficult to assess in sinonasal malignancies because of the complex anatomy and the proximity with critical structures (such as the brain, orbit, internal carotid artery, etc.). In skull base surgery, piecemeal is often performed even by open surgery. En bloc resection and wide exposure of the tumor are, indeed, quite difficult to assess. Moreover, piecemeal resection of malignant tumors does not seem to compromise oncologic results as long as clear margins are confirmed with frozen section [24–26]. Whatever the approach and the type of resection (en bloc or piecemeal), lateral-oriented margins have to be taken at the end of the procedure. Tumor removal is considered complete as soon as all margin samples are negative (but the diagnosis is made difficult by the small frozen section samples) [26].

Endoscopic surgery seems, in selected cases, to have the same oncologic results with less morbidity and improvement in quality of life [27, 28]. Main contraindications to endoscopic approach are lateral or anterior involvement of frontal sinus, lateral involvement of the dura, invasion of the brain, involvement of the facial skin, or tumor extensions requiring orbital clearance or total maxillectomy [22]. Thus, endoscopic resection has to be planned with the intention to remove the tumor with the same margins as might be achieved by an open procedure. If not possible, open surgery might be considered. Rarity, histological heterogeneity and

long natural history of sinonasal malignancies make it difficult to perform prospective studies comparing endoscopic resection with open approach.

In mucosal melanoma, prognosis is poor with 5-year overall survival between 20 % and 30 % (8–48 %), median overall survival of 24 months, and median disease-free survival around 21 months [29]. Death comes from both local recurrence and metastatic disease. This poor prognosis despite major open resections supports the development of mini-invasive surgery with various studies showing comparable outcomes. Lund et al. in a 115 cases single-institute cohort of sinonasal mucosal melanomas observed no difference in prognosis using open approach or endoscopic surgery [29].

Moreover, perioperative observation of pluri-focal disease (even submucosally, far from the primitive site) could explain, at least partially, this therapeutic failure.

Margins

A common recommendation historically consists of upfront surgical resection with clear margins. This definition may be challenged by the use of endoscopic minimally invasive surgery as discussed below. Recommended adequate margins in mucosal melanomas of the head and neck are 1.5–2 cm of visible and palpable normal mucosa. Frozen-oriented section margin assessment should be recommended intraoperatively to avoid unassessable margins (depending on type of surgical section) or residual disease. Clear margins are defined as the distance from the invasive tumor front that is 5 mm from the resected margins. Close margins are <5 mm without contact with tumor. Shrinkage can be observed after fixation. Obtaining adequate margins may require resection of a functionally relevant adjacent structure. Reconstructive closure with local/regional flaps or other grafts is performed according to team's expertise and extent of anatomic defect. Management of major cranial nerves is determined by the pre- and intraoperative assessment, with conservation as a rule except in case of macroscopic involvement.

The notion of a clear margin is disputable given the increasing use of minimally invasive surgery and endoscopic approaches (as an alternative to radical open surgery) where the definition of margins is complex. Such approaches dramatically change the way the tumor is removed, and fragmented tumor pieces with close/uncertain margins are common. This therapeutic trend, although not sustained by a strong level of evidence (randomized trials being difficult to perform in such rare diseases), is supported by the relevance of not choosing highly morbid options in patients whose disease has a very high metastatic potential in the first years following diagnosis even with radical surgery.

Neck Management

The performance of a neck dissection is part of the treatment of the primary tumor. Neck dissection should be based either on the observation of macroscopically involved nodes or on a risk level estimation generally over 10 %. Over 25 % of patients with oral cavity melanoma present with neck metastasis, while only 6 % of sinonasal melanoma patient present initially with neck involvement. Additionally, a thickness of 2 mm has been associated with poorer outcomes in oral cavity mucosal melanomas [30] and should probably warrant elective neck dissection. Tumor sites of bilateral lymphatic drainage or approaching the midline warrant bilateral neck dissection. When indicated, the extent of neck dissection is performed based on the nodal areas involved and site of primary disease, similar to surgical guidelines in carcinomas. Elective neck dissection might be omitted if postoperative radiation is planned. This decision should however be confirmed by the multidisciplinary team.

Consistent with the rarity of cervical involvement on initial presentation in sinonasal mucosal melanomas, prophylactic neck dissection cannot be advocated. In sinonasal cases, recurrence tends to be either local or distant. Even the regional control of a neck dissection does not provide much benefit. There is no sufficient evidence to date to recommend neck dissection in many of these patients given the high likelihood of distant metastatic spread. Overall there is little role for nodal intervention. However, sentinel lymph node biopsy might represent an option to be investigated in patients with a relatively high nodal risk (advanced T stage, perineural invasion, emboli, etc.

For oral mucosal melanoma, prophylactic neck dissection has been debated more due to the greater frequency of regional metastasis upon initial presentation. The rate of regional recurrence in oral mucosal melanomas is much greater—estimated around 70 %. This increased rate of recurrence has led to more frequent prophylactic neck dissections in treatment of oral mucosal melanoma. It may result in more accurate staging, yet the benefit on survival outcomes is to be demonstrated. In N0 necks, in particular in oral cavity melanomas, sentinel lymph node biopsy and prophylactic neck dissection are yet investigational. Data are extrapolated from cutaneous melanoma where the role of sentinel lymph node biopsy/dissection is still being questioned in several randomized trials. Like in cutaneous melanomas, improved staging accuracy may not necessarily result in improved outcomes. Additionally, sentinel node biopsy has been reported as inefficient in preventing delayed neck metastasis.

37.2 Radiation Therapy

37.2.1 Radiobiological Aspects

One particular aspect of melanoma cells is the typical broad shoulder of their survival curves suggesting a high capacity for repair of sublethal DNA damage. A parameter of fractionation sensitivity of tissues is the "α/β ratio." A high α/β

ratio indicates low fractionation sensitivity, whereas tissues with low ratios are more sensitive to high doses per fraction. The α/β values for cutaneous melanomas range from 1.6 to 6 Gy. Although a variety of chromosomal abnormalities may induce variations in the α/β ratio of mucosal melanomas [16], it is estimated that mucosal melanomas are in the same order of α/β ratio as cutaneous melanomas. These data support the use of fraction sizes higher than 4–6 Gy to overcome the relative radioresistance of melanoma cells. Better local control and/or survival might be expected when hypofractionation is employed [31]. However, a limitation of using high total dose with hypofractionation for tumors in sinonasal areas is their proximity to the optical structures and the central nervous system. These tissues are highly sensitive to large fractional doses, and one has to be wary of a potentially increased complication risk.

37.2.2 Clinical and Technical Aspects of Radiation Therapy

Radiation therapy has typically been advocated in the adjuvant setting based on several retrospective studies yielding consistent results. Temam et al. demonstrated greater improved local control (62 % vs 26 %) in patients treated surgery and radiation therapy versus those with surgery alone [32]. Similarly, Owens et al. found a similar benefit in local control (83 % vs 55 %) in patients receiving surgery with postoperative radiation therapy compared with those receiving surgery alone [33]. Krengli and the International Rare Cancer Network confirmed a benefit of adjuvant radiotherapy with 3-year control rates of 57 % and 71 % after surgery alone versus surgery and radiotherapy [34]. Overall and disease-free survival rates, respectively, were 41 % and 31 % at 3 years and 14 % and 22 % at 10 years, being as poor as in other published series. Stage I and presence of visible pigment at diagnosis were favorable prognostic factors, while radiotherapy was not in multivariate analysis [34]. More recently, Benlyazid and the French group of head and neck surgeons GETTEC (Groupe d'Etude des Tumeurs de la Tete et du Cou) [35] reported the patterns of failure according to treatment modality, with an emphasis on the role of postoperative radiotherapy in 160 localized head and neck mucosal melanoma patients treated during a 28-year period in a multi-institutional setting. After adjusting for tumor stage (T1/T2 vs T3/T4), locoregional control was significantly improved in irradiated patients. Regardless of their treatment, patients who had a locoregional relapse during follow-up had an increased risk of subsequent distant metastasis and death. Further, the higher rate of distant metastasis in the radiotherapy group was due to more advanced disease in this group, and this unfavorable bias might partially explain why radiotherapy has no impact on survival [35]. Although there are contradicting studies, these four retrospective studies are among the largest and consistently show a benefit of radiotherapy on local control. Based on these pivotal although retrospective studies, an American panel of experts has adopted adjuvant radiation therapy in their NCCN guidelines [36].

It should be noted, however, that adjuvant radiation therapy only improves local control and disease-specific survival but not overall survival. The major reason for this observation is that a majority of patients die from metastases. However, optimizing local control is relevant to preserve quality of life. Most studies being retrospective, such data are still lacking. Another limitation of the pivotal papers is their heterogeneity. The current recommendation advocates radiation therapy regardless of disease extent and thickness, but there likely is a subset of patients who do not benefit from adjuvant irradiation. For example, limited TNM T stage N0M0, stage I level I, melanomas of the nasal cavity might be controlled with surgery alone, at the price sometimes of repeated surgeries over years and with good functional results (personal experience [37]).

Classical fractionation consisting of 1.8–2 Gy per fraction up to 60–70 Gy (and up to 74 Gy in unresectable disease) over 6–7 weeks using tridimensional irradiation is currently a recommended scheme. The current practice of IMRT/VMAT/tomotherapy can logically be applied to these tumors owing to the proximity of sensitive organs at risk and tissues, despite limited descriptions in the medical literature to date. Intriguingly, the current level of evidence does not support the use of hypofractionation despite the low α/β ratio of these tumors. Hypofractionation (formally defined as doses over 2.5 Gy per fraction) can be used with any technique and is a common fractionation in stereotactic irradiation protocols (using doses per fraction of up to 20 Gy per fraction, made possible by the steep gradients and high accuracy of dose delivery that this technique allows).

Target delineation and optimal dose distribution require close cooperation and interdisciplinary management and experience in head and neck imaging, as well as expertise in the patterns of disease spread. For sinonasal mucosal melanomas, clinical target volumes include the gross tumor (based on preoperative imaging assessment and operative findings) plus 2–3-cm margins or anatomic compartment. For oral cavity and pharyngeal melanomas, the same margins are applied around the gross tumor. Elective prophylactic neck irradiation (to 50 Gy) is recommended unless the neck was operated on and is pathologically negative. However, this recommendation is controversial, as neck irradiation often has additional acute and late toxicity and does not impact overall survival. In cases of more than two pathologically involved nodes, one single node exceeding 3 cm, or extracapsular nodal disease, the neck should also be irradiated according to recommendations used in head and neck

carcinomas up to 60–66 Gy, and the indication is comforted from Australasian data in cutaneous head and neck melanomas. While hypofractionation using large doses per fraction and 3D irradiation is quite a standard in cutaneous melanomas, especially considering their low alpha-beta ratio (the lower the ratio, the higher the impact of higher doses per fraction), its use in mucosal sites has been limited by the proximity of critical healthy tissues. However, this may change with technological advances. IMRT has been shown to be useful in reducing long-term toxicity in head and neck cancers by reducing the dose to healthy tissues. Another area of progress lies in stereotactic irradiation which creates very steep dose gradients, advantageous for nearly organs at risk.

Additionally, the physical advantage of charged particle therapy in terms of dose distribution (the so-called Bragg peak) has emerged as way to overcome the anatomic limitations of hypofractionation. In addition, carbon therapy offers a radiobiological advantage, i.e., has better biological efficacy with a similar physical dose deposition. In conjunction, the physical and biological aspects of carbon therapy have resulted in an increasing number of clinical investigations using carbon therapy to treat head and neck mucosal melanomas in countries that are highly equipped with carbon therapy, such as Japan. A landmark paper with that respect was published by Yanagi et al. [38]. This large prospective series of 72 patients treated with moderately hypofractionated carbon therapy (52.8 GyE to 64 GyE given in 16 fixed fractions over 4 weeks) between 1994 and 2004 showed a surprisingly high 5-year local control rate of 84 %. However, the 5-year overall and cause-specific survival rates were 27 % and 40 %, respectively. Of note, 85 % of the patients who developed distant metastases were free from local recurrence. Additional studies have suggested that carbon therapy techniques are safe and effective, achieving high local control rates and acceptable toxicities. These studies have also suggested that these radiation therapy modalities may be sued in lieu of surgery and may yield comparable results as with surgery. This may be of utmost importance when the extent of the planned surgery is associated with major morbidity.

An additional issue to be investigated is the impact of the increasing use of endoscopic minimally invasive surgery on the prescription of radiotherapy. Practically, margins are more difficult to assess with fragmented surgery. This questions the fact whether margins should be considered as positive (at least microscopically) and thus whether the radiation therapy dose advocated should be increased in these situations (high dose to the whole tumor bed and preoperative gross tumor volume to 66 Gy).

Primary radiation therapy can only be advocated for unresectable disease or medically inoperable patients. Data are limited to a small number of cases. Gaze et al. demonstrated complete clinical response in 8/13 patients with primary radiation therapy alone. Other articles, however, did not show a benefit for primary irradiation. This option may be better explored with the new technologies that radiation therapy now allows, i.e., techniques that allow hypofractionation with reasonable sparing or critical structures, such as photon-based stereotactic irradiation or intensity-modulated radiation therapy or proton therapy (Fig. 37.4a–c). Less accessible but of increasing interest due its radiobiological advantage and excellent tumor control rates is carbon therapy. Perhaps counterintuitively, no significant difference in local control rates in head and neck melanomas was observed in a retrospective comparison between proton therapy and carbon therapy [39]. Thus the impact of these advanced techniques warrants further analyses.

37.3 Systemic Treatments

Owing to the limited chemosensitivity of melanomas, systemic treatments are only advocated for mucosal melanomas in the metastatic setting.

37.3.1 Adjuvant Systemic Therapy

Although most patients with mucosal melanoma have micrometastases at the time of diagnosis of the primary tumor, there is limited data on the role of adjuvant therapy. One randomized prospective study was conducted in China and involved patients with completely resected mucosal melanoma of the head/neck, genitourinary, and anorectal regions. Results of this study showed that patients treated with chemotherapy consisting of 6 cycles of adjuvant cisplatin and temozolomide had improved progression-free and overall survival compared to both high dose interferon alpha-2b and observation [40]. Patients with head/neck mucosal melanoma (57 patients) represented the largest subgroup in this study, and subgroup analysis indicated a benefit for chemotherapy in patients with this specific type of mucosal melanoma. Nevertheless, this was a single-institution study, and it is possible that the biology of mucosal melanoma differs in Chinese patients that composed this study. While adjuvant chemotherapy could be discussed with patients based upon the results of this study, additional prospective evaluation is necessary to confirm these findings in a larger, more diverse patient population before chemotherapy is accepted as the standard of care in adjuvant treatment.

Some other retrospective studies have suggested an advantage of adjuvant chemotherapy on survival, but the retrospective nature and sample size [41] are limiting factors to constitute a sufficient level of evidence to advocate strongly for this approach. It is possible that newer therapies such as ipilimumab, antibodies targeting the programmed cell death-1 (PD-1) axis, and c-KIT tyrosine kinase inhibitors (based on the higher rate of c-KIT genetic aberrations in mucosal melanoma) will ultimately have a role in the adjuvant treatment of

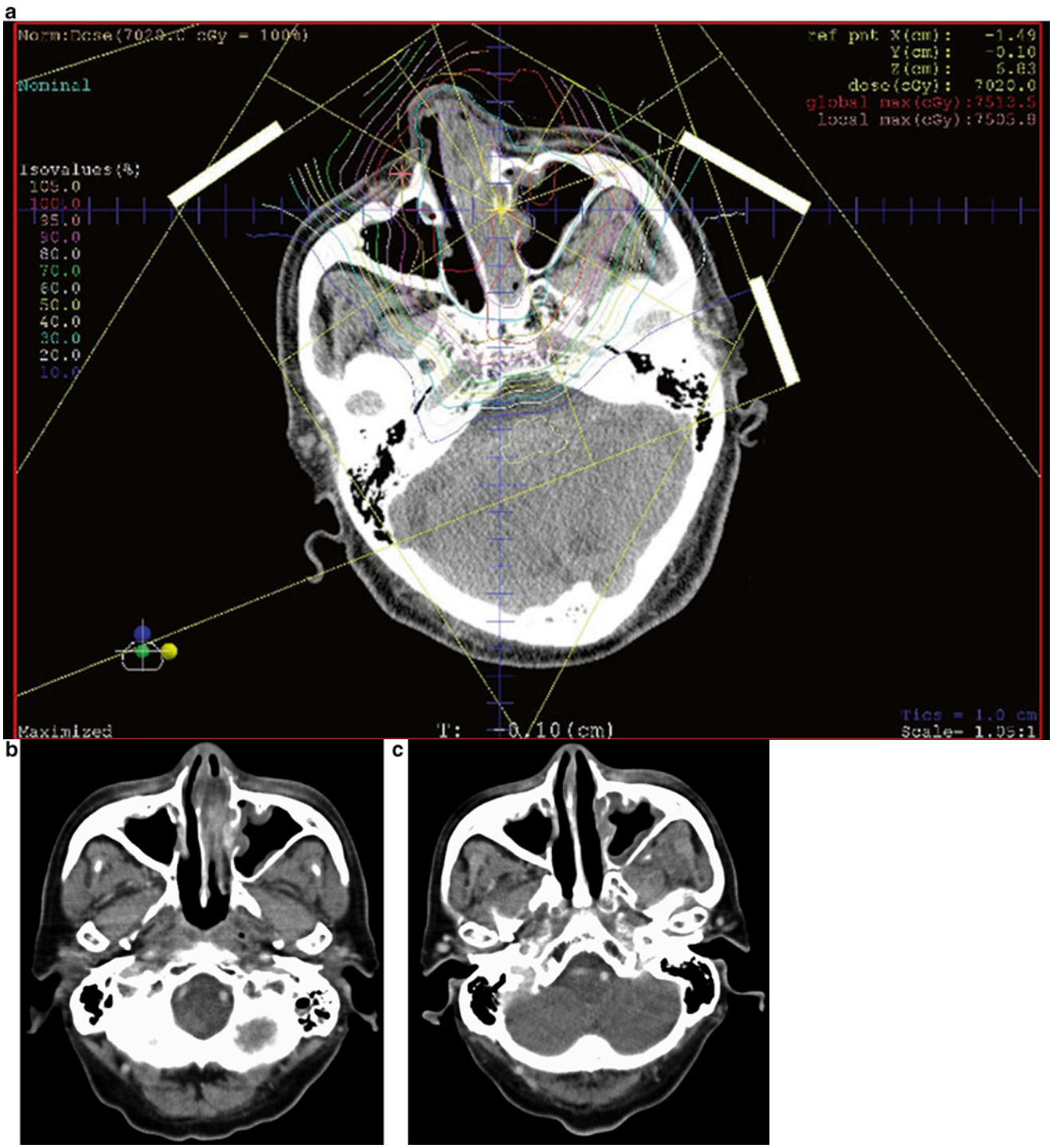

Fig. 37.4 A 78-year-old male with mucosal melanoma of the left nasal cavity T3N0M0 (UICC 7th ed) treated with (**a**) proton therapy 70.2 GyE/26 fractions. (**b**) Five months response shows partial response and (**c**) 11 months complete response

patients with head and neck mucosal melanoma. Further study is needed, and given the rarity of this type of melanoma and the even greater rarity of patients with specific molecular subsets within this melanoma subtype, future clinical trials will need to be carefully designed and powered to enable meaningful results in a reasonable timeframe.

37.3.2 Systemic Therapy for Metastatic Disease

Patients with metastatic disease from a mucosal primary have been, until recently, commonly treated with standard regimens for cutaneous melanoma, extrapolating from the literature

largely derived from patients with cutaneous melanoma. Treatment modalities used for advanced cutaneous melanoma have historically included dacarbazine, temozolomide, the Dartmouth regimen (dacarbazine, cisplatin, carmustine, and tamoxifen), biochemotherapy, and high-dose interleukin-2 [42–44]. The response rate for single-agent treatment with dacarbazine in advanced cutaneous melanoma was reported to be around 20 % in a 30-year overview [45], whereas more recent, large trials suggest it to be lower than that (7–14 %) [46, 47]. Combinations of chemotherapy result in higher response rates but are associated with significant toxicity and have not been proven to increase overall survival [42].

The landscape of systemic treatments for advanced melanoma has dramatically changed with a better understanding of specific oncogenic mutations such as the BRAF and c-KIT mutation which can be targeted with novel therapeutics. These advances are directly relevant to patients with mucosal melanoma given the higher proportion of c-KIT mutations in mucosal melanoma compared to patients with cutaneous melanoma. Curtin et al. were among the first to show c-KIT genetic alterations in melanomas [48]. They showed that c-KIT amplification/mutation occurred in 39 % of mucosal melanomas, but none of non-chronic sun-damaged cutaneous melanoma cases. Other studies reported smaller than expected prevalence rates of these mutations in mucosal melanoma in the 5–22 % range [49–51]. Mucosal melanomas also exhibit amplifications or increased copy numbers of the 4q12 locus by comparative genomic hybridization. Mutations, such as those including the activating K462E mutations of the c-KIT kinase domain, which are known to render sensitivity to imatinib (a tyrosine kinase inhibitor) in other tumor types, are also commonly seen in mucosal melanomas. The presence of c-KIT genetic aberrations in patients with mucosal melanoma is therapeutically relevant given the development of c-KIT inhibitors such as imatinib. In patients with c-KIT genetic aberrations treated with imatinib in prospective phase II studies, depending on the type of mutation observed, objective responses have been seen [52, 53]. It is likely that the specific type of c-KIT mutation is relevant as most responses have been seen in patients with exon 11 and 13 mutations, and aberrations affecting other exons may be less responsive to c-KIT inhibition. Since BRAF mutations can occur in patients with mucosal melanoma, albeit at a less common frequency than cutaneous melanoma, it is worth testing patients for BRAF mutations to enable them to benefit from BRAF-targeted approaches [46, 54].

Immunotherapeutic approaches have also led to dramatic recent successes in patients with melanoma in general [52, 55, 56], but the efficacy in patients with mucosal melanoma is less well known. Several retrospective series have shown that some patients with mucosal melanoma can respond to ipilimumab [57–59]. Additional investigations are being continued to clarify the role of PD-1 inhibitors in patients with mucosal melanoma, but anecdotal responses are being reported [60].

37.3.3 Follow-up and Surveillance Guidelines

Similar to high-risk cutaneous melanoma, close follow-up with thorough physical examinations and appropriate imaging studies for symptomatic patients is necessary for patients with mucosal melanoma after surgical resection. A recommended follow-up program includes history and physical examination every 1–3 months at year 1, every 2–6 months during year 2, every 4–8 months in years 3–5, and annually from years 5 and on. Posttreatment baseline imaging of primary (and neck if treated) is recommended within 6 months of treatment with further reimaging only indicated based on signs/symptoms. Follow-up exams are chosen based on risk of relapse, second primaries, treatment sequelae, and toxicities. Thyroid-stimulating hormone (TSH) is recommended every 6–12 months if the neck was irradiated, with speech/hearing and swallowing evaluation and rehabilitation as clinically indicated, smoking cessation and alcohol counseling as clinically indicated, and dental evaluation.

37.3.4 Prognosis and Outcomes

Primary melanoma arising in the mucous membranes is an aggressive disease [61]. The best likelihood for favorable outcome is early detection and excision, but as stated, many patients present with advanced disease at diagnosis. Even for patients with presumed early-stage disease, the outcome is generally poor, possibly because of occult metastases at presentation. Local treatment failure is a significant problem for most treated patients, and distant metastases are also very common. Local recurrence is usually a harbinger for concurrent or subsequent distant metastases. There are very few data available regarding the prognosis of patients with metastatic mucosal melanoma because most studies coalesce all metastatic cases regardless of the site of the primary. Distant spread in general is associated with rapid clinical deterioration and a short survival time.

Melanoma of the mucosal membrane appears to have a lower prevalence of regional lymph node metastases than melanoma of the skin, both at presentation and at recurrence. Lesions of the oral cavity have a higher prevalence than those occurring in either the nasal or the pharyngeal cavities. Overall, 18 % of patients have lymphatic metastases at presentation. The average distant metastatic rate at presentation is 10 %. Primary site recurrence occurs in approximately 40 % of nasal cavity lesions, 25 % of oral cavity lesions, and 32 % of pharyngeal tumors. Overall

Table 37.2 Main differences between mucosal and cutaneous melanomas

	Skin	Mucosal surfaces
Mean age at diagnosis (years old)	55	67–71
Ethnic origin	White >>> Black	White >> Black
Risk factors	Sun exposure	Unknown
Staging	AJCC	AJCC > Ballantyne +/− Prasad
Presentation	<1/3 with advanced stage	>1/2 with advanced stage
Amelanotic/achromic	1.8–8.1 %	20–25 %
Activating *c-KIT* mutations	<5 %	15–22 % Caution required with respect to such observations in invasive component
$BRAF^{V600E}$	50–60 %	Rare/irrelevant
Surgery (primary site)	Main treatment	Main treatment Controversy: similar local control rates with carbon therapy as with surgery plus radiation therapy
Surgery (neck)	Neck dissection for node-positive melanomas Controversy: sentinel node biopsy	Neck dissection for node-positive melanomas Prophylactic neck dissection in oral cavity subsites Role for sentinel node biopsy to be determined
Adjuvant radiation therapy	No role	Generally recommended Recommended: modern techniques, fractionation (counterintuitive given radiobiological characteristics) Controversy: may be omitted in a subset of T1 nasal cavity mucosal melanomas, carbon therapy versus proton therapy
Systemic therapy	Adjuvant: controversial Metastatic: based on mutational status Dacarbazine, temozolomide, the Dartmouth regimen biochemotherapy, and high-dose interleukin-2, or ipilimumab, PD-1 inhibitors	Adjuvant: not used despite high metastatic rate Metastatic: impact of mutational status to be fully investigated K462E mutations of the c-KIT kinase domain might indicate sensitivity to imatinib Promising immunotherapy with ipilimumab Ongoing investigations on PD-1 inhibitors

primary site recurrence ranges from 55 % to 66 % and 16 % to 35 % for nodal recurrence. Most recurrences occur within the first 3 years (Table 37.2).

37.4 Conclusion

Mucosal melanomas of the head and neck carry a poor prognosis. Early diagnosis followed by surgical excision remains the mainstay of treatment, and postoperative radiation therapy is almost always recommended to achieve local control. Current controversies include the role of minimally invasive endoscopic approaches, in particular with their challenges in terms of margin assessment and radiation therapy dose. There is also a need for a better level of evidence for sentinel node biopsy in patients with mucosal melanoma who do not have palpable lymphadenopathy. As for the modalities of radiation therapy, the current level of evidence pleads in favor of optimized tridimensional conventionally fractionated radiation therapy. However, technological advances suggest that carbon therapy might be preferred to proton therapy because of a radiobiological advantage and proton therapy to photon-based irradiation (IMRT/VMAT/tomotherapy) because of dose distributions and safer ability toward hypofractionation. The domain of medical oncology and genetic research may provide further clues, especially in light of benefits noted of KIT inhibitors and the proportion of mucosal melanomas with this genetic aberration. Finally, mucosal melanomas of the head and neck deserve central pathology reviews and case discussions within multidisciplinary rare disease networks, aware of all the above mentioned challenges. Adequate methodology needs to be developed for rare diseases with specific therapeutic challenges, and patient associations, patient-reported outcomes, and quality-adjusted life-years (QALY) should be part of the assessment of the treatment modalities.

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Head and Neck Cutaneous Melanoma

38

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Abstract

Melanoma is an aggressive skin malignancy whose incidence is on the rise, partly due to an increase in sun exposure and tanning practices and partly due to improved detection. Classically it presents as a pigmented lesion with many of the following features: asymmetry, border irregularity, color variegation, and diameter greater than 6 mm. The major subtypes are superficial spreading melanoma, nodular melanoma, acral-lentiginous melanoma, and lentigo maligna melanoma. Excisional biopsy is recommended for diagnosis and staging. Melanomas are preferably treated by surgical resection, and reconstruction of the defect is delayed until negative margins are confirmed on final pathology. Sentinel lymph node biopsy can be considered, as biopsy-based neck dissection improves disease-free survival in patients with intermediate-thickness melanomas who have nodal metastasis. It remains an open question whether micrometastasis mandates completion neck dissection. Patients with stage IIB, stage IIC, or stage III melanoma are candidates for adjuvant therapy with interferon or peginterferon. Those with distant metastases may undergo immunotherapy with interleukin-2 or with antibodies to CTLA-4 or PD-1, while stage IV patients with a BRAF mutation are candidates for BRAF inhibitors or MEK inhibitors.

Keywords

Melanoma • Superficial spreading melanoma • Nodular melanoma • Acral-lentiginous melanoma • Lentigo maligna melanoma • Desmoplastic melanoma • Sentinel lymph node biopsy • MSLT • Immunotherapy • BRAF

38.1 Epidemiology

The United States is expected to see 76,100 new cases of cutaneous melanoma in 2014, making it the fifth most common cancer in men and the seventh most common cancer in women [1]. It is estimated that 2.9 % of white American men and 1.9 % of white American women will develop a cutaneous melanoma in their lifetime [1]. The incidence of cutaneous melanoma has been rising by 2.1 % every year for American men and by 2.3 % every year for American women [2].

Globally, nearly 85 % of cutaneous melanomas occur in developed countries [3]. Australia and New Zealand have incidence rates 2–3 times higher than anywhere else; in Europe, the disease is most frequently diagnosed in Switzerland, Denmark, Norway, and Sweden [3]. The past few decades

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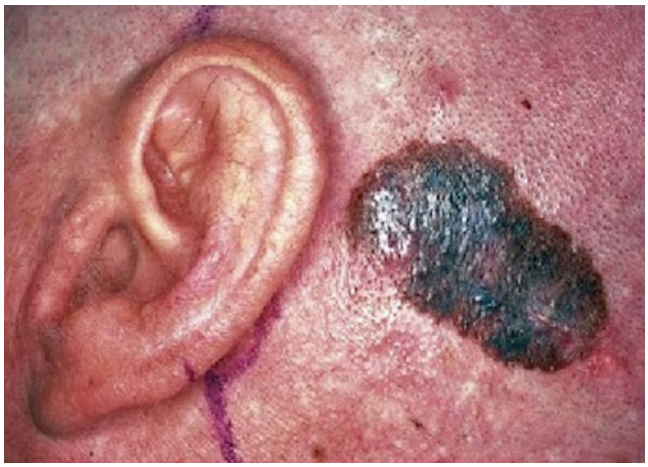

Fig. 38.1 Postauricular malignant melanoma [Reprinted from Shah JP, Patel SG, Singh B (eds). Jatin Shah's head and neck surgery and oncology, 4th edition. Philadelphia, PA: Elsevier; 2012. Copyright© 2012 by Jatin P. Shah, Snehal G. Patel, Bhuvanesh Singh.]

have seen a uniform increase in the incidence of cutaneous melanoma across nations with predominantly fair-skinned populations, attributed in part to the rising popularity of outdoor leisure activities and indoor tanning and in part to earlier detection of malignancy [3]. Thanks to the "ABCD" mnemonic originally disseminated by New York University in the 1980s, there is enhanced public awareness of the early warning signs of melanoma—asymmetry, border irregularity, color variegation, and diameter greater than 6 mm (Fig. 38.1) [4].

38.2 Pathogenesis

The most frequent chromosomal alterations in cutaneous melanoma are the loss of 9p (81 %), which contains the CDKN2A locus, and the loss of 10q (63 %), which contains the PTEN locus [5]. Loss of CDKN2A lifts the inhibition on phosphorylation of Rb, allowing the cell cycle to continue from G1 to S phase, whereas loss of PTEN lifts the inhibition on PI3K signaling.

Common gain-of-function mutations are the V600E substitution in BRAF (40–50 % of melanomas) and activating mutations in NRAS (15–20 %) [5]. Both BRAF and NRAS mutations lead to increased signaling through the MAPK pathway. More recently, mutations at the promoter of telomerase reverse transcriptase (TERT) have been discovered in up to 71 % of melanomas, leading to augmented transcription of TERT and facilitating the immortalization of melanocytes [6].

38.3 Clinical Presentation

The four major clinical subtypes of cutaneous melanoma are superficial spreading melanoma (SSM), nodular melanoma (NM), acral-lentiginous melanoma (ALM), and lentigo maligna melanoma (LMM) [7].

Superficial spreading melanomas (Fig. 38.2a) account for 65 % of melanomas. These arise primarily on the intermittently sun-exposed skin of the trunk and extremities, on patients with multiple melanocytic nevi. SSM begin with a radial growth phase, manifesting as variegated patches of brown, gray, or black, and then enter a vertical growth phase in which they acquire thickness. Histopathologically, one sees what is called a pagetoid growth pattern: nests of enlarged melanocytes scattered upward within the epidermis [8].

Nodular melanomas (Fig. 38.2b) constitute 20 % of melanomas and tend to grow more aggressively. They are more invasive, are more frequently ulcerated, and exhibit more mitoses than SSM. However, they are also more likely to evade notice as they often display border regularity and homogeneous color [7].

Acral-lentiginous melanomas (Fig. 38.2c) make up about 10 % of melanomas and characteristically occur on the palms, on the soles, or under the nails. They commonly involve the sweat glands. Ultraviolet radiation does not appear to be a causative factor in ALM, and they occur at similar frequencies across patients of different ethnic backgrounds [8].

Lentigo maligna melanomas (Fig. 38.2d) make up the remaining 5 % of cutaneous melanomas. These grow in chronically sun-damaged skin with high cumulative UV exposure and do not typically arise from a precursor nevus. LMM are poorly circumscribed; on the histologic level, they show a lentiginous growth pattern, in which melanocytes are solitarily spaced along the basilar epidermis in such a way that it is difficult to tell where the lesion ends and normal skin begins [8].

Among the rarer subtypes that deserve mention is desmoplastic melanoma, 37–68 % of which occur in the head and neck region. These are distinguished by their frequent perineural invasion and extension along nerves, as well as their high local recurrence rate [9].

38.4 Workup

When faced with a pigmented skin lesion suspicious for melanoma, the clinician may choose to evaluate it with dermoscopy or with confocal microscopy, if these tools are available and if she/he has the experience. Diagnosis will still ultimately require tissue. It is ideal not to perform a shave or punch biopsy, as this will miss the full depth of the lesion and result in inadequate management. Both the British Association of Dermatologists' guidelines and the American Academy of Dermatology's guidelines recommend excisional biopsy for diagnosis [10]. Prior to biopsy, photographic documentation is advisable to record the precise anatomic site and physical characteristics of the lesion so that definitive excision can be planned accurately.

In asymptomatic patients with localized melanoma, blood tests and imaging are not required for workup [11]. Imaging tests such as chest X-ray, CT, PET, and ultrasound have a high false-positive rate and low sensitivity for occult metastases.

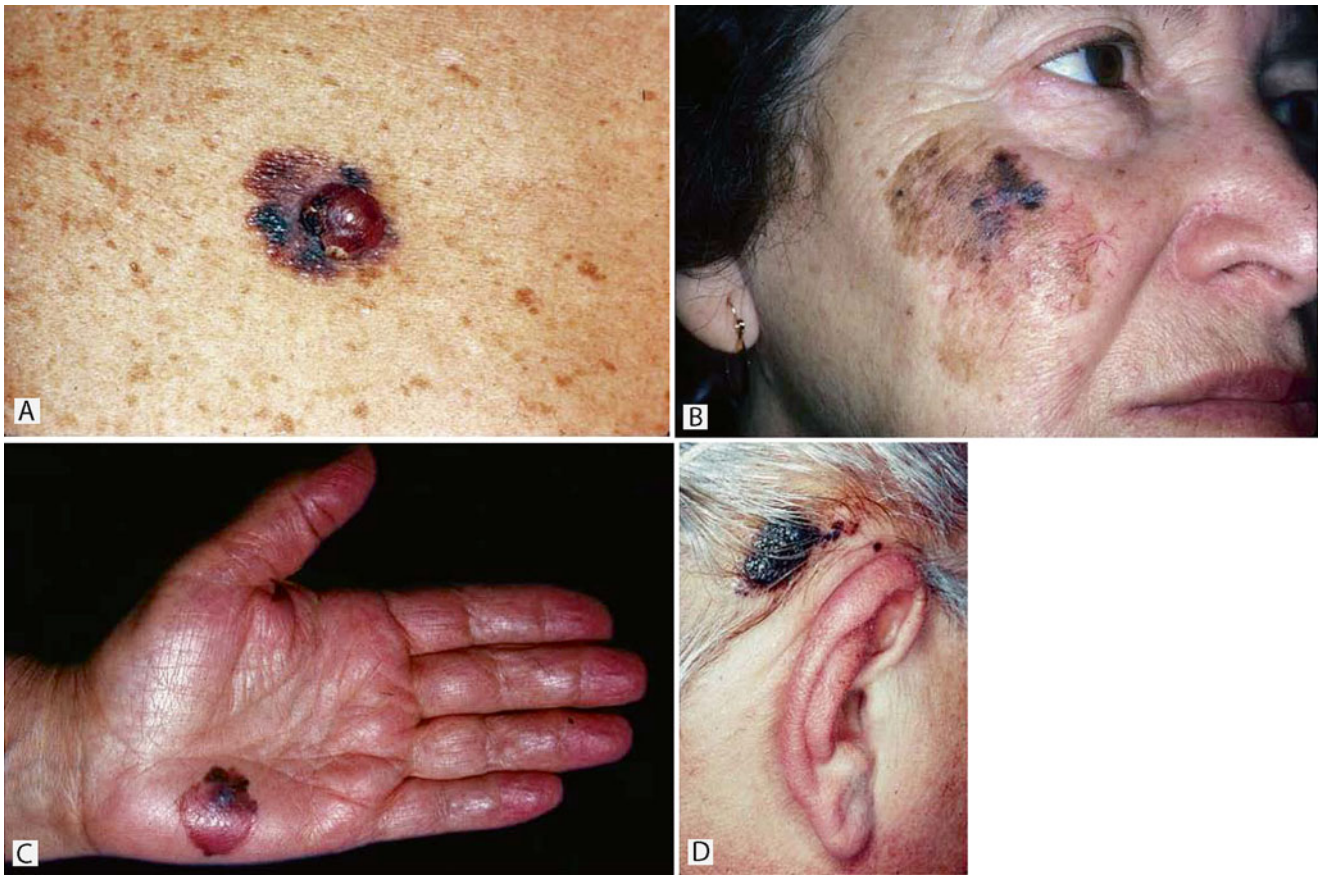

Fig. 38.2 Clinical variants of melanoma. (**a**) Superficial spreading melanoma. (**b**) Nodular melanoma with satellitosis. (**c**) Acral-lentiginous melanoma. (**d**) Lentigo maligna melanoma [Reprinted from Shah JP, Patel SG, Singh B (eds). Jatin Shah's head and neck surgery and oncology, 4th edition. Philadelphia, PA: Elsevier; 2012. Copyright© 2012 by Jatin P. Shah, Snehal G. Patel, Bhuvanesh Singh.]

38.5 Staging

The American Joint Committee on Cancer (AJCC) staging system for cutaneous melanoma was most recently updated in 2010 with the seventh edition (Tables 38.1, 38.2, 38.3 and 38.4) [12]. Derived from multivariate analysis of nearly 39,000 patients, this was the first version to include tumor mitotic rate as a T staging criterion, as well as the first to incorporate the serum lactate dehydrogenase (LDH) level in M staging [13].

The 5-year survival rate ranges from 97 % for patients with T1aN0M0 melanoma to 53 % for patients with T4bN0M0 melanoma. Five-year survival ranges from 70 % for patients with T1-4N1aM0 melanoma to 39 % for patients with T1-4N3M0 melanoma. One-year survival rates are 62 % for M1a, 53 % for M1b, and 33 % for M1c melanomas [13].

Table 38.1 T staging of melanoma

T stage	Thickness (mm)	Ulceration/mitoses
Tis	NA	NA
T1	Up to 1.00	a. Without ulceration and mitosis < 1/mm^2 b. With ulceration or mitoses at least 1/mm^2
T2	1.01–2.00	a. Without ulceration b. With ulceration
T3	2.01–4.00	a. Without ulceration b. With ulceration
T4	More than 4.00	a. Without ulceration b. With ulceration

38.6 Treatment of the Primary

The standard treatment for cutaneous melanoma is surgical resection. The American Academy of Dermatology guidelines recommend margins of 0.5–1.0 cm for melanoma in situ, 1 cm for a tumor up to 1 mm thick, 1–2 cm for a tumor 1.01–2.0 mm thick, and 2 cm for a tumor thicker than 2 mm [11]. Wider margins are suggested for lentigo maligna melanoma given its biology. Recommended depth of excision is to the level of muscle fascia where possible [11]. Reconstruction of the defect is delayed until after negative margins are confirmed with histopathologic staining [14]. The reader is referred elsewhere for a

Table 38.2 N staging of melanoma

N stage	Number of metastatic nodes	Nodal metastatic burden
N0	0	NA
N1	1	a. Micrometastasis b. Macrometastasis
N2	2–3	a. Micrometastasis b. Macrometastasis c. In transit metastases or satellites without metastatic nodes
N3	4+ metastatic nodes, or matted nodes, or in transit metastases, or satellites with metastatic nodes	NA

Table 38.3 M staging of melanoma

M stage	Site	Serum LDH
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases Any distant metastasis	Normal Elevated

Table 38.4 Overall TNM staging of melanoma

	Clinical staging				Pathologic staging		
0	Tis	N0	M0	0	Tis	N0	M0
IA	T1a	N0	M0	IA	T1a	N0	M0
IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0	IIC	T4b	N0	M0
III	Any T	N>N0	M0	IIIA	T1-4a	N1a	M0
					T1-4a	N2a	M0
				IIIB	T1-4b	N1a	M0
					T1-4b	N2a	M0
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a	N2c	M0
				IIIC	T1-4b	N1b	M0
					T1-4b	N2b	M0
					T1-4b	N2c	M0
					Any T	N3	M0
IV	Any T	Any N1	M1	IV	Any T	Any N	M1

detailed description of surgical resection and reconstruction procedures [15].

In lentigo maligna melanoma, radiation is an option for primary definitive treatment. Radiation can be delivered in the postoperative adjuvant setting for melanomas that exhibit high-risk features such as thickness, ulceration, and satellitosis or for desmoplastic melanoma given its neurotropism and high local recurrence rate [16].

38.7 Sentinel Lymph Node Biopsy

Cutaneous melanoma initially spreads through the intradermal lymphatics to regional lymph nodes, and later spreads hematogenously. In melanomas of intermediate thickness, where there is risk of occult nodal metastasis but low risk of distant metastasis, lymphoscintigraphy and sentinel lymph node biopsy (SLNB) are performed for staging. Small sections of

the first-echelon node are examined by immunohistochemistry for micrometastasis. This provides prognostic information by potentially upstaging the patient and also prevents overtreatment because a negative sentinel node usually means that all other nodes are negative as well.

The first Multicenter Selective Lymphadenectomy Trial (MSLT-I) randomized melanoma patients to two treatment arms: wide excision plus SLNB, followed by completion lymphadenectomy when the sentinel node was positive, or wide excision plus observation, with lymphadenectomy as indicated by clinical nodal recurrence. SLNB conferred significantly improved disease-free survival among patients with intermediate-thickness melanomas, defined as 1.20–3.50 mm, and those with thick melanomas, defined as greater than 3.50 mm. For those with intermediate-thickness melanomas and nodal metastases, biopsy-based management improved the 10-year distant disease-free survival and the 10-year melanoma-specific survival [16].

Recent advances in sentinel node mapping technology include the use of [^{99m}Tc] tilmanocept (Lymphoseek®), which is an engineered CD206 receptor-targeted radiopharmaceutical. Its multiple mannose moieties serve as ligands for multivalent binding to mannose receptors (CD206) expressed on the surfaces of reticuloendothelial cells that are normally present in lymph nodes. Lymphoseek has been reported to identify more melanoma-containing nodes compared to vital blue dye injection in two nonrandomized phase III trials [17]. However, Lymphoseek has not been assessed directly in comparison with other available radiopharmaceuticals. We are currently investigating the use of a clinically translated, integrin-targeting nanoparticle platform for use with both PET and optical imaging for sentinel node mapping in melanoma [18]. The use of such agents that are able to selectively probe critical cancer targets may allow important insights into cellular and molecular processes that govern metastatic disease spread.

38.8 Treatment of the Neck

The second Multicenter Selective Lymphadenectomy Trial (MSLT-II) will answer the question of whether patients with a positive sentinel node truly require a full neck dissection. Patients with sentinel node metastases are randomized to either completion lymphadenectomy or observation with serial ultrasound with lymphadenectomy as necessary, and the primary outcome to be measured is melanoma-specific survival [19].

For now, the National Comprehensive Cancer Network (NCCN) guidelines state that a patient with a positive sentinel node should either undergo complete lymph node dissection or enter a clinical trial [20]. Patients with clinically positive nodes should have tissue confirmation of nodal positivity and then complete lymph node dissection, with possible adjuvant radiation to the neck based on high-risk pathologic features such as location, size, and number of involved nodes or extranodal extension [20].

38.9 Systemic Treatment

After complete surgical resection of cutaneous melanoma from the head and neck region, NCCN guidelines recommend a program of surveillance based upon the assessed risk of the primary tumor and presence or absence of lymph node metastases. Surveillance typically involves physical examinations. The role of surveillance imaging to detect metastatic disease remains controversial but is often pursued in patients with high-risk disease, such as stage III melanoma.

Adjuvant systemic therapy with high-dose interferon alfa-2B or peginterferon alfa-2b should be considered for patients with stage IIB, IIC, or III melanoma. Across randomized clinical studies, high-dose interferon alfa-2B has been shown to improve recurrence-free survival compared to observation [21–23]. The effect of high-dose interferon on overall survival, however, remains controversial as the overall survival benefit observed in initial trial reports was not maintained with longer follow-up [24]. High-dose interferon alfa-2B can be associated with side effects such as constitutional symptoms (fatigue, myalgia, fevers), laboratory abnormalities (cytopenias and transaminitis), and neuropsychiatric effects. Each individual patient should weigh the benefits and risks of this treatment carefully. Peginterferon alfa-2b has been shown to improve relapse-free survival but not overall survival [25]. In patients with palpable lymphadenopathy who undergo resection, peginterferon alfa-2b cannot be recommended as there were no apparent benefits of peginterferon alfa-2b seen within this specific subgroup of patients [25].

Unfortunately melanoma can often metastasize to distant organs. Several new systemic treatment approaches involving immunotherapy and targeted therapy have demonstrated substantial benefits for patients with recurrent, metastatic disease. The most promising immunotherapeutic approaches involve increasing antitumor immunity by inhibiting normally negative regulators of immunity such as cytotoxic T lymphocyte antigen-4 (CTLA-4) and the programmed cell death 1 receptor (PD-1). Ipilimumab is an antibody against CTLA-4 and has improved overall survival in two phase III studies [26, 27]. Nivolumab is an antibody against PD-1 and has similarly shown an overall survival benefit [28]. The response rate to nivolumab is high (~30 %) [29] and similar to that of another anti-PD-1 antibody, pembrolizumab [30, 31]. The cytokine interleukin-2 (IL-2) is an older treatment, but remains an option for fit patients without other significant comorbidities. IL-2 requires inpatient administration and close monitoring given the potential for systemic inflammatory immune responses, but it can result in durable long-term benefit in a small percentage of patients [32].

For patients who have a BRAF mutation, targeted therapy directed against the oncogenic BRAF mutation or its downstream partner, MEK, is an option. Agents that target mutant BRAF (vemurafenib and dabrafenib) have been shown to improve overall survival compared to chemotherapy [33, 34]. MEK inhibition has also been shown to improve overall survival compared to chemotherapy [35]. Recent studies have demonstrated improved response rates and, in some circumstances, overall survival, when BRAF inhibitors are given in combination with MEK inhibitors [36, 37]. For patients with metastatic BRAF mutant melanoma, whether it is preferable to start with BRAF inhibition or immunotherapy remains unknown. Generally, patients who have symptomatic disease or brain metastases are best suited for initial BRAF inhibition given the high response rates with this approach and proven efficacy in the brain [38].

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39 Cervical Lymph Node Metastases of Squamous Cell Carcinoma from an Unknown Primary Site

Nicholas Pavlidis and Georgios Plataniotis

Abstract

Cancer of unknown primary (CUP) is a well-recognized clinical disorder where the primary site cannot be identified after a standard diagnostic approach and it accounts for 3–5 % of all tumors. CUP is distinguished into two different clinicopathological entities, favorable or unfavorable. The subset of squamous cell carcinoma metastatic to cervical lymph nodes constitutes the 5 % of all head-and-neck cancers. For detection of the primary site, all patients need a detailed clinical examination and imaging investigation including PET scans, panendoscopy with directed biopsies, and possibly bilateral tonsillectomy. Lymph nodal stage, extracapsular spread, and HPV status are considered as the most prominent prognostic factors. Although, randomized trials are lacking concerning the optimal therapeutic management, combined-modality treatment is offering the most encouraging results. Surgery alone is indicated in N1 or N2a stages. Radiotherapy is used as a single modality for early-stage pN1 without extracapsular extensions or combined with neck dissection as postoperative therapy in more advanced disease. Chemoradiation can also be given in a neoadjuvant setting followed by surgery in certain cases as well in patients with comorbidities. Prognosis in general is encouraging with 5-year progression-free and overall survival rates of 85 % and 75 %, respectively.

Keywords

Cancer of unknown primary • Metastatic squamous cell carcinoma • Cervical nodes • Treatment • Prognosis

39.1 Introduction

Cancer of unknown primary (CUP) represents a heterogeneous group of malignancies presenting with distant metastases without an identified primary tumor at diagnosis. The nature of CUP remains unanswered. The primary tumor may either have a slow growth rate or it may possibly involute.

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In a general medical oncology service, metastatic carcinoma of unknown primary site is not a rare diagnosis. CUP accounts for 3–5 % of all tumors. Similarly, in a head-and-neck or otolaryngology department, the proportion of patients presented with cervical lymph node metastatic disease of not known origin follows more or less the same pattern.

Today, the definition of CUP includes patients who present with histologically confirmed metastatic cancer in whom a detailed medical history, complete physical examination, full blood count and biochemistry, urinalysis and stool occult blood testing, histopathological review of biopsy material with the use of immunohistochemistry, chest radiography, computed tomography (CT scan) of the abdomen and pelvis and in certain cases mammography, magnetic resonance imaging (MRI), and position emission tomography (PET scan) fail

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to identify the primary site. Recently, gene expression-profiling platforms were shown to accurately assign CUP to a primary tissue of origin with, however, unknown impact on patient outcome [1–3].

In general, CUP is associated with dismal prognosis with a median survival of 9–12 months. Nowadays, CUP patients are divided into various subsets of favorable or unfavorable prognosis. Patients with cervical lymph node metastases from an unknown primary site of squamous cell histology (SQ-CUP) belong to the favorable prognostic subsets of CUP [1, 2].

Every medical or surgical specialty could come across to a CUP patient, and therefore they should be aware of the optimal diagnostic and therapeutic approach of these patients.

39.2 Incidence

In 1957, the first definition of cervical lymph node metastasis of an unknown primary site was reported by Comess et al. [4].

Cervical lymph node metastases from SQ-CUP constitute approximately 5 % (range 1–10 %) of all head-and-neck cancers [5]. The annual incidence of SQ-CUP tumors is 0.34 cases per 100,000 per year [6]. Median age is around 57–60 years (range 30–80 years) and almost 80 % of the patients are males. They usually carry a history of chronic tobacco or alcohol use.

Squamous cell histology is the most common type representing the 75 % of the cases, followed by undifferentiated carcinoma and adenocarcinoma [7]. Regarding the distribution of involved cervical lymph nodes, jugulodigastric nodes are the most commonly affected (71 %) followed by midjugular nodes (22 %) [8].

In this chapter only patients with squamous cell histotype will be discussed, since patients with other histological types are managed differently and carry different prognosis.

39.3 Diagnostic Evaluation

The diagnostic approaches in patients with SQ-CUP refer firstly to the establishment of the histopathological type of the tumor and secondly to the detection of the primary tumor site.

Therefore, the diagnostic maneuvers include (a) physical examination, (b) fine-needle aspiration (FNA) or biopsies, (c) endoscopic examination, and (d) imaging studies.

39.3.1 Physical Examination

A painless and unilateral cervical mass is the most common clinical presentation. The site of palpable cervical lymph nodes could be useful in suggesting the possible primary tumor site. In patients with squamous cell histotype, the jugulodigastric and midjugular lymph nodes are most commonly involved, whereas metastatic adenocarcinoma is more frequently diagnosed in the low cervical or supraclavicular areas.

In addition, based on the metastatic lymph node level, several probable sites of the primary tumors can be predicted, that is:

(a) If submandibular nodes (level I) are involved, the primary site could be in the floor of the mouth, lips, and anterior tongue. (b) If jugulodigastric or upper jugular nodes (level II) are affected, search for a primary tumor in the epipharynx, base of the tongue, tonsils, nasopharynx, and larynx. (c) If middle and lower jugular nodes (levels III and IV) are involved, the most likely primaries are located in the hypopharynx or larynx. (d) If supraclavicular nodes (level V) are the metastatic sites, the possible primary tumors could be derived from the lungs, thyroid, breast, gastrointestinal, or genitourinary system [8, 9] (Table 39.1).

The most commonly involved level is level II (30–50 %), followed by level I and III (10–20 %) and levels IV and V (5–10 %).

39.3.2 Cytology and Histopathology

Fine-needle aspiration (FNA) is most commonly used as a first step diagnostic procedure to establish malignancy. The diagnostic accuracy of FNA in these patients is close to 95 % [10].

Incisional biopsy of enlarged cervical nodes remains controversial since higher rates of local recurrence has been observed due to seeding of tumor cells along the tract [11, 12]. However, open biopsy is indicated if the mass is suspected to be lymphoma, sarcoma, melanoma, or adenocarcinoma.

While traditional histochemistry has been established as a useful technique in other tumor types, it has not proven

Table 39.1 Location of neck nodes and possible site of primary tumor

Level	Neck nodes involved	Possible primaries
I	Submental, submandibular nodes	Mouth's floor, lips, anterior tongue
II	Jugulodigastric/upper jugular nodes	Epipharynx, base of tongue, tonsils, nasopharynx, larynx
III	Middle jugular nodes	Supraglottic larynx, inferior pyriform sinus, post-cricoid region
IV	Inferior jugular nodes	Hypopharynx, subglottic larynx, thyroid, esophagus
V	Supraclavicular	Lungs, thyroid, breast, gastrointestinal system

particularly helpful in the diagnostic workup of SQ-CUP. Advanced molecular techniques such as in situ hybridization or polymerase chain reaction could be useful as surrogate markers in detecting Epstein-Barr virus (EBV) or human papillomavirus (HPV), differentiating a nasopharyngeal or oropharyngeal primary cancer, respectively [13, 14].

39.3.3 Endoscopic Examination

If history, physical examination, and imaging studies are unrevealing to identify a primary site, the patient should undergo a panendoscopy under anesthesia with the use of a flexible nasopharyngoscope. Blind biopsies from the nasopharynx, tongue base, tonsil, and pyriform sinus are recommended. Esophagoscopy and bronchoscopy are also parts of panendoscopic examination [8, 15].

39.3.4 Imaging Studies

Imaging investigation in SQ-CUP patients include CT scan, MRI, and PET scan. The goals of performing imaging studies in these patients include, first, the detection of primary site in the head-neck region or in the lungs and, second, the staging evaluation of lymph nodal status before any local-regional treatment.

Imaging should be performed prior to any invasive procedure or treatment in order to avoid any diagnostic misinterpretation.

CT scan is considered as the imaging study of choice, because it has a low cost and offers detailed anatomical information. Primary tumor detection rate is approximately 22 % [16, 17].

MRI has a higher accuracy in identifying the primary site of 36 %. Due to better soft tissue definition compared to CT scan, it makes it more useful for investigating the area of the nasopharynx and oropharynx [18, 19].

PET has also been used in patients with SQ-CUP. In both prospective studies and meta-analysis, ^{18}F-FDG PET showed a diagnostic accuracy in detecting the primary site up to 28 % with sensitivity and specificity of 84 % and modification of treatment plans in almost 30 % of the patients [20–23].

A disadvantage of FDG-PET, however, is its lack of anatomic information with precise localization of FDG accumulation. Therefore, the application of combined FDG-PET/CT or MRI could offer a greater value for the detection of primary site.

Recently, there is evidence that narrow band imaging with magnifying endoscopy might be useful in the detection of unknown head-and-neck primary sites. A detection rate of 45–55 % has been reported [24, 25].

Table 39.2 Nodal staging in patients with SQ-CUP

Nodal disease	Nodal characteristics
N1	Single ipsilateral node <3 cm
N2a	Single ipsilateral node 3–6 cm
N2b	Multiple ipsilateral nodes <6 cm
N2c	Bilateral or contralateral nodes <6 cm
N3	Lymph node >6 cm

39.4 Prognostic Factors

The prognostic outcome of patients with SQ-CUP is based on several endpoints such as the overall survival, disease-free survival, distant failure, or local-regional control.

Numerous treatment and patient- or tumor-related variables have been implicated. However, the most prominent prognostic factors correlated with disease outcome are two tumor-related variables, the lymph nodal stage and the extracapsular spread [5].

Table 39.2 demonstrates the neck nodal staging.

39.5 Treatment

The optimal therapeutic management of patients with SQ-CUP remains controversial as a result of the absence of randomized studies comparing treatment options. Therefore, the treatment is mainly based on nonrandomized evidence as well as on institutional policies.

39.5.1 Surgery

Surgical therapy includes excisional biopsy, neck dissection ("radical," "modified," or "selective"), and tonsillectomy.

"Radical neck dissection" refers to the removal of the levels I–V neck nodes, which at the same time sacrifices the spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle. "Modified radical neck dissection" removes the same nodal levels but spares the rest of the neck structures. It is important to notice though that preservation of spinal accessory nerve saves shoulder mobility. "Selective neck dissection" targets specific nodal groups and it is considered as the safest operational procedure.

Patients with N1- or N2a-limited disease without extracapsular extension could be treated with surgery alone. Local-regional control rates range from 80 % to 90 %, median nodal recurrence rate about 34 %, and 5-year overall survival rate up to 65 % [26–29].

Therefore, neck dissection alone is advocated only for patients with N1 and N2a disease without extracapsular spread, whereas postoperative irradiation is indicated in

cases with an incisional or excisional biopsy and in patients with extracapsular extension.

Tonsils are considered as one of the commonest site of a hidden primary site in patients with SQ-CUP. Although the true incidence is not known, it is estimated to be between 18 % and 40 % [30].

Various reports suggest that directed random biopsies or unilateral or even bilateral tonsillectomy should be part of the screening for detection of the occult primary tumor [30–34]. It is interesting that in 10 % of the cases, the primary tonsilar lesion is located in contralateral to the metastatic cervical nodes [30].

Nowadays, several specialized centers recommend bilateral tonsillectomy (screening tonsillectomy) as standard procedure in the investigation of patients presented with subdigastric, mid-jugulocarotid, or submandibular nodal metastases.

39.5.2 Radiotherapy

Radiotherapy (RT) in SQ-CUP is used as:

(a) A single modality for early-stage pN1 without extracapsular extension (involved field RT) or after excisional or incisional biopsy of the neck before definitive treatment
(b) Combined with neck dissection as postoperative RT in stages N1 with extracapsular extension or stages N2–N3
(c) Initial chemoradiation followed by operation (in those patients who do not achieve a clinical or metabolic (PET), complete response) in stage N1 with extracapsular extension, stages N2–N3, and large nodes fixed to the adjacent structures (e.g., to the carotid sheath)
(d) Chemoradiation in patients with comorbidities, which make them unable to tolerate radical surgery

Although the value of irradiation of the potentially (occult) primary sites has not been confirmed by randomized studies, some authors have observed that mucosal irradiation reduced both the emergence of primary tumor and regional recurrence but without affecting overall survival [35–38]. A higher 5-year overall survival rate has been reported, although in a retrospective study, for patients treated with extensive radiotherapy including neck nodes and the entire pharyngeal mucosa relatively to those treated by more limited volumes (57.6 % vs. 24 % $p<0.01$) [39]. However extensive bilateral and mucosal RT seems not to be indicated for all patients, particularly if close follow-up is provided.

Radiotherapy portals encompass the sites shown in Table 39.3, according to the level of the neck affected (Fig. 39.1) [41, 42]. The dose usually given with standard fractionation (dose per fraction of 1.8–2 Gy) is for the neck, 65–70 Gy to the involved nodal stations and 50 Gy for the uninvolved sites, and for the mucosal sites usually 50–60 Gy. In case of clinically suspicious mucosal sites, a dose of 60–64 Gy is recommended. However IMRT (integrated

Table 39.3 Occult primary sites to be included in radiotherapy fields, according to the level of the enlarged lymph nodes

Levels of the neck	Sites to be irradiated
I	Oral cavity, Waldeyer's ring, oropharynx, both sides of the neck. Protection of larynx
II, III, (upper) V	Nasopharynx, oropharynx, hypopharynx, larynx, both sides of the neck, to the level of the clavicles
IV only	Waldeyer's ring, larynx, hypopharynx, both sides of the neck
Lower level V	Larynx, hypopharynx, both sides of the neck, generous regional portal to include adjacent apex of the axilla
Preauricular	Radiotherapy alone (or combined with parotidectomy). Squamous cell carcinoma is suggestive of skin cancer

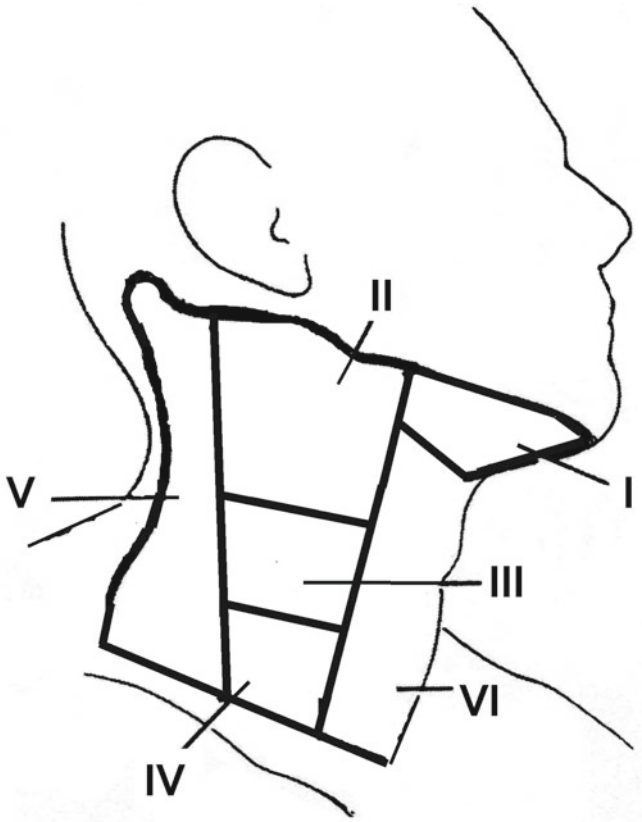

Fig. 39.1 The head-and-neck lymph node areas are currently classified into six levels (I–VI): I, submandibular and submental; II, jugulodigastric (base of skull to hyoid); III, deep cervical (hyoid to cricoid); IV, Virchow's nodes (cricoid to clavicle); V, accessory spinal (superior and inferior posterior triangle). VI, Supraclavicular The lymphatics of the head and neck follow several drainage pathways depending on their origin (see also Table 39.3). This is an important information for the design of radiotherapy portals in squamous cell cancer of the neck, of unknown primary. The figure roughly illustrates the six levels. For detailed description, see reference [40]

boost intensity-modulated radiotherapy) allows treatment to be given keeping overall treatment time as short as 6 weeks and allows boost doses of hypofractionated radiation (2.2 Gy/fraction) to be given to gross nodal disease simultaneously with standard-fraction radiation (range, 1.8–2 Gy) to sites at risk of harboring microscopic disease [43].

In a report from MD Anderson Cancer Centre [43] on IMRT, among a total of 52 patients, 26 patients had undergone neck dissection, 13 before and 13 after IMRT; 14 patients had undergone excisional biopsy and presented for IMRT without evidence of disease. Fourteen patients had received chemotherapy. All patients underwent IMRT to targets on both sides of the neck and pharyngeal axis. After a median follow-up time of 3.7 years, the 5-year actuarial rate of primary mucosal tumor control and regional control was 98 % and 94 %, respectively. The 5-year actuarial disease-free and overall survival rate was 88 % and 89 %, respectively.

In the above study [43], the nodal targets in the head and neck included the retropharyngeal nodes and both sides of the neck based on the approach that a significant proportion of patients with neck metastases have an occult malignancy in the pharyngeal axis. Inclusion of the neck node levels was determined by the involvement of the side of the neck. The dose prescribed to the entire mucosa of the pharyngeal axis was 54 Gy at 1.8 Gy/fraction. On the side of the neck containing disease, the uninvolved nodes at levels IB and V were treated electively to 54–60 Gy. The median dose prescribed to the CTV for gross nodes with a margin of 0.5–1 cm was 66 Gy (range, 60–72). The median dose prescribed to the dissected necks was 60 Gy (range, 60–70). The prescribed dose to the uninvolved contralateral neck was 54 Gy; level II–IV nodes were treated and included in either the IMRT fields or a separate low-neck field. The nodes at levels IB and V were not treated in the uninvolved sides of the neck.

If the operative bed extended into the low-neck field, or if gross adenopathy was present within 1 cm of the junction, a boost dose of 6–10 Gy was delivered to the neck on the involved side using either an appositional electron beam or photons.

Sites of gross nodal disease were treated with 66 Gy in 30 fractions, with consideration of an electron boost to 70 Gy. Uninvolved, nonoperated lymph node-negative regions of the neck were treated to 54 Gy in 30 fractions. In postoperative RT positive neck was treated to 60 Gy in 30 fractions with or without a boost to the involved site to 64 Gy if ECE is present.

The most noteworthy advantage of IMRT in the treatment of head-and-neck cancer of unknown primary origin appears to be related to its ability to preserve salivary function. Local-regional control and survival are significantly improved after 3D-CRT or IMRT, but even with IMRT, the acute and late toxicity of extensive elective irradiation of potential primary sites and *both* sides of the neck is significantly more pronounced than when RT is limited to the involved neck [40]. The advantage of IMRT over 3D conformal is suggested by recent studies [43–50].

The use of systemic treatment is expected to yield similar improvement in outcome as has been observed for known head-and-neck primary tumors. Chemo-radiotherapy has been mainly suggested for patients with extracapsular spread of the disease or with stages N2b–N3. In case of initially bulky neck disease, induction chemotherapy followed by chemo-radiotherapy is sometimes given, although higher toxicity is expected and this is not supported by clinical studies. In the study by Sher et al. [48] on 24 patients treated by IMRT and concurrent or induction chemotherapy, the median involved nodal dose was 70 Gy and the median mucosal dose was 60 Gy. With a median follow-up of 2.1 years, the 2-year actuarial overall survival and local-regional control rate was 92 % and 100 %, respectively. Only 25 % of the patients had grade 2 xerostomia, although 11 patients (46 %) required esophageal dilation for stricture.

In another larger retrospective study by Chen et al. [49], with 51 patients treated either with conventional RT (24 patients) or with IMRT (27 patients), the proportions of those who also received chemotherapy were 54 % and 63 %, respectively. The 2-year estimates of overall survival, local-regional control, and disease-specific survival for the entire patient population were 86 %, 89 %, and 84 %, respectively, but there were no significant differences in any of these endpoints with respect to radiation therapy technique. However the incidence of severe xerostomia in the late setting was 58 % and 11 % among patients treated by conventional RT and IMRT, respectively ($p<0.001$). The percentages of patients who were G-tube dependent at 6 months after treatment were 42 % and 11 %, respectively ($p<0.001$).

An interesting finding from dosimetric analysis was that the use of IMRT resulted in significant improvements with respect to mean dose and V_{30} to the contralateral parotid gland. In addition, mean doses to the ipsilateral inner and middle ear structures were significantly reduced with IMRT ($p<0.05$ for all).

In another report [50], 25 patients were treated with IMRT with a median radiation dose of 70 Gy. The bilateral neck and ipsilateral putative pharyngeal mucosa were included in the target volume and, from the 25 patients, 18 (72 %) received platinum-based chemotherapy in a combined-modality setting. With a median follow-up of 38 months, the overall survival, disease-free survival, and local-regional control rates were all 100 % at 3 years. No occurrence of primary cancer was observed during the follow-up period. The reported rates of xerostomia reduced with the interval from the completion of treatment. Nine patients (36 %) reported grade 2 or greater xerostomia at 6 months, and only 2 (8 %) of them reported the same grade of salivary function toxicity after 24 months of follow-up.

Main acute radiation toxicity consists of dysphagia and mucositis especially in patients treated with combined chemo-radiotherapy compared with those treated with radiotherapy alone. Xerostomia is the main late complication of radiotherapy. Other late effects are persisting edema of the larynx or skin, soft tissue fibrosis, necrosis, and osteoradionecrosis. Combining postoperative complications and post-chemotherapy toxicity can potentially affect the quality of life especially of the long-term surviving patients. This underlines the significance of advanced radiotherapy techniques, such as 3D conformal but mainly IMRT, regardless of any anticipated benefit on tumor control.

According to the abovementioned retrospective study from MD Anderson Cancer Centre [43], severe late complications were uncommon after IMRT combined with surgery and/or chemotherapy. The most severe toxicity was grade 3 dysphagia due to esophageal stricture, experienced by 2 out of 52 patients.

The HPV status of the tumor can be used as a marker of radiosensitivity. Several retrospective studies [51–54] and a prospective analysis of data from a clinical trial [53] confirmed that HPV positivity confers a 60–80 % reduction in risk of death from cancer relative to similarly treated HPV-negative tumors. HPV positivity, particularly in nonsmokers, might be considered (although not definitely confirmed so far) an indication for less intensive or single-modality treatments [40].

39.5.3 Chemotherapy

Concurrent chemo-radiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck significantly improves response rate and overall survival [55–57]. In addition, the combination of platinum-based chemotherapy with cetuximab increased efficacy as first-line treatment in patients with recurrent or metastatic head-and-neck cancer [58]. All these studies are large well-conducted randomized studies published during the last few years.

Unfortunately, up to now, there are no randomized reports on the efficacy of chemo-radiotherapy in patients with SQ-CUP. To the best of our knowledge, there are only four retrospective studies with approximately 100 patients treated with various cytotoxic drugs (platinum or non-platinum). Chemotherapy was administered before, during, or after radiotherapy, and results in some studies were compared with historical controls [39, 59–61].

In the oldest study, complete response rate to combined treatment was 81 % and median survival was 24 months [59]. In the second study, the 5-year progression-free and overall survival rate was 87 % and 75 %, respectively [60]. In the third report, the local-regional control and overall survival rates were 95 % and 89 %, respectively [61]. In the last report published in 2007, chemotherapy was administered as neoadjuvant or concomitantly to radiotherapy in 52 % and 48 % of the patients, respectively. Disease-free survival and 5-year overall survival were 17 % and 26.5 %, respectively [39]. It is worthwhile to notice also that acute or late toxicities following aggressive combined treatment were acceptable in these small studies.

Based on these encouraging preliminary results, prospective multicentric studies in a larger number of SQ-CUP patients will be warranted, in order to establish the efficacy of concurrent chemo-radiotherapy in a cohort of patients with bulky neck disease.

39.6 Discovery of Primary Site

The incidence of the appearance of primary site is around 10 % (ranging between 5 % and 30 %), and it usually occurs within the first 2 years of treatment. Several authors consider primary tumors arising later than 5 years after primary diagnosis as second primaries [5, 15].

The most common sites of the appearance of primary tumors include the nasopharynx, base of the tongue, tonsil, and pyriform sinus. Patients undergoing bilateral tonsillectomy have threefold increase chance to discover the primary site in the tonsils [62]. On the contrary, patients treated with radiotherapy bilaterally to the neck as well as to mucosa sites seem to decrease considerably the appearance of mucosal primary sites [63].

39.7 Conclusions

SQ-CUP most commonly affects middle-aged men and typically presented as a painless neck mass. More than 90 % of these cases represent squamous cell carcinoma originating within Waldeyer's ring (nasopharynx, tonsil, and base of tongue). The other 10 % comprised of other histologies such as adenocarcinoma, undifferentiated carcinoma, or other variants. Following diagnosis of metastatic cervical disease, all patients require a thorough head-and-neck history and clinical examination, radiographic imaging including PET scan, panendoscopy with directed biopsies of Waldeyer's ring, and possibly bilateral tonsillectomy.

Lymph nodal stage and extracapsular spread are considered as the most prominent prognostic factors.

The optimal treatment of SQ-CUP has not yet been defined. Randomized trials are lacking. Definitely, combined-modality treatment is offering a better outcome. Surgery alone is indicated in early stages (N1 or N2a), whereas neck dissection followed by postoperative radiotherapy is indicated in more advanced disease. The extent of radiation portal coverage though remains controversial. The role of chemotherapy as neoadjuvant, concomitantly, or adjuvant modality is waiting to be elucidated. Nevertheless, the 5-year survival rates are still encouraging.

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The Management of Thyroid and Parathyroid Cancer

40

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Abstract

Thyroid and parathyroid cancers are both relatively uncommon malignancies; however, the yearly incidence of thyroid cancer has nearly tripled since 1975. The mainstay of treatment of these endocrine malignancies has been surgical resection and radioactive iodine treatment for thyroid cancer. Differentiated thyroid cancers encompass papillary and follicular carcinomas and are responsive to radioactive iodine treatment and TSH suppression, in contrast to medullary thyroid cancer. There is now a greater understanding of the molecular pathogenesis of differentiated thyroid cancers, poorly differentiated and anaplastic thyroid cancers, and medullary thyroid cancer. This has prompted numerous phase studies utilizing oral biologically targeted agents that inhibit a variety of tyrosine kinase inhibitors, such as the vascular endothelial growth factor receptors, c-Kit, RET, and PDGFR. This review will discuss the epidemiology, histologies, pathogenesis, and issues in management of thyroid and parathyroid cancers.

Keywords

Thyroid cancer • Parathyroid cancer • Tyrosine kinase inhibitors

40.1 Introduction

Thyroid cancers constitute a heterogeneous group of malignancies of differing histologies. While they are relatively uncommon compared to other solid tumors, thyroid cancer is the most common endocrine malignancy. In the United States, approximately 63,000 new cases of thyroid cancer will be diagnosed in 2014 compared with 37,200 cases in 2009 [2]. For undefined reasons, thyroid cancer incidence has nearly tripled since 1975, while its mortality has remained stable [1, 2]. The rise in incidence may be accounted in part for by the increased detection of small papillary thyroid cancers [3, 4]. However, a series of analyses found increases in thyroid cancer incidence rates across gender and racial/ethnic groups, as well as increased incidence by tumor size (both small and large tumors). These consistent increases across multiple categories suggest that enhanced detection may not be the sole factor driving the observed trend [5–7]. By 2019, one study predicts that papillary thyroid cancer will double in incidence and become the third most common cancer in women of all ages at a cost of $18–$21 billion in the United States [8].

Parathyroid cancer is rare, but often fatal, as identification of malignancy against the backdrop of benign parathyroid disease is challenging. Parathyroid cancer will be discussed later in this chapter.

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40.1.1 Epidemiology

Epidemiological evidence shows that an estimated 5 % of all non-medullary differentiated thyroid cancers have a familial occurrence. Most cases of familial non-medullary thyroid cancer (FNMTC) are papillary thyroid cancer with an autosomal dominant pattern of inheritance with incomplete penetrance and variable expressivity [9–12]. Hereditary non-medullary thyroid cancer (HNMTC) may occur as a component of familial cancer syndromes (Gardner's syndrome, Cowden's disease, Carney complex type 1, Werner syndrome, McCune–Albright syndrome). The risk of developing thyroid cancer is five to ten times higher in individuals with a first-degree relative who has thyroid cancer than in the general population [9, 13–17]. That risk is higher when the family member is a sibling and even higher when a sister is affected [18]. A familial case of hereditary NMTC is defined as a patient with two or more first-degree relatives diagnosed with thyroid cancer of follicular cell origin without another familial syndrome [19]. When two first-degree family members are affected, there is a 31–38 % risk that the patient displays a familial thyroid cancer syndrome. The risk of FNMTC increases to >94 % when there are three or more affected first-degree family members [20]. Most studies suggest that HNMTC is more aggressive than sporadic differentiated thyroid cancer with a higher rate of multicentric tumors, extrathyroidal invasion, lymph node metastasis, and recurrence [21–29].

The only clearly established nonhereditary risk factor for thyroid cancer is ionizing radiation exposure, particularly in childhood [30–32]. Case control studies have found associations for non-radiation risk factors, including benign thyroid conditions (i.e., goiter, hypothyroidism, hyperthyroidism, adenoma/nodule, or thyroiditis), inadequate or excess iodine intake, never smoking, and obesity, particularly in women [14, 33, 34],

A prospective study of a cohort of 90,000 US radiology technologists that examined the associations of potential non-radiation risk factors with thyroid cancer also found that obesity and benign thyroid conditions increased and current smoking decreased the risk of thyroid cancer [35]. There also have been reports of an association between thyroid cancer and hepatitis C virus infection, possibly due to increased thyroid autoimmunity [36]. Two genetic variants, 9q22.33 and 14q13.3, are apparently associated with an increased risk of papillary and follicular thyroid cancers in a European population. Those individuals who are homozygous for both alleles have a 5.7-fold higher risk of developing thyroid cancer [37]. The incidence of thyroid cancer is higher in women, although male gender is associated with a worse prognosis [38]. The elderly also are more prone to develop thyroid cancers and these are often the more aggressive histologies, such as anaplastic and follicular cancer [39]. Reasons for this are unknown, but one hypothesis is that the elderly have a greater rate of autoimmune phenomena with end-organ effects on thyroid tissue. It is well documented that the prognosis of differentiated thyroid cancers among patients over the age of 45 is worse than in a younger population. For instance, the 10-year survival of patients over the age of 45 who had a lymph node recurrence is 41 %, versus 100 % in the younger group [40].

40.2 Histological Classification and Prognosis

40.2.1 Differentiated Thyroid Cancers

Thyroid cancers originate from two different cell types. Papillary, follicular, and anaplastic thyroid cancers arise from the follicular cells (papillary and follicular cancers are commonly referred to as differentiated thyroid cancer (DTC)), while medullary cancers arise from the parafollicular C cells. The majority of thyroid cancers are DTC, with papillary thyroid cancer (PTC) being the most common (80–90 %) histology. Follicular thyroid cancer (FTC) and the Hürthle cell variant account for 10–15 % and are associated with male gender, older age, larger tumor size, multifocal carcinoma, and distant metastases compared to PTC [41].

The 20-year tumor-specific survival is worse in FTC (74 %) than PTC (90 %). Tall cell variant is a histological subtype of PTC that is associated with more aggressive biological behavior, a high prevalence of *BRAF* mutation (74.7 %), and an increased rate of nodal and distant metastases [42, 43].

When the major prognostic factors for thyroid cancer are controlled for, including age and ETE (extrathyroidal extension), tall-cell histology alone remains a significant prognostic factor for disease-specific death [44]. It is thought that an initial well-differentiated thyroid cancer dedifferentiates over time and may eventually progress to the more aggressive anaplastic thyroid cancer (ATC), which accounts for 2 % of diagnoses [45].

An intermediate stage in this process is a variant of thyroid cancer known as poorly differentiated or insular thyroid cancer, which also carries a poor prognosis.

40.2.2 Prognosis

Overall, DTCs carry a good long-term prognosis, although a small subset of patients are not cured and require ongoing follow-up and treatment. Features associated with a worse prognosis include distant metastases, extrathyroidal extension, age >45, and larger tumor size [41]. In addition, other risk factors for locally persistent and recurrent local and systemic disease include male gender, >10 involved lymph nodes at the time of surgery, extracapsular nodal extension,

and tumors >4 cm [46, 47]. Many of these characteristics are components of various staging methods. However, there is no clear consensus regarding the use of one system over another. One classification is the MACIS (metastasis, age, completeness of resection, invasion, and size) prognostic score, which has been validated to correlate with survival [48]. Another simple method is the AMES system (age, metastasis, extent, size) which divides patients in to high- and low-risk groups [49].

The low-risk group includes younger patients, those without distant metastases, papillary cancers confined to the thyroid, or a primary tumor <5 cm. The National Thyroid Cancer Treatment Cooperative Study (NTCTCS) prospectively studied a staging approach that was based on patient age, tumor histology, size, multifocality, metastases, and extra-glandular invasion [50]. When this was applied across 14 institutions, 5-year survival was 100 % for stage I and II disease, 92 % for stage III disease, and 49 % for stage IV disease. The TNM by the American Joint Committee on Cancer (AJCC) system is widely used among other solid tumors. Compared to the TNM system for other tumors, thyroid cancer is distinct in that age is a component of the staging classification. The great majority of patients <45 years of age are classified as stage I, with stage II disease assigned only to those with distant metastases. In contrast, patients over age 45 years with distant metastases are classified as stage IV [51]. As with other systems, stage IV disease is associated with a worse prognosis. Recent studies have questioned the use of the age of 45 years old as a cutoff to upstage patients using the AJCC TNM system [52, 53].

Since the AJCC/TNM staging system does not adequately predict the risk of recurrence in differentiated thyroid cancer, the 2009 version of the ATA thyroid cancer guidelines proposed a risk stratification system that classified patients as low, intermediate, or high risk of recurrence [54]. Low-risk patients were defined as having intrathyroidal papillary thyroid cancers with no evidence of extrathyroidal extension, vascular invasion, or metastases. Intermediate risk patients demonstrated microscopic extrathyroidal extension, cervical lymph node metastases, RAI avid disease in the neck outside the thyroid bed, vascular invasion, or aggressive tumor histology. High-risk patients had gross extrathyroidal extension, incomplete tumor resection, distant metastases, or significantly elevated postoperative serum Tg values. Several studies have retrospectively validated the 2009 ATA risk of recurrence staging system and reported the estimates of patients who subsequently had no evidence of disease (NED) in each ATA risk category after total thyroidectomy and radioactive iodine remnant ablation: (a) low risk 78–91 % NED, (b) intermediate risk 52–64 % NED, and (c) high risk 31–32 % NED. NED was defined as a stimulated Tg < 1 ng/mL with no other radiological or clinical evidence of disease [55–58].

None of the currently available initial staging systems consider new data obtained during the course of follow-up to modify the initial risk estimate. Tuttle and colleagues suggest a restaging classification that incorporates response to therapy variables such as thyroglobulin level and imaging (structural and functional) obtained during follow-up to redefine the clinical status of the patient and to assess the individual response to therapy [57]. In their study, the ATA risk of recurrence staging system was used to guide early surveillance and therapeutic management decisions. Response to therapy data was used to re-stratify patients into four categories (excellent, incomplete biochemical, incomplete structural, indeterminate). The addition of the response to therapy assessment to the initial ATA staging system resulted in improved predictive ability. The PVE (proportion of variance explained) values were significantly higher than those seen with initial staging systems.

For those patients who do recur with distant metastatic disease, the clinical course is variable. Many patients have indolent, asymptomatic metastatic disease and remain relatively stable with levothyroxine therapy and TSH suppression. However, in other patients, recurrent thyroid cancer is more aggressive and can be lethal. In one retrospective analysis, the 10-year disease-specific survival of patients with PTC and distant metastases was 45 %. Markers of poor prognosis included older age at the time of detection of distant metastases, metastatic sites other than the lungs, metastatic sites over 2 cm in size, and a poorly differentiated histology [59].

40.2.3 Medullary Thyroid Cancer

Medullary thyroid carcinoma (MTC) arises from the calcitonin (CT)-producing parafollicular C cells of the thyroid and accounts for 5–8 % of all thyroid cancers. MTC is mainly sporadic in nature, but an autosomal dominant hereditary pattern is present in 20–30 % of cases [60]. The hereditary forms include multiple endocrine neoplasia type 2 A (MEN 2A) characterized by MTC in combination with pheochromocytoma and hyperparathyroidism and MEN 2B characterized by MTC in combination with pheochromocytoma, multiple mucosal neuromas, and marfanoid habitus. Familial MTC is a clinical variant of MEN 2A in which MTC is the only manifestation. Medullary thyroid cancers (MTC) are not iodine avid and are not sensitive to the presence of TSH. It is important to perform biochemical testing to rule out pheochromocytoma and hyperparathyroidism before surgery to avoid perioperative complications. The preoperative biochemical evaluation should include basal serum calcitonin, CEA, calcium, PTH and plasma metanephrines and normetanephrines, or 24 h urine collection for metanephrines and normetanephrines. After surgical resection, there is no standard adjuvant therapy for MTC. A greater under-

standing of the prognostic features of MTC is needed. Known adverse features of MTC include the presence of nodal and distant metastases at diagnosis [61].

In one series, somatic RET mutations in exons 15 and 16 in sporadic cancers were also associated with a worse prognosis [62]. The ATA Medullary Thyroid Carcinoma Guidelines recommend that all patients diagnosed with MCT should be offered germline RET testing since knowledge of the codon mutation can inform treatment and determine if other family members are at risk [63].

40.3 Molecular Pathogenesis

With the ongoing refinement of genomic sequencing techniques and our ability to analyze and elucidate important signal pathways, we have entered an era of numerous exciting developments in molecular basis of thyroid cancers. Furthermore, beyond simply identifying these mechanisms, great strides are being made in incorporating this knowledge into the clinical management of thyroid cancer. Recently, the Cancer Genome Atlas (TCGA) Research Network published an analysis of approximately 496 papillary thyroid cancer samples. Whole exome DNA sequencing of 402 of these tumor samples highlighted that the greatest mutation density was seen in less-differentiated cancer samples [64].

40.3.1 Papillary Thyroid Cancers

A greater understanding of the pathogenesis of the various types of thyroid cancer has facilitated the development and study of newer therapies for advanced disease. This is summarized further in Table 40.1. While the pathogenesis of sporadic and radiation-induced tumors differs, the primary molecular events associated with the development of PTC involve alterations of genes downstream of the MAPK pathway [65]. The initiating event consists of nonoverlapping activating mutations in one of the following four genes that are components of the MAPK signaling pathway and are detectable in 70 % of papillary thyroid cancers: RET/PTC rearrangements, BRAF mutations (V600E), NTRK1 (neurotrophic tyrosine kinase receptor 1) rearrangements, or the less common RAS mutations [66–68].

RET is a proto-oncogene that encodes a tyrosine kinase receptor. DNA damage causes the fusion of the RET oncogene with one of ten partner genes, resulting in at least 15 characterized rearrangements. The prevalence of the RET/PTC rearrangements in PTC has been reported to be 3–85 % based on detection method and geographical location [65]. Though numerous RET/PTC rearrangements have been identified in sporadic and especially in radiation exposure-related papillary thyroid cancers, RET/PTC1 and RET/PTC3 are the two most common mutations [69–71]. Of note, murine models of RET/PTC1 and RET/PTC3 highlight that the presence of these mutations induces thyroid neoplasms but additional alterations are required for the neoplasms to become metastatic [65].

BRAF encodes a protein-serine/threonine kinase that participates in the mitogen-activated protein kinase (MAPK) cascade [72]. Over 65 different BRAF missense mutations have been identified to date [73]. In particular, BRAF mutations have a prevalence of approximately 45 % in papillary thyroid cancer, with the specific mutation being the T1799A transverse point mutation of BRAF, resulting in the production of the BRAF-V600E mutant protein. This variant has constitutive activation of its serine/threonine kinase and plays a pivotal role in maintaining tumor growth as illustrated in xenograft models. In an analysis of 320 thyroid tumors, BRAF mutations were detected in 38 % of papillary

Table 40.1 Molecular events associated with thyroid cancer

Primary molecular events	
Papillary thyroid cancer	RET/PTC rearrangements BRAF mutations NTRK1 (neurotrophic tyrosine kinase receptor 1) rearrangements RAS mutations EIF1AX (eukaryotic translation initiation factor 1A, X-linked) mutations PPM1D (protein phosphatase, Mg2+/Mn2+ dependent, 1D) mutations CHEK2 (checkpoint kinase 2) mutations TERT (telomerase reverse transcriptase) promoter mutations
Follicular thyroid cancer	RAS mutations PAX8-PPARg rearrangements
Medullary cancer	RET mutations
Potential secondary molecular events	
Transformation to poorly differentiated/anaplastic thyroid cancer	VEGF EGFR PI3K/Akt p53

carcinomas, 13 % of poorly differentiated carcinomas, and 10 % of anaplastic carcinomas, but not in follicular or Hürthle cell malignancies [74]. Thus, BRAF mutations are restricted to PTC and poorly differentiated or anaplastic carcinomas arising from PTC. BRAF mutations correlate with adverse clinical features, such as extrathyroidal invasion, lymph node metastases, advanced stage, risk of recurrence, loss of I-131 avidity, and increased risk of death [75–78]. However, a recent large-scale retrospective study, analyzing 1849 patients with PTC and the impact of BRAFV600E mutation, showed that though the presence of this mutation appears to be associated with poor outcomes, once adjusted for clinical and histopathologic characteristics of aggressive thyroid cancers, this association loses significance [79]. Thus, though BRAF represents a promising focus for development of targeted therapies and prognostic models, further work is required to clarify the prognostic and therapeutic implications of the BRAF V600E mutation in PTC.

Recent work by the TCGA Research Network has helped highlight various BRAF subtypes. Their work highlighted that with regard to overall mutations involving single nucleotide variants/insertion/deletions, most alterations of BRAF involved V600E substitutions. They also identified 13 BRAF fusions involving unique gene partners; three were SND1/BRAF fusions (as seen in gastric cancer cell lines) and others involved the MKRN1 gene [64].

BRAF mutation has been shown to correlate with lower expression of the sodium iodide symporter (NIS), which could provide a molecular explanation for the dedifferentiation process and loss of iodine avidity that occurs in the more aggressive BRAF-mutated thyroid cancers [80]. Given the role that mutated BRAF and RET/PTC-activating mutations play in oncogenesis, inhibition of downstream effectors of the MAPK pathway becomes an obvious therapeutic target for advanced iodine refractory thyroid cancers [81]. Preclinical data from cell lines that harbor either BRAF, RAS, or RET mutations indicate that presence of a BRAF mutation predicts sensitivity to MEK inhibition with AZD6244 [82]. A study by Ho et al. illustrated that treatment with AZD6244 (selumetinib) produced meaningful increase in retention of iodine in certain patients with radioiodine refractory disease. In this small trial, of 24 patients screened, 20 were evaluable; nine had BRAF mutations and five had NRAS mutations. Treatment with selumetinib increased iodine-124 uptake in four of the nine patients with BRAF mutations and in five of the five patients with NRAS mutations [83]. The ongoing trial [NCT00970359] has finished accrual and further follow-up and analysis of results is pending.

NTRK1 encodes a high-affinity receptor for NGF [nerve growth factor], which has inherent tyrosine kinase activity and can activate the Ras, phosphatidylinositol 3-kinase (PI3K), phospholipase C (PLC)-γ, and signaling pathways controlled through these proteins, such as the mitogen-activated protein kinase (MAPK). Oncogenesis of NTRK1 involves rearrangements with a number of other gene partners which includes TPM3 and TPR on chromosome 1q and TFG on chromosome 3q. The prevalence of NTRK1 rearrangements in PTC is approximately 12 % and there does not appear to be an increased incidence in patients with radiation exposure. Further studies are ongoing to better characterize the role of these gene arrangements in the tumorigenesis of PTC [84].

Among papillary thyroid cancers, RAS (HRAS, NRAS, KRAS) mutations appear to be mutually exclusive from other molecular events. According to the COSMIC database, the incidence of KRAS mutations in thyroid carcinomas is 3 %, HRAS is 4 %, and NRAS is 6 %. Most mutations are activating point mutations, most commonly codons 12/13 and 61, in various cancers. Specifically in thyroid cancers, most mutations involve codon 61 in NRAS or HRAS. Furthermore, the frequency of RAS mutations varies in different types of thyroid follicular cell-derived tumors. In papillary thyroid carcinomas, the incidence is 10–20 %, 40–50 % in conventional-type follicular carcinoma and 20–40 % of conventional-type follicular adenomas [85]. Studies are underway to investigate the optimal approach to targeting RAS for differentiated thyroid cancers, including utilizing MEK inhibitors. Currently a trial is underway (NCT02152995) to evaluate the utilization of the MEK1/2 inhibitor trametinib to increase iodine uptake and incorporation in thyroid cancer patients.

Efforts to study ALK rearrangements in thyroid cancer have highlighted the presence of ALK translocations in both differentiated and dedifferentiated thyroid cancer. Recently, Kelly et al. have reported the presence of a novel gene rearrangement involving the ALK gene and the striatin [STRN] gene. This rearrangement results in the production of a STRN-ALK fusion production with constitutive activation of the ALK kinase function via dimerization activity mediated by the coiled-coil domain of the STRN protein. Xenograft studies have highlighted that the presence of this fusion protein induces TSH-independent proliferation and tumor formation of thyroid cells. Furthermore, this fusion gene has been indentified in both well-differentiated papillary thyroid cancer and anaplastic thyroid cancer. Furthermore, in vitro studies illustrated that the ALK inhibitor, crizotinib, showed some degree of inhibition of the fusion protein's ALK kinase activity. Therefore, with further study and research efforts, this fusion gene may become a candidate for targeted therapy [86].

The potential role of molecular testing in thyroid cancer has been advanced significantly by recent work published by the TCGA Research Network that has identified new and emerging molecular markers that may play a pivotal role in the development of targeted thyroid cancer therapies in the future. In their in-depth genomic characterization of papillary thyroid cancer, the TCGA effort highlighted mutations

in EIF1AX as novel new driver mutations. They also uncovered new alterations of known driver genes, including RET, BRAF, and ALK fusions. Beyond the driver mutations, they discovered individual genes, including CHEK2, ATM, and TERT, which serve to define clinically relevant subclasses of thyroid cancer. Though further work is required to elucidate the relationships among the various new and novel genetic alterations and the development, pathobiology, and subclassifications of thyroid cancer, this effort provides a road map for the improvement of traditional therapies and the development new targeted therapies [64].

40.3.2 Follicular Thyroid Cancers

The primary molecular events that contribute to the development of FTCs include RAS mutations and PAX8-PPARγ rearrangements (t(2;3)(q13;p25)) [65]. The fusion of the thyroid transcription factor PAX8 and the steroid nuclear hormone receptor PPARγ has been detected in up to 50 % of FTCs but not in follicular adenomas or PTCs [87]. A distinct genetic signature differentiating FTC tumors with the fusion gene from those without it has been characterized [88]. The rearrangement functions as a dominant negative inhibitor of the wild-type PPARγ receptor, which is likely a tumor suppressor. In cell lines, this activated oncogene promotes accelerated cell growth, inhibition of apoptosis, and promotes anchorage-independent and contact-uninhibited growth [89]. In vitro, PPARγ agonists led to reduced growth of follicular carcinoma tumor cells, and thus the clinical study in follicular cancers of PPARγ modulators such as the thiazolidinediones (pioglitazone and rosiglitazone) is warranted [90].

RAS mutations, which occur in up to 50 % of follicular cancers, and PAX8-PPARg rearrangements are rarely found in the same tumor suggesting two distinct pathogenic pathways for follicular thyroid cancer [91]. Point mutations in HRAS and NRAS have been detected in FTCs, but it is not clear how these mutations relate to prognosis [92, 93].

40.3.3 Molecular Events Related to Progression/Transformation

While the genes discussed above are involved in the initial pathogenesis of thyroid cancers, other growth factor receptors likely play key roles in determining the progression and phenotype of thyroid carcinomas. The most aggressive examples of this evolution are the development of anaplastic and undifferentiated thyroid cancers which are not responsive to radioactive iodine and are felt in many cases to arise from preexisting DTC. For instance, pathological series have described remnants of papillary or follicular thyroid cancer coexisting with anaplastic thyroid cancers, suggesting that clonal evolution has occurred [94–96]. Aberrations that may be involved in this transformation include VEGF, EGFR, the PI3K signaling pathway, and p53. The vascular endothelial growth factor (VEGF) is present at increased levels in papillary and follicular thyroid cancer cells compared with hyperplastic or benign thyroid tissue and is associated with increased risk for recurrence and metastatic disease [97–100]. In addition, compared to benign tissue, thyroid cancers are noted to have increased levels of VEGF, VEGF-C, and angiopoietin-2 and in the tyrosine kinase receptors KDR and Flt-4. VEGF and Flt-1 have also been associated with a larger-sized primary thyroid tumor [101]. Thus, increased angiogenesis is not specific to a particular histological subtype of thyroid cancer but seems to be related to more aggressive tumors in general. Preclinical data have shown a reduction in tumor size in xenografts of PTC and ATC treated with a monoclonal antibody against VEGF [102, 103].

Patients with Cowden's syndrome, who have a loss of PTEN resulting in activation of the Akt pathway, are at increased risk of developing thyroid cancer, prompting further study of this pathway in thyroid cancer cells. Mutations in PTEN and PI3-K have been detected in ATC cells, and thus this pathway is thought to be critical to progression to the more aggressive thyroid cancers [104, 105]. In follicular and papillary thyroid cancer cells, activation of Akt has also been observed, and inhibition of Akt decreased cell proliferation and increased apoptosis in thyroid carcinoma cell lines in vitro [106]. A mouse model of follicular thyroid adenoma has been generated by engineering a loss of PTEN in the thyroid follicular cells, but another genetic event is likely required for malignant transformation, such as mTOR activation [107, 108].

Alterations in p53 have also been detected in anaplastic carcinoma cell lines but not in the more differentiated histologies [109, 110]. In one series, evidence of p53 mutations was noted in cells that also harbored BRAF mutations, suggesting that both events are important to malignant transformation and development of an aggressive phenotype.

With all of the observations made regarding the molecular basis for the phenotype and progression of various thyroid cancers, researchers strove to construct accurate models of thyroid cancer progression and transformation. Antico-Arciuch et al. generated the first mouse model of anaplastic thyroid cancer (ATC) by combining, in the mouse thyroid follicular cells, p53 loss with constitutive PI3K activation, via deletion of the PTEN tumor suppressor. In experiments with this new mouse model, they observed that it takes at least 6 months for these mice to develop frank carcinomas, which suggests that additional genetic alterations are required for malignancy development. They therefore analyzed genes deregulated in their mouse model and compared them to two Affymetrix-based, publicly available, datasets containing human ATCs. This allowed them to define a set of 430 genes consistently and significantly deregulated in

both mouse and human ATCs. Thus, it was concluded that the identified set of genes was highly enriched in genes encoding proteins involved in the control of mitosis [111].

Antico-Arciuch et al. also evaluated the effect of constitutive PI3K activation. They followed 105 PTEN mutant mice for 2 years to determine the long-term consequences of constitutive PI3K activation in the thyroid follicular cells. In this study, at one year of age, PTEN mutant mice started showing signs of illness, and thyroid enlargement became macroscopically visible. It was also noted that that female mutant mice had a significantly reduced life span (mean survival 73 weeks) compared to male mutants (mean survival 83 weeks). The study authors also examined the pathologic features of thyroids in 54 mice, aged 8–12 months. They observed that 52 % of the females had developed thyroid follicular adenomas, compared to only 12 % of the males ($P=0.002$). They also analyzed 37 mice greater than one year of age and saw that 50 % of the females and 35 % of the males had invasive and often metastatic thyroid follicular carcinomas. When combined with the incidence of follicular adenomas, 93 % of the females older than one year had developed neoplastic features, compared to only 65 % of the males ($P=0.05$). They also studied effects of estrogen on thyroid proliferation by ovariectomizing a cohort of 4-week-old control and PTEN mutant immature mice ($n=6$) and then measured their thyrocyte proliferative index at 12 weeks of age by Ki-67 immunohistochemistry. Their analysis showed that complete estrogen ablation reduced the proliferative index of female thyroids to the same levels observed in mutant males. They also did candidate gene analysis, which highlighted p27 as possibly playing a role in tumorigenesis, which was confirmed by production of a PTEN mutant mouse with heterozygous knockout of p27. Further analysis of this mouse construct led the authors to conclude that p27 may be an important mediator of estrogen action in thyroid hyperproliferation and neoplastic transformation [112].

Russo et al. studied the effect of PLK1 inhibition in anaplastic (ATC) and poorly differentiated (PDTC) thyroid carcinomas. They treated human and mouse ATC and PDTC cell lines with the PLK1 inhibitor GSK461364A. They observed that GSK461364A inhibited cell proliferation and induced cell death in both mouse ATC- and PDTC-derived cell lines and in several human ATC cell lines carrying different driver mutations. The authors concluded that PLK1 targeting is a promising and effective therapeutic approach against PDTC cells and undifferentiated thyroid carcinoma cells [113].

Campa et al. did similar experiments, studying the blockage of certain signal pathways in in vitro models. They generated a compound mouse model carrying a constitutively active allele of KRAS (G12D) and a null p53 allele. They then generated two tumor cell lines derived from their mouse model, as well as a human ATC cell line, Cal62, which harbored the same genetic alterations and acted as an appropriate human counterpart to the mouse lines to study effects of MEK inhibition. The generated cell lines were treated with the MEK1/2 inhibitor GSK1120212 and demonstrated growth inhibition but lack of apoptotic response. They further determined that these cells showed elevated expression levels of two anti-apoptotic members of the Bcl2 family, Bcl2a1 and Mcl1. Subsequent treatment with the pan-Bcl2 family inhibitor obatoclax, but not the more restricted inhibitor ABT-263, which does not target Bcl2a1 and Mcl1, was able to induce tumor cell death even as a single agent and to cooperate with MEK inhibition both in cultured cells and, in vivo, in tumor cell allografts, as well as with doxorubicin treatment [114].

40.3.4 Medullary Thyroid Cancer

MTC harbors activating mutations in the RET proto-oncogene, a tyrosine kinase receptor. The majority (75 %) of MTCs are sporadic, and mutations in RET are detected in up to 25–66 % of this population [115]. Most somatic mutations are in exon 16. In contrast, the 25 % of MTCs that are familial as part of the multiple endocrine neoplasia type 2 syndrome (MEN2) all carry RET mutations, often in exons 10 or 11 [116].

40.4 Management of Thyroid Cancer

Papillary microcarcinomas, defined as tumors less than 1 cm, are usually cured by surgery alone. Given the low risk of recurrence and mortality from thyroid cancer, patients with microcarcinomas likely derive little benefit from radioactive iodine remnant ablation (RAI). However, there is a small group of patients with a more aggressive disease course. In one series of 900 patients, those with microcarcinomas who were at slightly higher risk of recurrence were those with multifocal tumors and nodal disease [117]. In the analysis of 900 patients, a total thyroidectomy and radioactive iodine ablation was not associated with improved outcomes. Current recommendations from the American Thyroid Association (ATA) Guidelines state that a thyroid lobectomy alone may be appropriate treatment for small, unifocal, intrathyroidal carcinomas in the absence of prior head and neck irradiation, familial thyroid carcinoma, or clinically detectable cervical nodal metastases [118]. Since RAI is now being used more selectively, the requirement for total thyroidectomy to facilitate RAI treatment is eliminated in those low to intermediate risk patients forgoing RAI. Thus for properly selected patients with tumors that are between 1 and 4 cm in size without clinical evidence of any lymph node metastases (cN0) or extrathyroidal extension, either a bilateral thyroidectomy (total or near-total) or a unilateral procedure (thyroid lobectomy) may be appropriate [119–122].

Given that the risk of surgical complications for total thyroidectomy is double that of lobectomy, the relative benefits and risks of total thyroidectomy vs. thyroid lobectomy should be carefully considered [123]. Total thyroidectomy is generally recommended for thyroid cancer if bilateral nodules are present.

40.4.1 Radioactive Iodine

The primary treatment for DTC and MTC is surgical resection. For DTCs, it is important to utilize clinical and pathologic features in order to appropriately characterize a patient's prognosis, as this will guide further recommendations. Currently, the consensus is to treat patients with an intermediate to high risk of recurrence with postoperative radioactive iodine, as this has been shown in retrospective series to significantly reduce the rate of recurrence [124–129].

RAI remnant ablation is not routinely recommended for unifocal or multifocal papillary microcarcinomas or low-risk DTC in the absence of other adverse features. The ATA recommends RAI for intermediate and high-risk DTC patients, such as those with nodal metastases, extrathyroidal or vascular invasion, aggressive histologies, macroscopic tumor invasion, incomplete tumor resection, or distant metastases. Thus, the final decision regarding RAI remnant ablation is individualized based on the postoperative risk stratification of the individual patient.

Toxicities of I-131 therapy include acute effects, such as nausea, taste disturbance, salivary gland swelling, and neck edema. Late effects include xerostomia, ocular dryness, and secondary malignancies. Thyrotropin stimulation before RAI remnant ablation/therapy or scanning is employed based on early observational research suggesting that a TSH >30 mIU/L was required for the thyroid remnant to significantly concentrate I-131. TSH stimulation can be achieved by withdrawing the patient from thyroid hormone for 3–4 weeks prior to administration of RAI. In recent years, recombinant thyrotropin hormone, rather than hormone withdrawal, has been used to obtain an elevated TSH in order to prime cancer cells for diagnostic iodine scans and I-131 treatment [130]. Recombinant thyrotropin (rhTSH) allows patients to be maintained in a euthyroid state and avoid potentially debilitating symptoms of hypothyroidism following hormone withdrawal. One randomized study compared both approaches prospectively, and at a follow-up period of 8 months after I-131 treatment, the primary end point of "no visible uptake in the thyroid bed, or if visible, fractional uptake less than 0.1 %" was attained in 100 % of patients in both groups [131]. In addition, patients who received rhTSH maintained a better quality of life and had less radiation exposure in the blood. In several randomized controlled trials (RCTs) of patients with well-differentiated thyroid cancer without distant metastases undergoing radioactive iodine remnant ablation (T1–T3, N1 or N0, all M0), the rate of successful remnant ablation was not significantly different after rhTSH preparation compared to thyroid hormone withdrawal, using I-131 dose activities ranging from 30 to 100 mCi [132–136].

Recombinant human thyrotropin is currently approved by the US Food and Drug Administration for use in preparation for radioactive iodine remnant ablation in patients who have undergone a near-total or total thyroidectomy for well-differentiated thyroid cancer and who do not have evidence of distant metastases. Preparation with rhTSH seems to be as effective as thyroid hormone withdrawal while sparing patients the adverse effects of hypothyroidism and the associated possible complications (e.g., worsening of psychiatric illness, respiratory compromise, central nervous system depression, aggravation of congestive heart failure, or coronary artery disease). This approach has been adopted in many centers. However, it should be noted that given the long natural history of thyroid cancer and the relatively short periods of follow-up in the aforementioned studies, long-term outcomes with the use of rhTSH are not fully known.

40.4.2 TSH Suppression

After thyroid remnant ablation post-surgery, the current standard in the management of DTC is administration of oral levothyroxine to suppress TSH, which is a known growth factor for thyroid cancers. Although this has never been validated in prospective, randomized trials, a meta-analysis has shown that suppressing TSH is associated with a decrease in disease-specific events [137]. Retrospective and prospective studies have demonstrated that TSH suppression to below 0.1 mU/L may improve outcomes in high-risk thyroid cancer patients, but no evidence of benefit has been documented in low-risk patients [138, 139]. Therefore, a risk-adapted approach is reasonable. The ATA recommends suppression to below 0.1 mU/L for high-risk DTC patients, while maintenance of TSH at or slightly below the lower limit of normal (0.1–0.5 mU/L) is appropriate for intermediate to low-risk patients. The optimal duration of TSH suppression is not known. TSH suppression may result in subclinical hyperthyroidism and can decrease the risk of heart disease osteoporosis, atrial fibrillation, exacerbation of angina and ischemic heart disease, resting tachycardia, and systolic/diastolic dysfunction [140–143]. Therefore, optimal TSH goals for individual patients must balance the potential benefit of TSH suppression with the possible harm from subclinical thyrotoxicosis.

40.4.3 External Beam Radiation Therapy

External beam radiation therapy (EBRT) is occasionally indicated in patients with DTC over the age of 45 who are at high risk of locoregional recurrence because of invasion of normal tissues (T4 primary) or who have a positive surgical margin [144]. Younger patients with iodine avid tumors are not felt to derive meaningful benefit from EBRT given the generally favorable prognosis of their disease. Thus, EBRT use is usually limited to elderly patients over the age of 60. At times though, EBRT may be indicated even in younger patients with non-iodine avid disease for palliative purposes or to treat a solitary refractory site of disease. Data for EBRT for the treatment of MTC are lacking.

Similarly, EBRT is often considered for patients with anaplastic thyroid cancer in order to prevent or delay the profound morbidity of uncontrolled locoregional disease. However, considering the dismal prognosis among this group of patients, especially those with metastatic disease, it is important to weigh the risks of therapy with the ultimate prognosis. In some cases though, there is a role for palliative radiation to aid in symptom management, even in patients with metastatic disease. For patients with resectable ATC confined to the thyroid, EBRT is indicated. It is usually given concurrently with chemotherapy (doxorubicin +/− cisplatin) in this setting [145–147]. For patients with unresectable ATC, EBRT with or without chemotherapy may still be a reasonable treatment option, given the morbidity of untreated and uncontrolled locoregional disease.

40.4.4 Surveillance and Follow-Up

Given the indolent nature of DTC, recurrences often become evident many years after the initial diagnosis, and thus long-term follow-up is required. DTCs are sensitive to thyroid-stimulating hormone (TSH) and produce the tumor marker thyroglobulin. Initial follow-up for low-risk patients who have undergone total or near-total thyroidectomy and I-131 remnant ablation is based mainly on TSH-suppressed Tg and TgAb and neck ultrasound (US). The presence of thyroglobulin antibodies will falsely lower serum Tg determinations in immunometric assays; thus, serum anti-Tg antibody should be measured in conjunction with serum Tg assay by an immunometric method [148]. Anti-thyroglobulin antibody levels that are declining over time are considered a good prognostic sign, while rising antibody levels suggest recurrent or persistent disease [149, 150].

Among patients who underwent a total thyroidectomy and radioactive iodine remnant ablation, measurement of serum thyroglobulin after rhTSH stimulation is a sensitive means to detect recurrent disease [151]. This approach has a high negative predictive value (NPV) of 98 %, and when combined with neck ultrasound, the sensitivity and NPV of both procedures are 96 % and 99.5 %, respectively [152–154]. If thyrotropin-stimulated Tg is elevated, a stimulated diagnostic whole body scintigraphy (WBS) at that time may be useful in locating iodine avid disease. Due to the sensitivity of a TSH-stimulated thyroglobulin, a common clinical conundrum is the management of a rising thyroglobulin without clinical evidence of gross disease. In these situations, the neck ultrasound may be normal or equivocal. In these patients, the trend in serum Tg over time will typically identify patients with clinically significant residual disease. In patients with elevated or rising Tg or Tg Ab and no evidence of disease on neck US or RAI imaging, CT imaging of the neck and chest with contrast may be considered. MRI of the neck is another means to detect otherwise clinically unapparent disease in the neck, a common site of recurrence [130, 155]. If TSH-stimulated Tg is significantly elevated (generally >10 ng/mL) and stimulated RAI WBS is negative, 18FDG-PET/CT should be considered following TSH stimulation if possible to increase the sensitivity of the FDG-PET/CT [156, 157]. FDG-PET is more sensitive in patients with aggressive histological subtypes such as poorly differentiated, tall-cell, and Hürthle cell thyroid cancer. Tumors that are 18FDG-PET positive generally do not concentrate RAI. As such, RAI therapy is much less likely to be effective treatment for FDG avid disease [158, 159].

If metastases are found following initial therapy, surgical excision of locoregional disease is the preferred intervention and may be curative. Additional RAI treatment of small volume iodine avid disease may be appropriate if surgical resection is not possible. Management of recurrent, metastatic disease that is not surgically resectable or iodine avid is discussed below.

40.4.5 Recurrent Disease: Cytotoxic Therapy

Recurrent locoregional disease can often be salvaged with resection and additional radioactive iodine treatment for iodine avid tumors. Given the indolent nature of differentiated thyroid cancers, it may also be reasonable in certain situations to treat solitary sites of distant metastatic disease with local therapy, such as surgery or radiation. Recurrent, metastatic disease that is not surgically resectable or iodine avid has historically been very difficult to treat. Doxorubicin was the first FDA-approved systemic agent for the treatment of advanced, incurable thyroid cancer; however, with the prevalence of targeted therapies, its relevance and use have significantly declined. Numerous small historical phase 2 studies of doxorubicin, with sample sizes ranging from two to 19 subjects, have yielded response rates ranging from 22 to 90 % [160–167]. It is likely that the effectiveness of doxorubicin was overestimated in these studies with small subject

numbers and varying antiquated criteria for assessing response [168, 169]. Doxorubicin has been studied in two contemporary trials. First, 17 subjects were treated with doxorubicin in combination with interferon alpha [170]. One patient had a partial response and ten had stable disease, with a median time to progression of 5.9 months. In another study, patients received doxorubicin monotherapy (either given weekly or once every 3 weeks) [171]. Among the subjects with papillary or follicular cancer, there was a partial response (PR) rate of 5 %, with 42 % of patients showing SD. Among patients with MTC, the rates of PR and SD were both 11 %. The Eastern Cooperative Oncology Group has studied etoposide for iodine refractory disease as well, and no sign of activity was noted [172].

The study of cytotoxic therapy for the treatment of metastatic anaplastic thyroid cancer has been limited. In a study of doxorubicin monotherapy, a response was only noted in one patient out of 21 [165]. In the same study, there was a slight improvement in response (six out of 18 patients) with the combination of cisplatin and doxorubicin. Additional studies of more intense combination regimens of cytotoxic therapy (cisplatin, doxorubicin, and bleomycin) have been studied in small numbers of patients with limited activity [173]. More recently, paclitaxel had antitumor activity, with a 53 % response rate, in a small study composed of 20 patients with anaplastic thyroid cancer [174]. Preclinical studies have also shown synergistic activity between paclitaxel and an oncolytic herpes simplex virus. Overall, though, the natural history and prognosis of this disease remain exceedingly poor.

40.5 Molecularly Targeted Therapies

In the past decade, ongoing advances in elucidating the pathogenesis of thyroid cancer in conjunction with the development of a variety of molecularly targeted therapies have caused a paradigm shift in the approach to treat thyroid cancer.

A range of orally available kinase inhibitors have been studied that include axitinib, motesanib diphosphate, pazopanib, vemurafenib, lenvatinib, sorafenib, and sunitinib. Most of these agents have multiple targets, including the vascular epithelial growth factor receptors (VEGFR), which play a central role in angiogenesis, tumor growth, and progression. Other targets such as platelet-derived growth factor receptor (PDGFR), KIT, and RET are also relevant to the clinical activity of these kinase inhibitors (Table 40.2).

40.5.1 Differentiated Thyroid Cancers

Sorafenib is now approved by the US FDA for the treatment of differentiated thyroid cancer. This small molecule inhibitor blocks the activities of BRAF, VEGF, c-Kit, and RET. Several studies have been designed to assess the activity and safety profile of sorafenib in advanced/metastatic thyroid cancer patients [175–178]. The pivotal DECISION trial included 417 patients (no prior targeted therapy or chemotherapy) with locally advanced or metastatic RAI-refractory DTC. Patients were randomized in a 1:1 manner to 400 mg sorafenib orally twice daily or to placebo. The median progression-free survival was significantly longer in the sorafenib group (10.8 months) compared to the placebo group (5.8 months; hazard ratio [HR] 0.59, 95 % CI 0.45–0.76; $P < 0.0001$). At the time that the results of the trial were reported, median overall survival (OS) has not been reached, and study investigators noted that this secondary end point would be impacted by the large number of patients (71 %) who were able to crossover to the sorafenib treatment arm. Complete responses were not seen, but the partial response (PR) rate was 12.2 % in the sorafenib arm compared to 0.5 % in the placebo arm; more patients experienced stable disease. The overall median duration of PR was 10.2 months. The rate of adverse events was 98.6 % in the sorafenib group with common adverse events being hand and foot skin reactions (76.3 %), diarrhea (68.6 %), alopecia (67.1 %), rash (50.2 %), fatigue, and hypertension. The most frequent serious adverse events were secondary malignancies (occurred in 4.3 % of patients in the sorafenib arm). In addition, based on multivariate analysis, the authors observed that neither BRAF nor RAS mutation status was predictive of sorafenib benefit for progression-free survival [179].

Targeted therapy against BRAF V600E mutant tumors is also being explored [180]. The initial phase I trial for vemurafenib, a selective RAF inhibitor, included three patients with metastatic PTC harboring the BRAF(V600E) mutation. At the end of the trial, one patient had a confirmed partial response with reduction of pulmonary target lesions by 31 % with a response duration of 7.6 months before the disease progressed in the lungs and the bones. The time to progression was 11.7 months. The other two patients had stable disease, and the time to progression was 13.2 and 11.4 months, respectively [181]. In a follow-up phase II study, patients with progressive papillary thyroid cancer that was refractory to radioactive iodine (RAI) and had been confirmed positive for BRAF V600E mutation were treated with the BRAF inhibitor, vemurafenib (960 mg twice daily). The trial enrolled 51 patients in two cohorts, about half of whom had received a prior TKI (cohort 2). The best overall response rate was 35 % in cohort 1 and 26 % in cohort 2. No complete response was reported, and the clinical benefit rate (defined as CR+PR+ stable disease (SD) = 6 months) was 58 % and 36 %, in C1 and C2, respectively. Median PFS at the time of data cutoff for the analysis was 15.6 months in C1 and 6.8 months in C2. They also highlighted that seven patients in C1 and 11 patients in C2 discontinued treatment due to progressive disease. In TKI-naive patients, the median PFS

Table 40.2 Molecularly targeted agents in treatment of medullary thyroid cancer (MTC) and differentiated thyroid cancer (DTC)

Drug	Target	Subtype	Toxicity
Sorafenib	VEGFR-2, VEGFR-3, PDGFR-β Flt-3 c-Kit RET RAF FGFR-1	MTC, DTC	Diarrhea Palmar-plantar erythema Skin rash HTN
Vandetanib	RET VEGFR EGFR	MTC	Rash Diarrhea QTc prolongation
Cabozantinib	RET MET VEGFR2	MTC	Diarrhea Hypopigmentation of hair
Lenvatinib	VEGFRs 1, 2, and 3 FGFRs 1 through 4 PDGFR α RET signaling networks KIT signaling networks	DTC	HTN Diarrhea Fatigue
Axitinib	VEGFR-1, 2, 3 PDGFR-α, β KIT	MTC, DTC	HTN
Motesanib	VEGF PDGF KIT RET	DTC	Diarrhea HTN Fatigue Weight loss
Sunitinib	VEGFR PDGFR c-Kit RET	MTC, DTC	Diarrhea Fatigue HTN Palmar-plantar erythema
Pazopanib	VEGF	DTC	Diarrhea Mucositis
Thalidomide	Anti-angiogenic, anti-TNF-α, immunomodulator	MTC, DTC	Hematological
Lenalidomide	Anti-angiogenic Anti-TNF-α, immunomodulator	MTC, DTC	Hematological

was reported as 15.6 months. The reported toxicities in this trial were consistent with those seen with vemurafenib treatment in melanoma patients but with higher rates of weight loss, dysgeusia, anemia, increased creatinine, and abnormal hepatic function panels. Other common adverse events included rash, fatigue, weight loss, and increased bilirubin (source: http://www.esmo.org/Conferences/Past-Conferences/European-Cancer-Congress-2013/News/Vemurafenib-in-Patients-With-RAI-Refractory-Progressive-BRAFV600E-mutated-Papillary-Thyroid-Cancer).

Lenvatinib is an oral multi-tyrosine kinase inhibitor of VEGFR1–3, FGFR1–4, PDGFRa, RET, and KIT, recently obtained US FDA approval for metastatic iodine refractory differentiated thyroid cancer. In a recent phase III trial, the SELECT trial, 392 patients with I-131-refractory differentiated thyroid cancer with documented disease progression were randomized 2:1 to lenvatinib (24 mg a day) or placebo (patients in the placebo group could cross over to the TKI arm upon disease progression). The trial's primary end point was PFS, and secondary end points were overall response rate (ORR; complete response [CR] + PR), overall survival (OS), and safety. Median PFS in the TKI group was 18.3 months compared to 3.6 months in the placebo group (hazard ratio 0.21, 95 % confidence interval [CI] 0.14–0.31; $P < 0.0001$). With regard to types of response, the rate of CR was 1.5 % in the TKI group and 0 % in placebo and PR was a remarkable 63.2 % in the TKI group and 1.5 % in the placebo group. At the time of analysis, median OS had not been reached. Common side effects (any grade) in the lenvatinib group were hypertension (68 %), diarrhea (59 %), appetite decreased (50 %), weight loss (46 %), and nausea (41 %). Significant side effects (grade 3 or greater) in the lenvatinib group were hypertension (42 %), proteinuria (10 %), weight loss (10 %), diarrhea (8 %), and decreased appetite (5 %) [182].

Axitinib is an oral multikinase inhibitor that has shown promising early results but was not subsequently developed further in this disease. In a phase II trial, patients with advanced, incurable thyroid cancer not amenable to surgery or radioactive iodine therapy were enrolled to receive axitinib at 5 mg orally twice a day. The primary end point was

response rate. Duration of response, progression-free survival (PFS), overall survival, safety, and modulation of soluble VEGFR were secondary end points. In this phase II trial, axitinib demonstrated selective inhibition of VEGFR with antitumor activity in all histological subtypes of advanced thyroid cancer. Of 60 patients, 45 had DTC with an overall response rate (ORR) of 31 %. Stable disease (SD) lasting ≥16 weeks was reported in another 44 % of patients. Median PFS in the entire cohort was 18.1 months. Axitinib was generally well tolerated, with the most common grade ≥3 treatment-related adverse event being hypertension ($n=7$; 12 %) [183, 184]. In a follow-up phase II trial, patients with advanced RAI-refractory DTC or unresectable disease with documented disease progression were treated with axitinib 5 mg orally twice a day. The primary end point was response rate, and secondary objectives were progression-free survival (PFS), toxicity profile, and biomarker correlation analysis. Of note, axitinib was first-line MKI therapy in 39 %, second line in 36 %, and subsequent lines 24 % of patients in the trial. Twenty-nine, of a total 41 patients enrolled, had DTC with a response rate of 41 %. Stable disease was reported in 18 % of patients. There were significant differences noted in PFS based on treatment line: first line 12.6 months, second line 8.6 months, and successive lines 3.9 months. The most common grade 3–4 adverse events were anorexia, diarrhea, and cardiac toxicity, which occurred in less than 5 % of pts [185].

Motesanib diphosphate (AMG 706) is a multi-targeted oral inhibitor of VEGF receptors, platelet-derived growth factor receptor, and KIT. In a phase 1 study, treatment with 125 mg of motesanib diphosphate once daily resulted in antitumor activity in patients with advanced solid cancers, including five patients with differentiated thyroid cancer [186]. A phase II study was designed to assess its efficacy and tolerability in progressive, locally advanced, or metastatic differentiated thyroid cancer. ORR was 14 %, 67 % of the patients had SD, and this was maintained for 24 weeks or longer in 35 % of the patients. The most common adverse events were diarrhea, hypertension, fatigue, and weight loss [187].

Sunitinib is another oral multi-targeted kinase inhibitor with activity against RET, VEGFR, and PDGFR. It has been tested in a phase II trial in patients with refractory DTC or MTC. Forty-three patients were enrolled (37 DTC) and treated with 6-week cycles of sunitinib malate 50 mg daily on a 4-week on/2-week off schedule. Primary end points were response rate by RECIST and biochemical response. Stable disease was observed in 68 % of 31 evaluable DTC patients who completed two cycles. Thirteen percent had a PR and 10 % had PD. The most common drug-related adverse events included fatigue, diarrhea, PPE, neutropenia, and hypertension. In patients with iodine refractory DTC with evidence of progressive disease, sunitinib (50 mg daily in a 4-week on, 2-week off schedule) was able to induce responses or disease stabilization [188]. In a similar study, 17 patients with advanced refractory DTC (12 patients) and MTC (4) were treated with sunitinib at similar doses (50 mg daily in a 4-week on, 2-week off schedule). Out of 15 patients that were evaluable for response, one had a PR and 12 had SD (with one pt with >90 % decrease of thyroglobulin and one pt with a dramatic decrease of symptoms). Toxicities were mainly hypertension, asthenia, mucositis, hand-foot syndrome, and thrombocytopenia. Grade 3/4 events were hypertension, asthenia, mucositis, and hand-foot syndrome [189]. Four patients required dose reductions. Continuous dosing of sunitinib at a dose of 37.5 mg orally daily was evaluated in a phase II study in 35 patients with metastatic, refractory DTC (26 patients) or MTC (seven patients). The primary end point was response rate by RECIST. Secondary end points included FDG-PET response rate (defined as 20 % reduction from baseline SUV) after 7 days of treatment, toxicity, overall survival, duration of response, and time to progression. The trial reported an objective response rate of 31 % (11 patients, 95 % CI: 16–47 %). The breakdown of outcomes was as follows: one complete response (3 %), ten partial responses (28 %), 16 with stable disease (46 %), and six with progressive disease (17 %). The median time to progression (TTP) was 12.8 months. Twenty-two patients had a repeat FDG-PET which revealed that median percent change (as average SUVs) was −11.7 %, −13.9 %, and 8.6 % for patients with a RECIST response. Reported common adverse events included fatigue (11 %), neutropenia (34 %), hand-foot syndrome (17 %), diarrhea (17 %), and leukopenia (31 %). Thus, continuous dosing of sunitinib is effective in patients with high-risk, metastatic thyroid cancer, as defined by FDG-PET [190–192].

Pazopanib, an oral anti-VEGF tyrosine kinase inhibitor, has been studied in a phase II trial of 37 patients with advanced and progressive radioiodine-insensitive DTC. The trial authors reported that 18 patients had a partial response (response rate 49 % [95 % CI 35–68]). By cancer type, responses were seen in eight (73 %) of 11 patients with follicular tumors, five (45 %) of 11 patients with Hürthle cell tumors, and five (33 %) of 15 patients with papillary tumors. Median overall survival at 1 year was 81 % (95 % CI 69–95) and progression-free survival (PFS) at 1 year was 47 % (35–68), with median duration of PFS being 11.7 months. Patients had dose reductions for increased AST/ALT, hypertension, proteinuria, peripheral neurological difficulties, weight loss, mucositis, radiation recall tracheitis, diarrhea, fatigue with weight loss, cough, abdominal pain, and patient request. The authors of the study concluded that though this TKI did achieve a good clinical response, further study is required in order to determine the impact on overall survival [193].

Additional anti-angiogenesis therapies have also been tested in advanced and iodine refractory thyroid cancer. Thalidomide offers modest therapeutic benefit in subsets of thyroid cancer patients with rapidly progressive metastatic disease. In a phase II trial, 36 patients with follicular, papillary, insular, or medullary thyroid carcinomas and distant, radioiodine-unresponsive metastases were treated with daily thalidomide (started at 200 mg orally and increased to 800 mg or maximum tolerated dose). Five patients had PR and nine patients had SD, for ORR of 50 %. Median survival was 23.5 months for responders (PR + SD) and 11 months for nonresponders [194]. Fourteen percent of patients had grade 3/4 infections, and 8 % had grade 3/4 fatigue. Fatigue was the most significant toxicity overall with 69 % of patients having some degree (grade 1/2) of fatigue related to therapy. A related drug, lenalidomide, has also been studied in a phase II trial in this patient population with a 67 % ORR (44 % SD + 22 % PR). Three patients continued to have a response for greater than 12 months. Lenalidomide was relatively well tolerated; hematological toxicities were common (44 % neutropenia, 22 % thrombocytopenia) but responded to dose reductions. Full accrual and long-term data analysis are pending [195]. Overall, while these agents did have activity, the toxicities are a concern, especially in light of the long-term duration of therapy that is possible in responding patients.

There is a lack of data and guidance with regards to sequencing of these TKIs. Lenvatinib is known to have activity in prior TKI-exposed patients and thus is an option for subsequent therapy. The SELECT trial demonstrated that when compared to placebo, treatment with lenvatinib significantly prolonged PFS (hazard ratio 0.21, 95 % confidence interval [CI] 0.14–0.31; $P < 0.0001$); median PFS was lenvatinib, 18.3 months (95 % CI 15.1 to not evaluable), and placebo, 3.6 months (95 % CI 2.2–3.7). In addition, combination studies are being conducted in this setting (NCT01263951—everolimus plus sorafenib, NCT01723202—dabrafenib plus trametinib).

40.5.2 Medullary Thyroid Cancer

Medullary thyroid cancer (MTC) is the most common cause of death in patients with hereditary syndromes caused by activating mutations in the RET proto-oncogene. RET activation is the initial oncogenic event, with the activity of other receptor tyrosine kinases, including VEGFR and EGFR, likely to contribute to tumor growth and metastasis. In the past few years, the development of therapies for this disease has resulted in two FDA-approved available agents, vandetanib and cabozantinib.

Vandetanib (ZD6474) is an oral multikinase inhibitor that targets RET, VEGFR, and EGFR tyrosine kinases. It demonstrated efficacy in a phase III study in 331 patients with unresectable, measurable, locally advanced, or metastatic hereditary MTC and a RET germline mutation. Patients were randomized in a 2:1 fashion to receive vandetanib 300 mg daily or placebo until the disease progression or unacceptable toxicity. The primary objective was to determine if vandetanib when compared to placebo improved PFS. Secondary assessments included objective response rate, disease control rate at 24 weeks, duration of response, overall survival, biochemical response (decreases in serum levels of calcitonin and carcinoembryonic antigen [CEA]), and time to worsening of pain. The vandetanib arm showed significantly improved PFS versus the placebo arm (HR, 0.46; median PFS for placebo arm 19.3 months and for the vandetanib arm median PFS not reached at time of analysis though predicted to be 30.5 months). Furthermore, PFS at 6 months was 83 % (vandetanib) and 63 % (placebo). Similarly, vandetanib arm showed significant advantages compared to placebo with regard to the secondary end points of objective response rate, disease control rate, and calcitonin and CEA biochemical response rates. Vandetanib was overall well tolerated; grade 3 adverse effects included diarrhea (11 %), hypertension (9 %), asymptomatic QT prolongation (8 %), and fatigue (6 %), all of which were tolerable. Due to the concerns regarding cardiac toxicity, prescribers must enroll in an REMS program and regular EKG, and electrolyte monitoring is required at the initiation of therapy (source: JCO January 10, 2012 vol. 30 no. 2 134–141).

Cabozantinib is an oral inhibitor of RET, MET, and VEGFR2. Initial activity was noted in a MTC-enriched expansion cohort of a phase I study [196]. The pivotal phase III EXAM trial further confirmed the efficacy of cabozantinib in MTC. This trial enrolled 330 patients who were assigned in a 2:1 fashion to either cabozantinib (140 mg/day) or placebo. The primary end point was progression-free survival (PFS) and secondary end points included tumor response rate, overall survival, and safety. The estimated median PFS was 11.2 months for the cabozantinib arm and 4 months for the placebo arm (hazard ratio, 0.28). Furthermore, the improved PFS in the cabozantinib arm was observed in all subgroups analyzed, which included by age, prior TKI treatment, and RET mutation status (hereditary or sporadic). Overall response rate was 28 % for cabozantinib and 0 % for placebo. The estimated 1-year PFS rate was 47.3 % for cabozantinib and 7.2 % for placebo. Common but significant side effects encountered in the cabozantinib arm included diarrhea, palmar-plantar erythrodysesthesia, decreased weight and appetite, nausea, and fatigue (source: JCO October 10, 2013 vol. 31 no. 29 3639–3646).

Sorafenib is an oral agent with documented efficacy in DTC, as has been illustrated by the results of the DECISION trial. It has also been shown to have some activity in MTC. In a phase II study, 16 patients with sporadic MTC were treated with 400 mg orally twice daily. Primary end point was objective response, and secondary end points included toxicity assessment, response correlation with tumor markers, functional imaging, and RET mutations. At the end of the trial, one patient achieved a partial response (PR; 6.3 %), 14 had stable disease (SD; 87.5 %), and one was non-evaluable. The median PFS for the trial was 17.9 months, and the median overall survival time was not reached at the time of data analysis. Significant, grade 3+ adverse events included hypertension, HFSR, diarrhea, joint pain, infections, thrombocytopenia, and hyponatremia. It should also be noted that several of the multikinase inhibitor trials that have been previously discussed also enrolled limited numbers of MTC patients. For instance, 12 patients with MTC were treated on the axitinib trial, with a resulting PR in 25 % and SD in 33 %. This data is especially interesting in light of the fact that axitinib is an anti-angiogenesis agent and does not target RET, thus, illustrating that targeting angiogenesis is a potent strategy in the treatment of this disease. As discussed previously, the sorafenib studies also included patients with MTC [177, 178]. In the study by Brose et al. that was updated at the 2009 American Society of Clinical Oncology Meeting, two patients with MTC were treated; one had SD and one had a PR. The phase II studies of sunitinib included patients with MTC, although in small numbers. In one study, six patients with MTC were enrolled. The best response in MTC patients was SD 83 % and PD 17 % [188].

Sunitinib is an oral multikinase inhibitor that targets multiple receptors, including RET, VEGFR2, PDGFR, and c-Kit. In a phase II trial, 25 patients with MTC who had evidence of disease progression within the prior 6 months and were not amenable to surgery or radiotherapy were treated with sunitinib 50 mg on a 4/2-week schedule (note that only 23 patients were analyzed). The authors of the trial reported that eight patients (35 %) achieved a partial response and 13 patients (57 %) had stable disease (SD). In pooled analysis, there was an overall response rate of 35 % and clinical benefit rate (PR + SD) of 91 %. Significant adverse events included lymphopenia (six pts), neutropenia (five pts), PPE (four pts), and mucositis. Thus, sunitinib has activity in MTC and may be associated with a durable response [197].

Finally, pazopanib, an oral anti-VEGF tyrosine kinase inhibitor that has shown promise in DTC, has also been studied in MTC. A phase II trial studied the efficacy and side effect profile of pazopanib in treating patients with advanced MTC who had disease progression within the preceding 6 months. The trial enrolled 35 patients, all whom were placed on pazopanib 800 mg daily. In the trial, five patients attained a partial response (14.3 %) and had a median progression-free survival and overall survival of 9.4 and 19.9 months. In addition, the common side effects encountered included new onset hypertension (33 %), fatigue (14 %), diarrhea (9 %), and abnormal liver tests (6 %). The authors of the trial concluded that based upon these results, Pazopanib shows activity in MTC with a manageable side effect profile [198].

40.6 Parathyroid Cancer

Parathyroid cancer is a very rare cancer, with an estimated incidence of 0.015 per 100,000 population and an estimated prevalence of 0.005 % in the United States [199, 200]. Mean age at presentation is 44–54 years, with similar incidence in both males and females. These tumors generally have low malignant potential and parathyroid cancer typically runs an indolent course. The major clinical manifestations of parathyroid carcinoma are hypercalcemia (65–75 %), neck mass (34–52 %), bone and renal disease (34–73 % each), and high serum parathyroid hormone (PTH) concentrations (5–10 times upper limit of normal). At initial presentation, very few patients with parathyroid carcinoma have metastases either to regional lymph nodes (<5 %) or distant sites (<2 %). A higher proportion of patients present with locally invasive diseases (into surrounding soft tissue, muscles, and nerves) [201–203].

There is an increased risk of parathyroid cancer in patients with multiple endocrine neoplasia 1, a p53 mutation, radiation exposure, and autosomal dominant familial-isolated hyperparathyroidism [204–207]. HRPT2 is a tumor suppressor gene that is located on chromosome 1 and encodes parafibromin, a protein involved in regulation of gene expression and inhibition of cell proliferation. Mutation of this tumor gene plays a central role in the molecular pathogenesis of parathyroid carcinoma [208–211]. Mutational analysis of tumors from patients with histologically confirmed parathyroid cancer and no family history found HRPT2/CDC73 somatic mutations of 60–70 % of cases [180, 182, 212, 213].

Germline DNA analysis for *HRPT2/CDC73* mutation is recommended in all patients with parathyroid cancer because molecular genetic analysis of seemingly sporadic parathyroid carcinomas reveals mutations in *HRPT2/CDC73* that are also present in the germline DNA in as many as 20–30 % of cases. The finding of a germline mutation may potentially benefit offspring and other first-degree relatives who should also have serum calcium screening [213].

Parathyroidectomy with en bloc resection of involved adjacent lymph nodes remains the mainstay in management of parathyroid cancer [214–216]. Adequate surgical excision requires removal of the ipsilateral thyroid lobe and isthmus, skeletonization of the trachea, and excision of any skeletal muscle intimately related to the tumor. The surgeon must be careful not to rupture the capsule of the tumor to

avoid seeding of the surgical field [217]. Central neck and ipsilateral-modified functional radical neck resection are usually performed only if enlarged or abnormal-appearing lymph nodes are found to be involved on frozen section analysis [213]. Both adjuvant chemotherapy and radiation therapy have generally given poor results. Use of either should be considered only when a patient is not a candidate for surgery and hypercalcemia cannot be controlled.

Approximately 40–60 % of patients experience a postsurgical recurrence, typically between 2 and 5 years after the initial resection. Recurrence is usually local and hypercalcemia is one of the harbingers of disease recurrence. Repeat surgical exploration with resection may be employed in cases of local recurrence. Removal of isolated metastatic sites may also help in alleviating symptoms associated with hypercalcemia. Because parathyroid carcinoma can be slow growing, resection of local recurrences or distant metastases can provide effective palliation without curing the patient. When the tumor is no longer amenable to surgical intervention, treatment becomes limited to control of hypercalcemia with hydration, a calcimimetic agent, or intravenous bisphosphonates [218–221]. Given the rarity of this disease and its indolent course, there is a paucity of clinical trials of systemic therapy and many patients would likely be candidates for phase I studies.

40.7 Discussion and Future Directions

Significant advances have been made in our understanding of the biology of thyroid cancer, and the introduction of molecularly targeted agents is transforming the treatment paradigm for incurable metastatic thyroid cancer. With the availability of FDA-approved agents for both differentiated and medullary thyroid cancer, patients have access to effective treatment options. Given the responses and clinical benefit that is possible with many of the agents discussed above, some key unanswered questions in the management of these patients include: (1) what is the best time to initiate systemic therapy, (2) what is the best treatment sequence of these newer agents, and (3) what are the mechanisms and patterns of resistance and cross-resistance to these agents? Although treatment with oral TKIs is fairly well tolerated, many patients develop grade 1 and 2 toxicities that do affect their quality of life especially with the very prolonged administration (years in some cases) that is required for a treatment that does not result in a sustained complete response or cure. Thus, for many patients with what is often an indolent, asymptomatic disease even when incurable and metastatic, a watchful waiting approach may be the most reasonable option.

The goal for the future of cancer therapy overall is to utilize validated biomarkers in order to guide treatment selection unlike the current practice of sequential, empiric therapy. Given the growing knowledge of key pathways involved in the initial pathogenesis and progression of thyroid cancer, future studies of this disease should also focus on the development of biomarkers that can help guide the selection of the TKI that is best for an individual patient. Also, defining prognostic markers would allow physicians to identify patients with the more aggressive tumors who should initiate treatment sooner or receive more aggressive combination regimens of TKIs. As oncology moves closer toward the practice of personalized medicine, the hope is that the expected benefit for each treatment will increase, and patients can be spared excessive toxicity to treatment.

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Head and Neck Paragangliomas

41

Julian Künzel, Michael Hainz, Heidi Rossmann, and Christoph Matthias

Abstract

Head and neck paragangliomas are highly vascularized neuroendocrine tumors derived from the extra-adrenal paraganglia of the autonomic nervous system. These tumors may occur either sporadically or in the context of a hereditary familial tumor syndrome, and multifocal presentations are observed, particularly in hereditary cases. Hereditary paragangliomas are mostly caused by mutations in the succinate dehydrogenase complex genes. Early imaging, with ultrasonography of the neck and magnetic resonance imaging (MRI) of the skull base, is essential for localizing and assessing the extent of the tumor, as well as for precise planning of the treatment approach. Views regarding the treatment of choice are generally moving away from radical resection toward surgical tumor reduction in order to preserve function and reduce morbidity. Radiotherapy modalities are alternative primary treatment options, depending on the individual situation (e.g., in relation to age, comorbidity, multifocal lesions, and risk of injury to the cranial nerves). Observation is an option in selected patients. The potential morbidity of surgical treatment must be weighed against the expectable quality of life, and comprehensive consultation with the patient about the possible treatment modalities is mandatory. Treatment decision-making should involve a multidisciplinary team of experts in the fields of nuclear medicine, genetics, pathology, radiology, radio-oncology, and surgery.

Keywords

Paragangliomas • Head and neck • Surgery • Radiotherapy • Observation • Cranial nerve deficit

41.1 Introduction

Paragangliomas (PGLs) are highly vascularized neuroendocrine tumors derived from the extra-adrenal paraganglia of the autonomic nervous system. Virtually all head and neck PGLs arise from the parasympathetic nervous system [1]. The nomenclature of PGLs is confusing and reflects the fact that these tumors are rare and poorly understood. At present, the World Health Organization Classification of Tumors prefers the term "paraganglioma," and this is the term that should therefore be used [2]. Generally, the site of origin defines the name given to these tumors (e.g., carotid PGL, tympanic or jugular PGL, vagal PGL, etc.) Previously, they were designated as chemodectomas, nonchromaffin PGLs,

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or glomus tumors. Glomus is the most frequently misused term, as it only refers to the morphology of the tumors [3]. Glomangiomas are benign tumors arising from neuromyoarterial cells surrounding cutaneous arteriovenous anastomoses that serve as temperature regulators [4].

PGLs may occur either sporadically or in the context of a hereditary familial tumor syndrome [5, 6]. Multilocular presentations of PGLs are observed in 10–20 % of sporadic cases and up to 80 % of hereditary cases. Hereditary PGLs are mostly caused by mutations in the succinate dehydrogenase complex (*SDHx*) genes, in particular *SDHD* [7]. The incidence is two to five times higher in women, and the age at manifestation is between 40 and 60 [8, 9]. The mean tumor-doubling rate has been reported as 4.2 years [10], with a mean growth rate of only approximately 0.2 cm per year [11]. They originate in the paraganglionic tissue in the area of the carotid bifurcation (carotid paraganglioma, CP), jugular foramen, and tympanic plexus (jugulotympanic paraganglioma, JTP), the vagal nerve (vagal paraganglioma, VP), the nose or paranasal sinuses [12], and the facial nerve [13].

PGLs only show histopathological signs of malignancy or metastases to nonendocrine tissue in approximately 3 % of cases. The metastatic rate has been shown to be highest in vagal tumors (16 %), followed by carotid PGLs (6 %) and jugulotympanic PGLs (4 %). The reported 5-year survival rate, based on the American National Cancer Database, is about 60 % when regional metastases are found [14]. The rate of malignancy also differs significantly between sporadic and familial cases. Among patients in our own institution, 6.3 % had a malignant PGL. Metastases develop most frequently (almost 70 %) in regional lymph nodes, followed by the spinal canal, lung, liver, or skin [15]. Diagnosing malignancy in PGLs is difficult, as there are no valid histomorphologic criteria for malignancy in these tumors. The diagnosis of malignancy is also controversial and is usually based on locally destructive and invasive growth, lymph-node metastases, and/or distant metastasis.

Surgical resection is the preferred treatment for isolated PGLs, but radiation therapy should be considered for patients who are at high surgical risk [16]. It is important to note that the goal of radiotherapy is disease control or growth inhibition, rather than tumor elimination. An observation strategy may be appropriate for selected patients. The potential morbidity of surgical treatment must be weighed up against patient-oriented factors to determine an appropriate course of action. Early rehabilitation is an important key factor for restoring function and quality of life.

41.2 Epidemiology and Genetics

Pheochromocytomas and PGLs are rare tumors of the autonomic nervous system (with a prevalence of one in 2500–6500 individuals [17]). They represent closely related tumor entities. While pheochromocytomas secrete catecholamine and are located in the adrenal medulla, PGLs arise from the extra-adrenal sympathetic and parasympathetic paraganglia. Pheochromocytomas have a substantially higher prevalence in comparison with PGLs [17].

Head and neck PGLs are generally parasympathetic. Parasympathetic PGLs are highly vascularized, mostly benign tumors, with an incidence of one in 100,000 to one in 1,000,000 per year [6]—representing an estimated 0.5 % of all head and neck tumors [7]. PGLs typically present in middle-aged adults (at a mean age of about 43 years). Most head and neck PGLs (over 60 %) originate from parasympathetic cells at the bifurcation of the carotid artery (carotid paraganglioma, CP), followed by the jugular and tympanic paraganglia and the vagal nerve (with VPs representing about 5 % of head and neck PGLs) [1, 18]. In rare cases, PGLs can arise in various additional locations, including the facial nerve [13], larynx, paranasal sinuses, nasopharynx, orbit, and thyroid gland, which all contain paraganglia.

Pheochromocytomas and PGLs can occur as sporadic tumors or, in up to 40 % of cases, as a manifestation of a hereditary tumor syndrome [19]. In recent years, 16 genes have been identified (Table 41.1) that predispose to the PGL/pheochromocytoma syndrome or related syndromes in which PGL and pheochromocytoma occur among other characteristic disease features. Related syndromes include von Hippel–Lindau (VHL) syndrome, multiple endocrine neoplasia type 2 (MEN2), and neurofibromatosis type 1 (NF1). Most of these syndromes are inherited with autosomal dominance, and paternal transmission of the disease has been established for some of the genes—succinate dehydrogenase complex, subunit D (*SDHD*), succinate dehydrogenase complex assembly factor 2 (*SDHAF2*), and MYC-associated factor X (*MAX*) [19–21]. Before the year 2000, the three classic syndromes MEN2, VHL, and NF1 were the only genetic conditions known to be associated with pheochromocytomas and PGLs. The rate of tumors with genetic causes was therefore dramatically underestimated. In 2000, Baysal et al. found that *SDHD*, a subunit of the succinate dehydrogenase (SDH) complex, was the cause of what is known as PGL1 disease [22]. SDH is involved in the aerobic electron transport chain and in the Krebs cycle. SDH deficiency results in a pseudohypoxic state in the cell, and the most common tumor in PGL1 disease is a PGL of the carotid body, a chemoreceptive organ that functions as a blood oxygen sensor. At that time, it was already known that hypoxia at altitudes over 2000 m increases the incidence of CPs [23]. These data suggest that de facto hypoxia and pseudohypoxia are both able to induce carotid body cell growth.

In subsequent years, the other subunits in the succinate dehydrogenase complex, *SDHB* [24], *SDHC* [25], *SDHA* [26], and the assembly factor *SDHAF2* [27], were identified as susceptibility genes for PGLs and pheochromocytomas. Along with several other genes—*VHL*, fumarate hydratase

Table 41.1 Germline mutations in paraganglioma/pheochromocytoma (PGL/Pheo) susceptibility genes

Gene name (HGNC)	Locus (HGNC)	Syndrome	Inheritance	Hormone secretion	PGL/Pheo location	Malignancy risk	Example additional disease characteristics
Gene product involved in the hypoxia pathway (cluster 1)							
SDHA	5p15	–	AD: tumor predisposition AR: Leigh syndrome	Unknown	HN, EA	Unknown	GIST, pituitary adenoma
SDHB	1p36.1–p35	PGL4	AD	MN, NMN, MTY, NS	HN, EA, A	Ca. 40 %	RCC, GIST, thyroid cancer, pituitary adenoma
SDHC	1q23.3	PGL3	AD	MN, NMN, NS	HN, EA, A	Low	RCC, GIST, thyroid cancer, pituitary adenoma
SDHD	11q23	PGL1	AD, PI	MN, NMN, MTY, NS	HN, EA, A	ca. 5 %	RCC, GIST, thyroid cancer, pituitary adenoma
SDHAF2	11q12.2	PGL2	AD, PI	Unknown	HN	Unknown	Unknown
VHL	3p25.3	VHL	AD	NMN	A, EA, HN	≤5 %	Hemangioblastoma, RCC, renal + pancreatic cysts, NET, ELST
FH	1q42.1	Hereditary leiomyomatosis and RCC	AD: tumor predisposition AR: fumarase deficiency	Unknown	A, EA	Unknown	Leiomyomas, RCC
EPAS1/HIF2A	2p21–p16	Familial erythrocytosis 3/Pacak–Zuhang	Unknown	Unknown	EA, A	Unknown	Polycythemia, somatostatinoma
EGLN2/PHD1	19q13.2	–	Unknown	Unknown	Unknown	Unknown	Polycythemia
EGLN1/PHD2	1q42.1	Familial erythrocytosis 4	Unknown	Unknown	Unknown	Unknown	Polycythemia
KIF1Bβ	1p36.22	–	Unknown	Unknown	Unknown	Unknown	Neuroblastoma, CMT2A2
Gene product involved in kinase receptor signaling and/or protein translation pathways (cluster 2)							
NF1	17q11.2	NF1	AD	NM, NMN	A	ca. 11 %	Café-au-lait spots, Lisch nodules, neurofibromas, gliomas, etc.
RET	10q11.2	MEN2	AR	NM, NMN	A	≤5 %	MTC, PHPT, adenoma, etc.
TMEM127	2q11.2	–	AD	NM, NMN	A, EA, HN	≤5 %	RCC?
MAX	14q23.3	–	AD, PI	NM, NMN	A	10–25 %	Unknown
BAP1	3p21.1	–	Unknown	Unknown	Unknown	Unknown	Melanoma, mesothelioma, meningioma

A pheochromocytoma (adrenal), *AD* autosomal dominant, *AR* autosomal recessive, *BAP1* BRCA1-associated protein-1, *CMT2A2* Charcot–Marie–Tooth syndrome type 2A2, *EA* extra-adrenal (abdominal and thoracic) PGL, *EGLNx* egl-9 family hypoxia-inducible factor X, *ELST* endolymphatic sac tumor, *EPAS1* endothelial PAS domain protein 1, *FH* fumarate hydratase, *GIST* gastrointestinal stromal tumor, *HGNC* HUGO Gene Nomenclature Committee, *HIF2A* hypoxia-inducible factor 2A, *HN* head and neck PGL, *KIF1B* kinesin family member 1B, *MAX* MYC-associated factor X, *MEN2* multiple endocrine neoplasia type 2, *MN* metanephrine, *MTC* medullary thyroid carcinoma, *MTY* methoxytyramine, *NET* neuroendocrine tumor, *NF1* neurofibromatosis type 1, *NMN* normetanephrine, *NS* nonsecreting, *PGL* paraganglioma, *PHDx* prolyl hydroxylase X, *Pheo* pheochromocytoma, *PHPT* primary hyperparathyroidism, *PI* paternal inheritance, *RCC* renal cell carcinoma, *RET* ret proto-oncogene, *SDHAF2* succinate dehydrogenase complex assembly factor 2, *SDHx* succinate dehydrogenase complex, subunit X, *TMEM127* transmembrane protein 127, *VHL* von Hippel–Lindau

Based on data from refs. [19, 21, 28, 38, 124]

(*FH*), egl-9 family hypoxia-inducible factors 1 and 2 (*EGLN1* and *EGLN2*, with the corresponding synonyms *PHD2* and *PHD1*), endothelial PAS domain protein 1 (*EPAS1*, synonym *HIF2A*), and kinesin family member 1B (*KIF1B*)—they are summarized as gene products that are involved in the hypoxia pathway (cluster 1) [21, 28]. The second cluster of genes that are associated with pheochromocytomas and PGLs codes for gene products that are involved in kinase receptor signaling and/or protein translation pathways. Cluster 2 comprises *TMEM127* [29, 30], *MAX* [31, 32], and *BAP1* [33], in addition to the classic syndrome-causing genes *NF1* and *RET* (rearranged during transfection) proto-oncogene (the cause of MEN2).

The rapid progress that has been made in this field was mainly triggered by two factors: firstly, the establishment of central registries for PGL/pheochromocytoma patients and the setting up of large collections of tumor tissue and genomic DNA, along with the establishment of clinical databases and secondly, the availability of next-generation sequencing methods. With the number of known disease-causing genes, the complexity of diagnostic genetic analyses and the associated costs increased, since identifying patients who are affected by a hereditary tumor syndrome is a prerequisite for genetic counseling and adequate follow-up for all mutation carriers—particularly in the light of recurrent, multiple, and possibly catecholamine-secreting tumor(s) and in some cases impending malignant disease. In parallel with this, the number of patients who had to be characterized genetically increased, as it was recognized that hereditary PGL/pheochromocytoma cases are much more common than had previously been assumed (see above). Clinical predictors have therefore been defined (Fig. 41.1) that help to identify patients who are particularly at risk for carrying a germline mutation in the PGL/pheochromocytoma susceptibility genes [17, 20, 34–36]. These clinical predictive factors are age ≤ 45 years, occurrence of bilateral or multifocal tumors, extra-adrenal tumors and other characteristic features of a known syndrome, a positive family history, malignancy, and detection of elevated dopamine or methoxytyramine levels in plasma or urine. Complex diagnostic algorithms were evaluated (Fig. 41.1), taking the following factors into account: the location and number of the tumors, possible hormone secretion or malignancy of a tumor, the biochemical profile of the tumor, its immunohistochemistry using *SDHB*- and *SDHA*-specific antibodies, the patient's age, possible further syndromic characteristics in the patient, and the general frequency of mutations in a gene in the population. For example, mutations in *SDHD* are more common than mutations in *SDHB*, and mutations in *SDHB* are more common than mutations in *SDHC*. The occurrence of multifocal tumors, one or more tumors localized in the head and neck, and paternal transmission of the disease are characteristics of *SDHD* mutation carriers. Malignancy and elevated dopamine or methoxytyramine levels are common in *SDHB* mutation carriers. Hemangioblastoma, clear cell renal carcinoma, renal and pancreatic cysts, and gastropancreatic neuroendocrine tumors are suggestive of VHL. MEN2 is characterized by medullary thyroid carcinoma and primary hyperparathyroidism, NF1 by café-au-lait spots, Lisch nodules, neurofibromas, gliomas, and a series of other features. A combination of PGL and polycythemia points to a mutation in the *EPAS1*/*HIF2A*, *EGLN2*/*PHD1*, or *EGLN1*/*PHD2* genes. The Carney–Stratakis triad—gastric gastrointestinal stromal tumor (GIST), pulmonary chondroma, and extra-adrenal PGL—or dyad (GIST and PGL) is often caused by mutations in the *SDHx* (SDHB, C, and D) genes.

However, what all of the diagnostic strategies and algorithms have in common is that they are complex and that in most cases the clinical picture is not complete—e.g., because the patient is relatively young and is affected by only one tumor. The question also arises of whether patients with apparently sporadic PGL or pheochromocytoma should undergo genotyping as well [37, 38], since recent data suggest that the frequency of mutation carriers even in groups of patients with "sporadic" tumors is 11–13 % [39]. The lack of a family history here, especially in cases of *SDHx* mutations, is not due to a high rate of de novo mutations but rather to incomplete penetrance of the mutations and the paternal transmission of the disease symptoms [17].

Next-generation sequencing is now available for diagnostic purposes. Exome sequencing [40] and a gene-panel sequencing approach [41] have already been applied successfully to PGL/pheochromocytoma syndrome. The latter method in particular is rapid and cost-effective and may soon be able to replace complex genotyping algorithms.

The precise pathological molecular mechanisms that lead to the development of paraganglial tumors are still largely unknown. Apart from *HIF2A* and the *RET* proto-oncogene, all of the genes listed in Table 41.1 are tumor suppressor genes. Deficiency of a cluster 1 gene product (e.g., *SDH*) probably plays a major role in increased cell proliferation, but germline heterozygosity ("first hit") for a mutation in a PGL susceptibility gene is usually not sufficient to cause tumor growth. According to Knudson's hypothesis [42], a second hit is necessary. In heterozygotes, loss of the second, functioning allele (loss of heterozygosity, LOH) causes complete deficiency for the relevant gene product, resulting in tumor growth. This mechanism is confirmed by the fact that LOH and deficiency of the respective protein (e.g., detection of *SDHB* or *SDHA* deficiency by immunohistochemistry) can usually be demonstrated in the cells of a tumor [43] that has developed on the basis of a germline mutation (e.g., in *SDHx*-caused tumors).

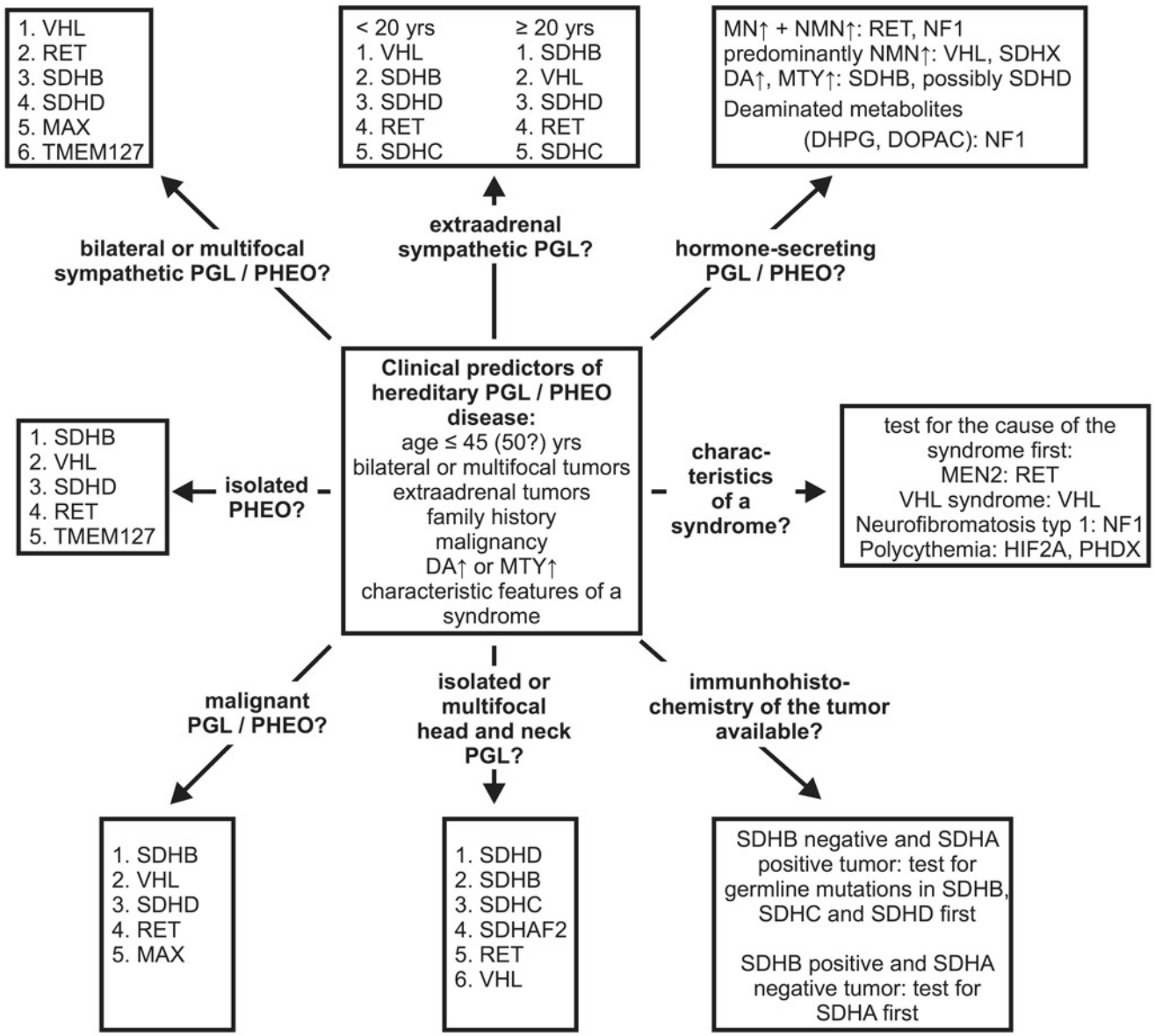

Fig. 41.1 Summary of possible genetic testing algorithms suggested in recent years. These relatively complicated algorithms may be replaced in the future by next-generation sequencing strategies (exome or panel sequencing, at least including the genes listed in Table 41.1), complemented by a method allowing the detection of large deletions and insertions. *DA* dopamine, *DHPG* 3,4-dihydroxyphenylglycol, *DOPAC* 3,4-dihydroxyphenylacetic acid, *HIF2A* hypoxia-inducible factor 2A, *MAX* MYC-associated factor X, *MEN2* multiple endocrine neoplasia type 2, *MN* metanephrine, *MTY* methoxytyramine, *NF1* neurofibromatosis type 1, *NMN* normetanephrine, *PGL* paraganglioma, *PHDX* prolyl hydroxylase X, *PHEO* pheochromocytoma, *RET* ret proto-oncogene, *SDHAF2* succinate dehydrogenase complex assembly factor 2, *SDHX* succinate dehydrogenase complex, subunit X, *TMEM127* transmembrane protein 127, *VHL* von Hippel–Lindau (based on data from refs. [17, 20, 34–36])

41.3 Anatomy, Physiology, and Histopathology

Paraganglia are in the majority of cases tiny structures that cannot be detected without the aid of a dissection microscope. They have a more or less symmetrical distribution along the central axis, lying on both sides of the midline. Paraganglia in the sympathoadrenal neuroendocrine system are closely associated with the sympathetic nervous system, while paraganglia in the head and neck are more aligned with the parasympathetic nervous system.

Paraganglia show an association between neural crest-derived cells and capillaries. One critical function they have is the production of catecholamines [44] before the adrenal medulla matures sufficiently to do so; another aspect is maintenance of vascular tension [45] before the sympathetic nervous

system reaches maturity. Most paraganglia increase in volume up to the age of three and undergo regression afterwards [46], but some persist without involution into adulthood [47]. The anatomic distribution and location of head and neck paraganglia imply a chemoreceptor role for this group. The largest accumulation is in the carotid body, first described by Taube and named "paraganglia" by Kohn [48].

The carotid bodies are chemoreceptors and baroreceptors, located on the medial surface of the common carotid bifurcation. The initial evidence that they have a chemoreceptor function was reported by Heymans et al. [49]. The carotid body weighs approximately 12 mg (combined) in adults [50], and its normal size is approximately 5 × 3 × 1.5 mm [51]. It is sensitive to changes in pH, blood flow, and partial pressure of oxygen. It acts to regulate respiration and maintain homeostasis of arterial gases by stimulating the cardiopulmonary system. Chronic hypoxic states such as chronic obstructive pulmonary disease, high altitude, and heart disease can induce hyperplastic changes in the carotid body that are identical to the development of PGLs. The increased incidence of these tumors at higher altitudes corroborates this [52].

The baroreceptor function of the carotid body–sinus complex is well known. The sinus is made up of stretch receptors and is in close proximity to the carotid body. The stretch receptors are in the adventitia near the carotid body and are stimulated when stretched by increased intraluminal pressure [53]. The nerve supply to the carotid sinus and body is mainly via Herring's nerve, a branch of the glossopharyngeal. Minor inputs come from the sympathetic chain and vagus nerves. Stretching of the carotid sinus increases the firing rate that is transmitted to the brain stem. This is relayed to the vagal center of the medulla to inhibit vasoconstriction, decrease the heart rate, and reduce blood pressure. This physiology is important, particularly in the surgical management of patients with bilateral carotid body tumors (discussed below).

PGLs generally have a slow rate of growth, but 2–19 % of PGLs in the head and neck region show signs of malignancy [54]. Physiological activity is rare.

PGLs contain two main cell types. What are known as "chief cells" (sometimes called glomus type I cells), which are more abundant, lie in small clusters (known as "Zellballen") or strands (Fig. 41.2). Using immunohistochemistry, chief cells stain readily with antibodies to chromogranin and synaptophysin (Fig. 41.3). The second type of cells can be stained with antibodies to S-100 and are known as sustentacular cells (or glomus type II cells). Care must be taken during evaluation, as antibodies against S-100 will also stain local Schwann cells (Fig. 41.4). Sustentacular cells flank the *Zellballen* and strands of chief cells and capillaries.

Chief cells have been divided into three different subtypes, due to different staining patterns and nuclear characteristics. These are termed light cells, dark cells, and progenitor/pyknotic cells [55]—although this classification does not have a known functional correlate. Both chief cells and sustentacular cells are embedded in a highly capillarized fibrovascular stroma. Due to the high degree of vascularization, chief cells are in an excellent position to sample the milieu and alter physiological parameters by hormonal means or neurotransmitter release in order to alter afferent nerve firing. Due to the neural crest origin of chief cells, commonly used histopathologic stains and antibodies that are used to identify PGLs are also positive in other neural crest-derived tumors. Other neural crest tumors should therefore always be included in the differential diagnosis. Close correlation with clinical and radiographic findings is essential in establishing a diagnosis of PGL.

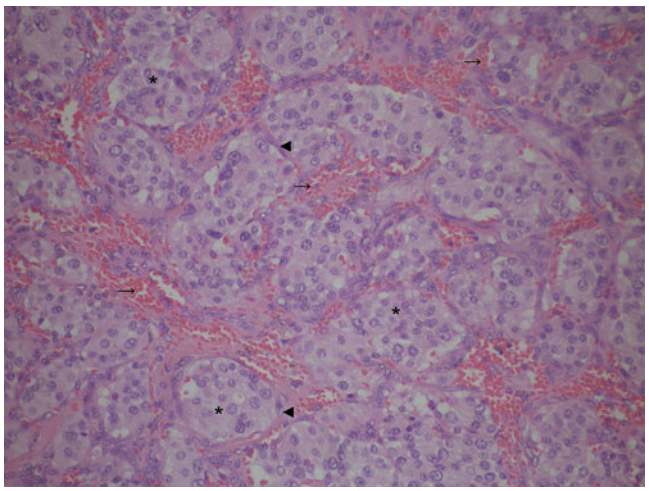

Fig. 41.2 Histopathology of paragangliomas. Clusters of type I chief cells (*asterisks*) surrounded by sustentacular cells (*arrowheads*) create the typical "Zellballen" pattern. Note the abundant stromal capillaries, indicated by *small arrows* (hematoxylin–eosin, original magnification ×200)

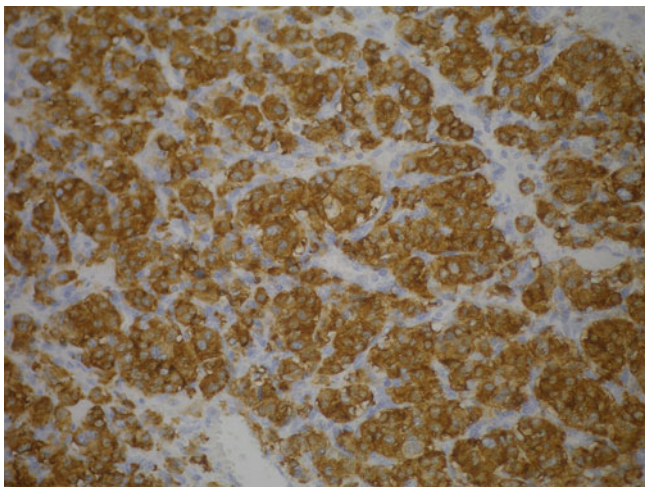

Fig. 41.3 Histopathology of paragangliomas. The chief cells show a prominent cytoplasmic reaction when incubated with antibodies against synaptophysin (original magnification ×200)

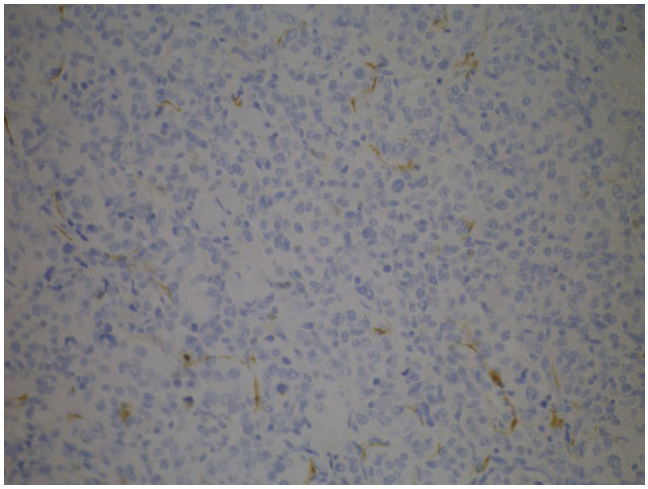

Fig. 41.4 Histopathology of paragangliomas. Sustentacular cells in the periphery of individual chief cells nests are highlighted with antibodies against S-100 (original magnification ×200)

The designation of PGLs is generally based on the anatomic site of origin. Following Glenner and Griley, four different subgroups (or five, counting the adrenal medulla) have been described [56, 57]. These groups are known as the adrenal, aorticosympathetic, intravagal, and branchiomeric groups. Paragangliomas in the head and neck region mainly consist of tumors in the branchiomeric and intravagal groups.

Most PGLs are composed mainly of neoplastic chief cells, the density of which is usually greater than in nonneoplastic paraganglia. Sustentacular cells are much rarer, representing 1–5 % of all cells in a given PGL [58]. A dominant inflammatory infiltrate, mostly of the chronic inflammation type, may rarely be seen. CPs may show an increase in stromal components, up to the point of mimicking an invasive malignant neoplasm with a desmoplastic reaction. These lesions are sometimes called sclerosing PGLs.

The histologic parameters for malignant behavior have still not yet been clearly established. Mitotic activity, vascular invasion, nuclear pleomorphism, and necrosis are not related to the metastatic potential. To the present day, malignancy is still determined by the clinical appearance of metastatic disease.

41.4 Clinical Features and Imaging

At the patient's first admission, a comprehensive history and physical examination are mandatory and should include a family history of relatives who may be suspected of having had PGLs or neck masses. CPs remain clinically silent before presenting in 60–70 % of cases as a painless, slowly growing mass in the lateral neck, in middle-aged patients [59]. In the remainder of cases, initial symptoms may include cranial nerve dysfunction (CND) [10]. In the present authors' view, all patients with a cervical mass should undergo ultrasonography of the neck as the initial diagnostic procedure, regardless of any imaging findings from external sources that may be available. To distinguish CPs from VPs, particularly on ultrasonography, it is helpful to recall that CPs typically displace the external carotid artery anteromedially and the internal carotid artery posterolaterally, while VPs displace both arteries anteriorly (Figs. 41.5 and 41.6).

Palpable pulsation and/or a bruit may be heard over the mass. Parapharyngeal extension demonstrated by a medial bulge of the lateral oropharyngeal wall may be present in large cervical PGLs. In VPs, common symptoms are an asymptomatic neck mass in approximately 65 % of patients, pulsatile tinnitus, hoarseness, and partial to complete loss of lower cranial nerves IX through XII [60]. According to Sykes et al. cranial nerve deficits are the initial findings with VPs in fewer than 50 % of cases [61].

Clinical examinations of the cranial nerves must be carried out both before and after treatment, in addition to endoscopic examinations and pure tone audiography. Before the start of treatment, all of the patients should undergo detailed vestibular nerve diagnosis. Facial nerve function should be classified in accordance with the House–Brackmann system [62]. JTPs may present as reddish, gleaming, or pulsating space-occupying lesions in a hypotympanic location on otoscopy in about 90 % of cases. The most frequent symptoms reported are pulsatile tinnitus in 90.0 % of cases and hypoacusis in about 75 % of cases. Facial nerve paresis and paresis of the lower cranial nerves can be observed in about 4–11 % [63]. Early imaging, with computed tomography (CT) of the petrous bone and MRI of the skull base, is essential for localizing and assessing the extent of the tumor, as well as for precise planning of the treatment approach—particularly in cases of suspected VP—in order to delineate the cranial extension to the skull base. The CT appearance of a PGL typically reveals a homogeneous, contrast-enhancing mass in well-defined locations: the carotid bifurcation (CP), posterior to the great vessels (VP), and jugular foramen (JTP) (Fig. 41.7c, d). On MRI, PGLs usually show a hyperintense signal on T2 weighting and clear contrast uptake on T1 weighting. A "salt-and-pepper" appearance on T1-weighted images is a typical morphological sign for paragangliomas. Due to their contrast uptake on MRI, PGLs can usually be distinguished from genuine cholesteatomas and other tumor entities in the differential diagnosis (Fig. 41.7f) [64, 65].

MRI angiography or CT angiography may also be carried out preoperatively. The external and internal carotid arteries are splayed when a CP is present—best described by the "lyre sign," named after the shape of the ancient stringed instrument. The great vessels are classically pushed anteriorly in the presence of VP (Fig. 41.8).

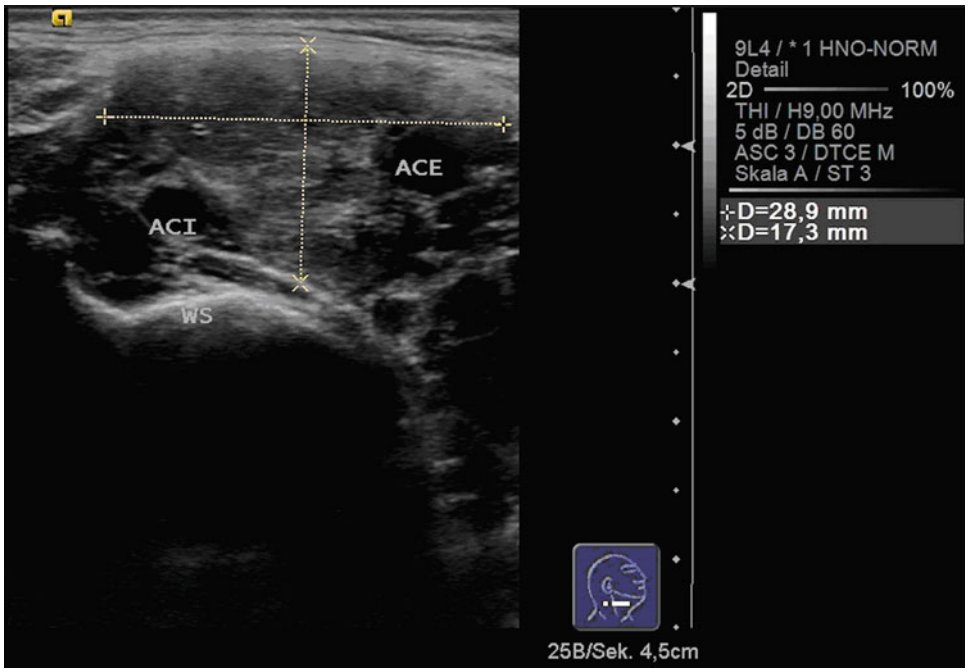

Fig. 41.5 Ultrasound of a carotid paraganglioma on the right side of the neck (B-mode). The tumor (28.9 × 17.3 mm) is displacing the external carotid artery (ACE) anteromedially and the internal carotid artery (ACI) posterolaterally. WS, spine

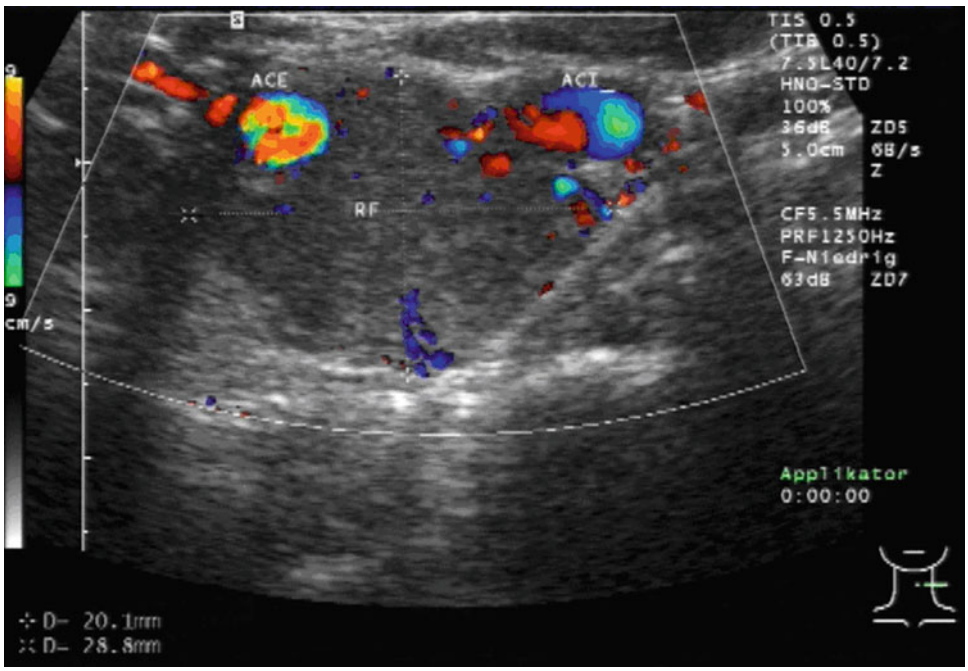

Fig. 41.6 Ultrasound of a vagal paraganglioma on the left side of the neck (duplex mode). The tumor (RF, 20.1 × 28.8 mm) is displacing the external carotid artery (ACE) and internal carotid artery (ACI) anteriorly

According to Boedeker et al., digital subtraction angiography (DSA) is the gold standard for the diagnosis of PGLs. In addition to allowing preoperative embolization, DSA provides arterial "mapping" of the tumor's vascular supply [10]. Embolization may be helpful in selected patients, particularly in cases of suspected VP, but should not be regarded as mandatory [66]. In cases of jugular and vagal tumors, but not in isolated tympanic tumors, additional preoperative embolization is often recommended. However, preoperative embolization for carotid PGL is not recommended, because of the inability to adequately embolize the tumor-feeding vessels, which only partially arise from the external carotid artery and instead arise from the adventitia surrounding the internal carotid artery [15].

Somatostatin-receptor scintigraphy is not widely available as a diagnostic method and is reserved for specialized centers. However, ^{18}F-dihydroxyphenylalanine (DOPA) positron-emission tomography (PET) appears to be superior

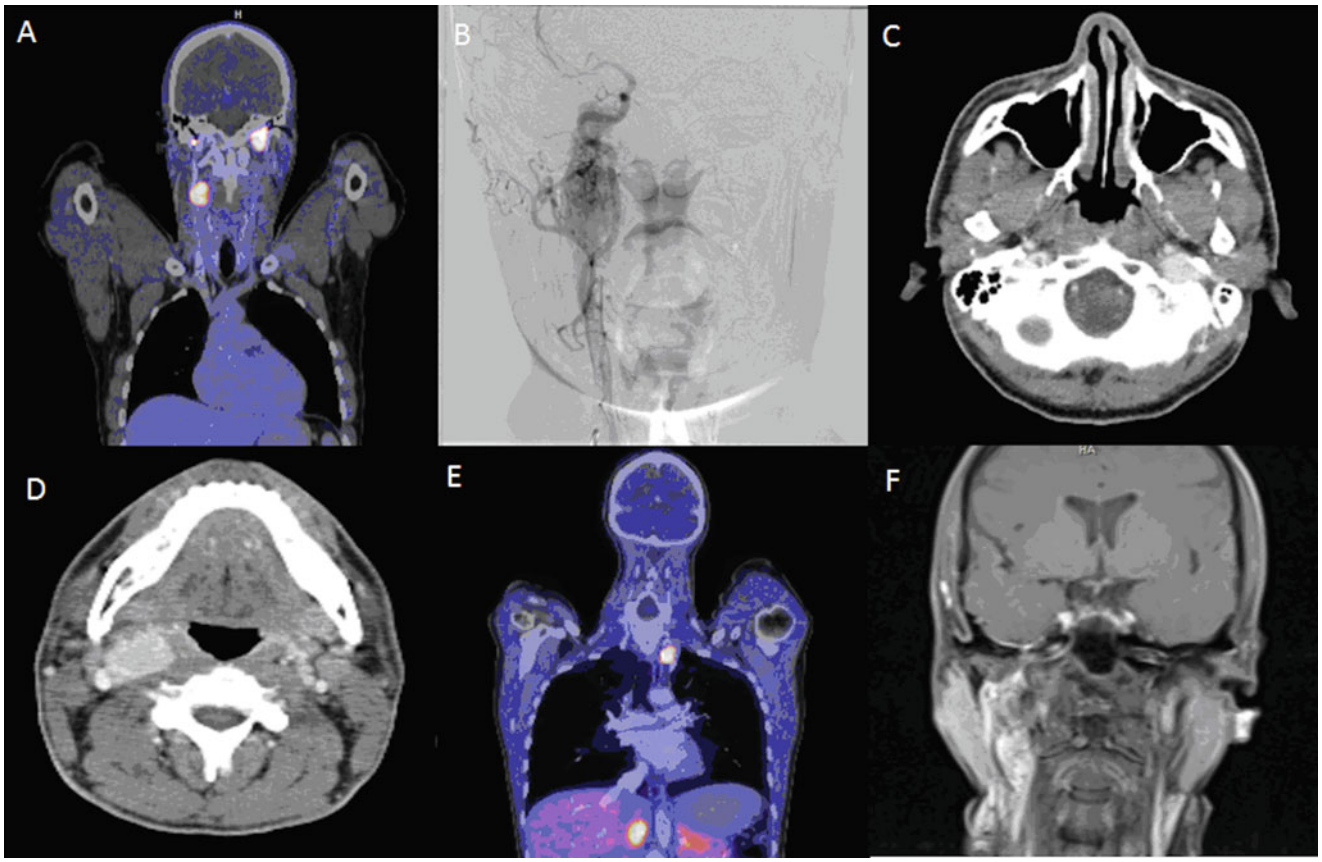

Fig. 41.7 (**a**) Positron-emission tomography (PET)/computed tomography (CT) scan, showing multiple manifestations of paraganglioma, with avid fluorodeoxyglucose (FDG) uptake. (**b**) Angiography study, showing a jugulotympanic paraganglioma (JTP) on the right side. (**c**) CT scan (axial pattern), showing a JTP in the left jugular foramen, with contrast enhancement. (**d**) CT scan (axial pattern), showing a cervical paraganglioma on the right side, with contrast enhancement. (**e**) PET-CT scan showing a paraganglioma in the upper mediastinum and hilum of the liver. (**f**) Magnetic resonance image (coronal pattern) with gadolinium enhancement, showing a right-sided JTP

to MRI in very small tumors (<1 cm) and it may therefore become more important as a screening method in the future in patients with hereditary paragangliomas [13].

Timmers et al. [67] reported sensitivities for localizing nonmetastatic PGL of almost 100 % for CT and/or MRI, 81 % for ^{18}F-DOPA PET, 88 % for ^{18}F-fluorodeoxyglucose (FDG) PET, 78 % for ^{18}F-FDA PET, and 78 % for ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy. For metastatic PGL, the sensitivity relative to CT/MRI was 45 % for ^{18}F-DOPA PET, 74 % for ^{18}F-FDG PET/CT, 76 % for ^{18}F-FDA PET/CT, and 57 % for ^{123}I-MIBG scintigraphy. The authors concluded that ^{18}F-FDA PET/CT is the preferred technique for locating the primary PGL and ruling out metastases. Second-best, equivalent alternatives are ^{18}F-DOPA PET and ^{123}I-MIBG scintigraphy. For patients with known metastatic PGL, ^{18}F-FDA PET is recommended in patients with an unknown genotype, ^{18}F-FDG or ^{18}F-FDA PET in *SDHB* mutation carriers, and ^{18}F-DOPA or ^{18}F-FDA PET in non-*SDHB* patients [67].

Blanchet et al. noted that ^{18}F-DOPA PET/CT is a highly sensitive and specific tracer for localizing PGLs, but the uptake of this radiotracer is almost always very intense regardless of genotype. In addition, ^{18}F-DOPA is not routinely available in many centers worldwide. In recent years, several studies have shown that besides detecting tumors, ^{18}F-FDG PET/CT may be able to characterize PGLs by possible genotype [68]. A study by Timmers et al. found that ^{18}F-FDG uptake was greater in patients with *SDHx* germline mutations. PGLs can be detected with ^{18}F-FDG PET/CT with good sensitivities (77–85 %) [69], but unlike ^{18}F-DOPA, the uptake is not consistently high; there is a wide range of uptake values among patients with PGLs.

In conclusion, imaging modalities with one of the abovementioned radiotracers should be used in patients with multiple presentations of head and neck paragangliomas (HNPs), in young patients, and in patients with a positive family history or a positive *SDH* mutation (Fig. 41.7a, e) [70]. Genetic testing and counseling is also appropriate in these cases.

Only 1–3 % of PGLs show clinical or biochemical evidence of hormonal activity, with symptoms of a hyperfunctional tumor such as headaches, excessive sweating, and palpitations. In these cases, evaluation of 24-h

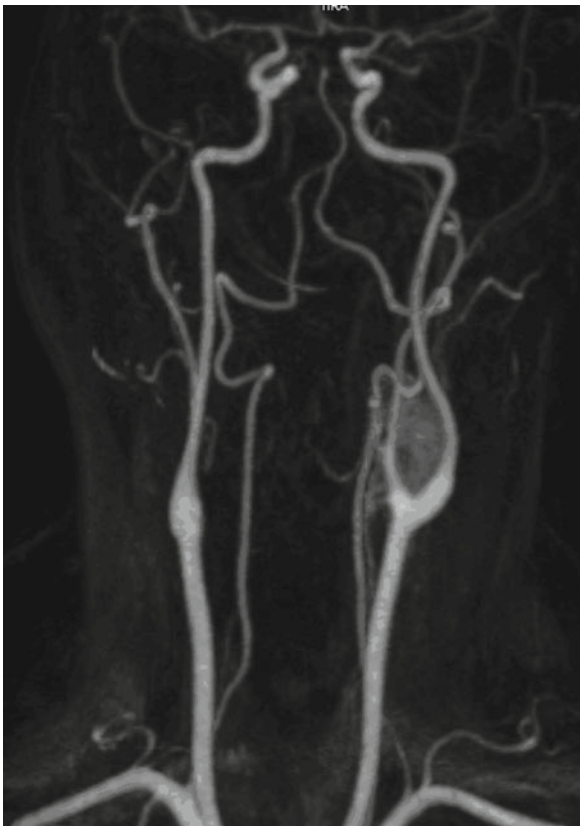

Fig. 41.8 Magnetic resonance angiography, showing a vascular mass in the carotid bifurcation on the left side

urinary catecholamine excretion is a prerequisite for excluding catecholamine excess, particularly when a surgical procedure is planned [53].

The current literature appears to overstate the numbers of catecholamine-secreting tumors. In a series in our own institution reported by Papaspyrou et al., the data indicate that the number of hormonally active PGLs in the head and neck area is negligible (1 of 175 patients) [15]. Routine testing for hormonal activity is not necessary, but endocrinology consultation is valuable in cases of suspected or confirmed hyperfunctional tumors. The management of patients with a secreting PGL includes surgery as the first option, but only if the elevated catecholamine levels are accompanied by symptoms [71].

41.5 Therapy

PGLs have traditionally been considered to be highly aggressive tumors, but our understanding of their natural history has improved in recent years, and the literature suggests that a change is taking place in the treatment paradigm. In principle, surgical removal is still the only therapeutic option that potentially offers a cure for the patient, and the goal of any form of surgery should be complete tumor removal [72]. Evidently, however, views regarding the treatment of choice are generally moving away from radical resection toward surgical tumor reduction in order to preserve function and reduce morbidity [73, 74]. Radiotherapy may be considered immediately postoperatively or in case of tumor progression [75]. Alternative primary treatment options, depending on the individual situation (e.g., in relation to age, comorbidity, multifocal lesions, and risk of injury to the cranial nerves), include stereotactic radiotherapy (SRT) or radiosurgical procedures such as the Gamma Knife or CyberKnife [9, 16, 76]. For radiotherapy planning, a contrast MRI (with a slice thickness of 1–3 mm) as well as individually prepared thermoplastic stereotactic masks and a planning CT with a slice thickness of 1–2 mm are necessary. MRI and CT data have to be fused for contouring of the target volume (a macroscopic tumor with a safety margin of 2–3 mm). The dosage should be standardized to the reference point, and single doses of 1.8–2.0 Gy, conventionally fractionated, should be administered up to a final dosage of 45 Gy [16]. There is no evidence that doses higher than 45 Gy improve the already high likelihood of tumor control. The risk of significant complications from 45 Gy is negligible, and most of the severe complications reported occurred in patients who received 55–65 Gy [71]. Dosages of 12–18 Gy are administered in radiosurgery.

According to Langerman et al., observation of PGLs is an option in selected patients [11]. This approach makes it possible to document the lesion's growth dynamics. The viewpoints of the treating physician and the definition of cure versus local control need to be balanced against the patient's overall health status, tumor-related symptoms, tumor details, and the patient's desire for treatment.

The National Cancer Data Base report on malignant paragangliomas of the head and neck currently recommends that if the physical examination or radiologic studies preoperatively suggest metastasis, resection of the tumor should be extended to remove adjacent regional lymph nodes [14].

41.6 Carotid Body and Vagal Paragangliomas

As mentioned above, the paradigm used in the treatment of patients with cervical PGLs is apparently changing at present, with an increasing trend toward individualized therapeutic strategies. Tumor control rates of 89–100 % after complete surgical resection of CPs have been reported [10, 77]. The internationally accepted clinical classification of CPs is the Shamblin system, with classes I–III corresponding to permanent postoperative side effects (Table 41.2) [78–80]. There is no internationally accepted classification system for VPs.

Table 41.2 The Shamblin classification for carotid paragangliomas (CPs)

Class	Characteristics
I	Tumors with splaying of the carotid bifurcation but little attachment to the carotid vessels
II	Tumors that partly surround the carotid vessels
III	Tumors that intimately surround the carotids

The risk of permanent postoperative cranial nerve deficits (CNDs) after treatment for carotid paragangliomas has been reported as 17 or 22 % [79, 81]. In a study by our own group, 20 % of the patients had permanent CNDs after surgery for 21 CPs, but no tracheostomies or gastric feeding tubes were necessary. Notably, none of these patients had CNDs at the initial presentation. This emphasizes the need for rapid and intense swallowing rehabilitation [77]. Surgery for class I CPs rarely causes CNDs and does not cause functional impairment. As reported in the literature in relation to Shamblin class III CPs, there is a significant increase in permanent vascular or neural deficits after surgery, due to the topographic relationship to important cranial nerves and due to possible intraoperative interruption of the carotid vessels and cerebral circulation [59]. Several authors have recommended that these severe complications should be minimized by preoperative tumor embolization and with vascular reconstruction using vascular shunts intraoperatively [82]. In the present authors' view, a good multidisciplinary team approach and careful treatment planning should be the gold standard for avoiding and reducing severe complications.

Rates of local tumor control for VPs may be up to 100 % if complete tumor resection can be achieved [73, 77]. In the vast majority of cases, however, the vagal nerve has to be sacrificed, and the rates of additional CNDs increase along with the size of the paraganglioma [83, 84]. As reported by Thabet and Kotob, all patients in whom VPs were surgically removed developed vagal paresis and/or other CNDs, with swallowing problems of various degrees [85]. Accordingly, younger patients and those with preoperative nerve paralysis tolerate vagus nerve resection better than older patients or those with no preoperative nerve paralysis. The slow nerve paralysis occurring with tumor growth allows the patient to compensate over time. In general, surgery in case of VP should be reserved for patients who already have a palsy or other symptoms, such as a mass effect. Even then, however, radiotherapy or observation is worth considering. On the other hand, when the vagus nerve is already paralyzed, surgery may help prevent other CNDs [71]. A promising study by Miller et al. described higher rates of preservation of the vagal nerve when microsurgical techniques were used [84]. In 2001, Hinerman et al. published their 35-year experience in the treatment of PGLs. They recommended resection of small cervical paragangliomas if the surgery did not require the sacrifice of major neural and/or vascular structures. SRT was recommended for all other patients. In their series, the rates of local tumor control with a multimodal treatment strategy were 96 % for CPs and 100 % for VPs [73].

Various authors have reported tumor control rates of 76–100 % after SRT, as recently confirmed in a meta-analysis by Guss et al. [86]. However, the degree of long-term tumor control achieved with radiotherapy has often been questioned, on the assumption that it causes tumor necrosis not by directly destroying tumor cells but rather through fibrosis and occlusion of the tumor's vessels [87]. Vital tumor cells can lead to recurrences even 10 years after the completion of radiotherapy, and there is a risk of rare but severe radiation-induced long-term sequelae such as osteoradionecrosis and radiogenic secondary malignancies [88, 89]. A strategy of observation is a possible option in selected patients, in the absence of worrisome symptoms [11]. In principle, surgical removal is the only therapeutic option that potentially offers a cure for the patient, and it has the further advantage that tissue for histological analysis is obtained [9, 90]. Although the metastatic potential of HNPs is low, it represents a limitation for nonsurgical treatment [82]. In patients with multiple HNPs, an individual multimodal treatment strategy is required in order to provide long-term tumor control and an acceptable quality of life.

41.7 Jugulotympanic Paragangliomas

The complex anatomy of the skull base and the highly vascularized nature of these tumors are a serious challenge for surgeons even today, although the further development of microsurgical techniques has also made complete removal of large JTPs possible [91–93]. As summarized by Sanna et al., the major problems include: firstly, adequate exposure—as these tumors may spread into three different compartments (intrapetrous, extracranial, and intradural); secondly, the close topographic relationship with the facial nerve; and thirdly, the intimate relationship with important neurovascular structures, such as the lower cranial nerves (CNs), the inferior petrosal sinus, and the internal carotid artery [94, 95]. Various surgical access routes have been described in the literature, such as the widely used infratemporal fossa approach type A (IFTA-A) first presented by Fisch in 1978 [96–102].

JTPs are categorized in accordance with the Fisch classification (Table 41.3).

Treatment for JTPs should ensure a high level of tumor control and should maintain function in cranial nerves VII to XII. As far as possible, an attempt should also be made to preserve hearing. During treatment planning, the risks of surgery have to be weighed up critically in comparison with the natural growth behavior of JTPs. To date, various surgical access routes in the lateral skull base have been developed in order to reduce the morbidity associated with

Table 41.3 The Fisch classification of jugulotympanic paragangliomas (JTPs)

Class	Characteristics
A	Limited to mesotympanum (glomus tympanicum)
B	Limited to hypotympanum, mesotympanum, and mastoid with/without erosion of the jugular bulb (glomus hypotympanicum)
C	Involvement and destruction of infralabyrinthine and apical compartments
C1	No invasion of vertical carotid canal; destruction of the jugular foramen
C2	Invasion of vertical carotid canal between foramen and bend
C3	Invasion along horizontal carotid canal
C4	Invasion of foramen lacerum and along carotid canal into cavernous sinus
D	Intracranial extension
De1	≤2 cm dural displacement
De2	>2 cm dural displacement
Di1	≤2 cm intradural extension
Di2	>2 cm intradural extension
Di3	Inoperable intracranial invasion

the operation [96, 97, 100, 103, 104]. Jackson et al. and Watkins et al. reported mortality rates of 0–4 % after surgical treatment [105, 106]. It is generally accepted that there is an absolute indication for a primary surgical procedure when patients are suffering from neurological effects of expansive tumor growth such as raised intracranial pressure or hydrocephalus [107]. As mentioned above, the degree of long-term tumor control achieved with radiotherapy has often been questioned, on the assumption that it causes tumor necrosis not by directly destroying tumor cells but rather through fibrosis and occlusion of the tumor's vessels [87]. According to Mumber and Greven, vital tumor cells can lead to recurrences even 10 years after the completion of radiotherapy [89]. On the other hand, Spector et al. and Hawthorne et al., among others, have demonstrated good local control after radiotherapy [108, 109]. Several studies in recent years have shown that SRT is effective in postoperative and also in primary therapy for JTPs [9, 75]. In general, SRT is considered to be indicated in older symptomatic patients or in situations in which there is a high risk of damaging intact cranial nerves. Various authors have reported tumor control rates of 76–100 % after SRT [90, 110, 111].

Despite the good results obtained with radiotherapeutic procedures, limitations of the method have also been reported in the literature. These include unclear tumor histology, the need for rapid reduction of the tumor mass when there are cranial nerve symptoms, tumor sizes larger than 3 cm, and tumor spread to below the base of the skull [90]. It has also been reported that there is a risk of rare but severe radiation-induced long-term sequelae, such as osteoradionecroses and radiogenic secondary malignancies in the irradiation field [88]. Ivan et al. [74] and Springate et al. [112] reported tumor control rates of 86 % with a primary surgical procedure, 69 % with subtotal tumor resection, 71–90 % with a combined procedure involving subtotal resection and adjuvant SRT, and 93–95 % with primary SRT. Ivan et al. [74] analyzed the data from 46 publications (in which the great majority of JTPs treated were size C and D) in relation to the rate of posttreatment CNDs after surgical treatment or SRT. Increases in paresis postoperatively were seen in CN IX in 38 % of cases, in CN X in 26 %, in CN XI in 40 %, and in CN XII in 18 %. After SRT, the rates were much lower, at 9–12 %. The authors concluded that the higher morbidity in the caudal cranial nerves following surgical treatment is not associated with increased tumor control and that SRT thus appears to be superior to primary surgical treatment, taking the current follow-up intervals into account [74, 112].

A study by Cosetti et al. reports on three patients who showed no tumor growth over periods of up to 33 years without therapy [113]. Particularly in largely asymptomatic patients with small JTPs who are reluctant to undergo treatment, or in patients at an advanced age, a "wait and scan" strategy may be justifiable.

Only a few studies to date have given special attention to the preservation of hearing in the context of treatment for JTPs [114–116]. The infratemporal access route described by Fisch, with closure of the external auditory canal and removal of the middle ear structures, is regarded in many institutions as the standard approach, although it is always associated with severe conductive hearing loss [96]. Accordingly, less invasive surgical procedures (such as hypotympanotomy) and protection of sound conduction structures are possible in many cases. In addition, active middle ear implants that are able to amplify and transport sound to the residual middle ear structures (e.g., the Vibrant Soundbridge) allow full hearing rehabilitation even in obliterated ears. In these situations, problems with MRI follow-up need to be taken into consideration.

In one of our own group's studies, no statistically significant differences were found between primary surgery and primary radiotherapy with regard to postoperative auditory function. This highlighted the fact that it is possible to preserve hearing in the context of surgical treatment for JTPs, with good tumor control at the same time, using modified surgical access routes [63]. For JTPs, it seems more logical to use surgery for small tumors that have a low risk of damaging hearing and cranial nerves and to treat the remainder of cases with radiotherapy. In this case, surgery can be reserved for salvage in case of tumor progression [71].

41.8 Multiple Paragangliomas

Currently, there are no standard therapeutic protocols for patients with multiple paragangliomas; some patients thus end up with overtreatment, while others are undertreated. Predictive factors for a positive mutation test include family history, previous adrenal or extra-adrenal pheochromocytoma, multiple HNPs, age ≤ 40 years, and male gender [35]. These predictive factors should also lead to early nuclear imaging in order to detect multiple paragangliomas. HNPs typically show avid uptake with different functional imaging techniques. In the authors' experience, a very high rate of long-term tumor control with low morbidity can be achieved using tailored and individualized approaches in patients with multiple HNPs. Treatment decision-making should involve a multidisciplinary team of experts in the fields of nuclear medicine, genetics, pathology, radiology, radio-oncology, and surgery. A complete diagnostic checkup, including genetic testing, should be part of the routine diagnostic program. This is particularly important in patients with multifocal paragangliomas. In the present authors' experience, some patients may become frightened of the morbidity of surgery following surgical treatment for a first paraganglioma, leading them to decline subsequent treatment options for a second or third paraganglioma. This shows the importance of discussing all of the available different treatment strategies with the patient [117]. Radiotherapy offers a similar chance of tumor control, with lower risks of morbidity in comparison with surgery. Surgical removal should be weighed up against the patient's age, the size of the tumor, predicted tumor growth, and cranial nerve function in order to minimize its impact on the patient's quality of life. Due to the slow growth of these tumors and their benign nature, many patients can be managed with clinical observation and/or radiotherapy [71].

41.9 Rehabilitation

Treatment for PGLs can cause significant morbidity. In experienced hands and with proper patient selection and counseling, the morbidity can be significantly reduced. A multidisciplinary team is necessary to manage these patients and often includes a head and neck surgeon, neuro-otologist, laryngologist, vascular surgeon, neurosurgeon, speech pathologist, audiologist, physical therapist, and a variety of other ancillary staff.

Resection of unilateral small CPs is well tolerated by most patients. If bilateral resections are planned, the procedures should be staged, as the vagus nerve is at risk on both sides. Bilateral vagal denervation could lead to acute and long-term sequelae such as severe dyspnea and aspiration. Tracheotomy and gastric tube dependency could be the consequence. If vagal paralysis occurs with the first operation, radiation or observation should be considered for the contralateral tumor.

In bilateral CPs, loss of baroreflex function can be problematic, leading to loss of the parasympathetic drive in this system. Measuring hypertension postoperatively in these patients is critical, especially in those who have undergone vascular repair or replacement [118]. Clonidine administration can be helpful, as compensation does occur in these patients, but the effects are unpredictable and variable.

Surgical treatment of VPs almost always results in significant morbidity due to vagal paralysis. Early speech and swallowing therapy and medialization of the paralyzed vocal fold are important tools to help the patients through the recovery process. Caution should be taken when considering therapy for vagal tumors in elderly or unhealthy patients. Younger patients and those with preoperative nerve paralysis tolerate vagus nerve resection better than older patients or those with no preoperative nerve paralysis. The slow nerve paralysis occurring with tumor growth allows the patient to compensate over time. Radiation therapy or observation should be strongly considered in these patients.

Damage to the cervical sympathetic chain can lead to two different issues—Horner's syndrome and first bite syndrome. According to Netterville et al., first bite syndrome is secondary to loss of sympathetic innervation to the ipsilateral parotid gland [60]. This loss of innervation leads to denervation of sympathetic receptors located on parotid myoepithelial cells. Patients complain of mild to severe pain with the first bite of food. Although the pain sometimes resolves spontaneously, it is often disabling. A recently described treatment with an intraparotid botulinum toxin injection appears to be the most effective first-line option at present, although the injection protocol (number of injections and total dosage injected) and the long-term efficacy of the treatment have not yet been clearly defined [119–121].

In summary, a comprehensive posttreatment examination and counseling of the patient are mandatory for early detection of functional problems and for initiating a rapid rehabilitation program embedded in a multidisciplinary team of experts.

41.10 Follow-Up

The long-term follow-up procedures for patients with PGL should differ depending on whether the occurrence is sporadic or familial. In sporadic cases, an annual MRI of the skull base and neck region should be carried out, particularly with jugulotympanic PGLs. Ultrasonography is adequate in cases of isolated carotid body or vagal tumors. In familial cases, a CT or an MRI scan of the chest should be carried out, and abdominal ultrasound should be additionally performed every 1–2 years [15]. ^{18}F-DOPA-PET should be used to confirm suspicious findings during the follow-up. Patients in whom an observation strategy without surgery or

radiotherapy is being used should be scanned at 6-month intervals initially in order to document the dynamic growth behavior of the lesion and establish whether it is stable or showing a slow growth rate. In patients with stable disease, annual MRI scans are sufficient, but if there is progression, reevaluation of therapeutic options should be discussed with the patient. In general, patients with significant morbidity secondary to the tumor or treatment require shorter clinical follow-up intervals and intensive rehabilitation.

41.11 Conclusions

Treatments for carotid paragangliomas (CPs) or vagal paragangliomas (VPs) are associated with different types of morbidity, and they should therefore be considered separately. A surgical procedure should be regarded as the treatment of choice in patients with class I CPs. In larger CPs, particularly in elderly patients with unimpaired cranial nerves, radical surgery should be regarded critically. The patient's symptoms, age, comorbidities, and environment should be taken into account during the decision-making process. There is good evidence in the literature that in large CPs, tailored surgery while preserving function represents an adequate treatment option, and staged stereotactic radiotherapy (SRT) may be considered postoperatively or in case of progression. As surgery for VPs regularly causes impairment of cranial nerves, with functional disturbances of various degrees, a comprehensive consultation with the patient is mandatory and nonsurgical strategies should be discussed.

Almost without exception, smaller jugulotympanic paragangliomas (JTPs) of sizes A and B can be resected completely using various surgical approaches. Larger JTPs of sizes C and D can be treated either with primary surgery or stereotactic radiotherapy, with function-preserving intent and with a comparable degree of tumor control. Particularly in young patients with unilateral tumors and evident cranial nerve paresis, we regard a primary surgical procedure, aiming for resection with healthy margins, as the treatment of choice. As with CPs, radical surgery for JTPs should be regarded critically, especially in older patients with normal cranial nerve function and acceptable auditory function, as a loss of function in the major cranial nerves is usually followed by a difficult and stressful rehabilitation process. However, if cranial nerve deficits are present preoperatively, surgical resection is better tolerated. The extent of the surgery should therefore be based on the preoperative and intraoperative findings. In many situations, reducing the size of the JTP while preserving function represents an adequate treatment option.

The question arises of whether postoperative radiotherapy may in general only be indicated when there is objective evidence of tumor progression. The development of improved radiation techniques, particularly stereotactic radiation, has provided patients with a viable modality that can slow or stop the growth of these tumors in selected cases. The patient may be able to avoid surgery altogether. However, the main limitation with this approach is that tumor eradication is not possible. However, radiation may be a realistic approach in some patients who have underlying comorbidities or other factors that are more likely to cause morbidity or mortality.

With regard to molecular diagnosis in paraganglioma patients, next-generation sequencing is now available for diagnostic purposes. Exome sequencing and a gene-panel sequencing approach have already been applied successfully to paraganglioma/pheochromocytoma syndrome. The latter method in particular is rapid and cost-effective and may soon be able to replace complex genotyping algorithms.

A multidisciplinary team of experts is necessary to manage these patients, including a head and neck surgeon, neuro-otologist, laryngologist, vascular surgeon, neurosurgeon, radiologist, radio-oncologist, molecular biologist, human geneticist, as well as a speech pathologist, audiologist and physical therapist.

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Systemic Treatment of Recurrent/ Metastatic Squamous Cell Carcinoma of the Head and Neck

42

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Abstract

Most patients with recurrent or metastatic head and neck squamous cell cancers qualify for palliative treatment. The management of these patients includes supportive care only, mono- or multiagent chemotherapy, and more recently targeted therapies. While platinum-based combinations are superior to single-agent therapies in terms of response rate, they are more toxic and so far have not shown to lead to meaningful survival benefit. Attempts to improve on this by using other or additional cytotoxic drugs were unsuccessful in the last 30 years. It was therefore an urgent need to investigate the efficacy of novel anticancer therapies that specifically target the tumor cells in such patients. A recent randomized trial showed that adding cetuximab, an EGFR-directed monoclonal antibody, to a standard platinum-based chemotherapy regimen led to an important survival benefit. Despite the still dismal prognosis, the outcome of this latter trial has changed practice in this category of head and neck cancer patients. The next challenge will be to sort out how to incorporate the numerous targeted agents that are currently studied into the existing treatment strategies, also in consideration of an optimization of their therapeutic index. Human papillomavirus status with immunohistochemical p16 expression as its surrogate marker represents promising prognostic and possibly predictive biomarkers that need to be prospectively validated in future randomized trials.

Keywords

Head and neck • Recurrent • Metastatic • Targeted therapies • Platinum • Monoclonal antibodies • Tyrosine kinase inhibitors • Immunotherapy

42.1 Introduction

Approximately 60–65 % of patients with head and neck cancer can be cured with surgery and/or radiotherapy [1]. While a large proportion of patients presenting with stage I and II squamous cell carcinoma of the head and neck (SCCHN) will remain disease-free after single modality treatment (either surgery or radiotherapy), the majority of patients presenting in a more advanced disease stage, and treated with whatever combined modality approach, will eventually relapse either locoregionally and/or at distant sites. A few patients with a locoregional recurrence can be salvaged by surgery or reirradiation. However, most patients with recurrent or metastatic (R/M) disease only qualify for palliative treatment. Treatment options in these patients include supportive care only or, in addition single-agent chemotherapy, combination chemotherapy or targeted therapies either alone or in combination with cytotoxic agents.

Treatment choice should be based on factors such as performance status, comorbidity, prior treatment, symptoms, patient preference, and logistics [2]. Goals of treatments in

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these circumstances are mainly symptom control and prevention of new cancer-related symptoms, improvement in quality of life (QoL), and, if assessable, objective tumor response (OR), disease stabilization (SD), or both combined (disease control; DC) and in addition prolongation of overall survival (OS) and progression-free survival (PFS). Unfortunately, correlation between objective tumor reduction (or DC) and subjective benefit (symptom control and QoL) has not been adequately studied, underscoring the importance of clinical trials in this patient group [3].

42.2 Associated Problems

Patients with R/M-SCCHN can have specific problems related to their social habits such as ongoing heavy tobacco and alcohol use or the use of other carcinogens, which may lead to poor cognitive function, comorbid medical conditions (cardiovascular and/or pulmonary diseases), and malnutrition. Moreover, typically disease-related problems may be present, such as infections (local, aspiration pneumonia, systemic), hypercalcemia, local pain, or bleeding (arterial, venous, capillary), which all can influence QoL and OS and may necessitate active supportive care [4].

42.3 Prognostic Factors

Several clinical prognostic factors have been proposed to define patients who are most likely to benefit from palliative chemotherapy and these can be categorized as patient related, tumor related, or treatment related. Already for a long time, it is known that the performance status is one of the most important prognostic factors that not only influences the incidence of response to chemotherapy but also affects the OS of these patients regardless of the response to the applied chemotherapeutic agents [4, 5]. Patients with only local recurrence with or without regional lymph node involvement and no bony erosion after definitive treatment have a better chance to respond to chemotherapy than do patients with systemic and visceral metastases. Other factors that have been reported to influence outcome are a good response to prior induction (neoadjuvant) chemotherapy or radiotherapy, a long interval between primary and recurrence, good organ functions, poorly differentiated histotype, and the response to palliative treatment [4, 6–8]. Data from two more recently conducted US trials in R/M-SCCHN (E1395 and E1393) were combined and analyzed for prognostic factors for response and survival. The median follow-up of the patients in these two trials was 4.7 years; survival rates at 1, 2, 3, and 5 years were 32, 12, 7, and 3.6 %, respectively, and median OS was 7.8 months. The OR rate was 32 %. On multivariate analysis, the investigators were able to identify one pathologic feature (tumor cell differentiation) and four clinical baseline characteristics (Eastern Oncology Cooperative Group (ECOG) performance status, weight loss, location of the primary tumor, and prior radiotherapy) as independent predictors of OS. They constructed a prognostic model for OS based on the presence of these five independent prognostic factors and were able to categorize the patients into two groups with significantly different outcome, i.e., one in which patients had only 0–2 adverse prognostic factors and another in which patients had ≥3 poor prognostic factors. The first group had a median survival that was nearly twice that of the second group (0.98 years vs. 0.52 years). In this study, 283 of the 399 patients included in the analysis had three or more adverse factors, explaining the median survival of only 7.8 months [9]. They also identified that the same variables and the presence of residual tumor at the primary site were independent predictors of response to chemotherapy. In fact, response to chemotherapy was found to be of prognostic significance. When the investigators added response to chemotherapy to the model, the location of the primary tumor lost its prognostic significance but all other parameters, including tumor cell differentiation, retained their significance as independent predictors of survival. Predictors of 2-year survivorship were the response to chemotherapy [complete response (CR) or partial response (PR) vs. no response], white race (vs. others), ECOG performance status of 0 (vs. 1), poor cell differentiation (vs. well/moderate), and no prior radiotherapy. Interestingly, all long-term survivors had locally recurrent disease at study entry. The findings in this study suggested that (1) there is an urgent need of better therapy for this category of patients; (2) response to systemic therapy has a major impact on survival; (3) patients with locally recurrent disease, but not the patients with distant metastases, who are primarily treated with chemotherapy, rarely will be cured from their disease; and (4) future trials in patients with R/M-SCCHN should take the five adverse prognostic factors into consideration.

R/M-SCCHN patients who fail the platinum-based first-line therapy do very poorly. León et al., in a retrospective analysis of the outcome of patients with R/M-SCCHN who were progressing while on platinum-based palliative chemotherapy, reported no responses using traditional chemotherapeutic agents and a median OS of 3.4 months [10]. More recently performed phase II/III trials, albeit with slightly better outcome, are in line with this [11–17] (Table 42.1). These data can be used as a reference when evaluating the effectiveness of new agent(s) in previously treated patients.

42.4 The Chemotherapeutic Approach

Squamous cell carcinoma of the head and neck is one of the more chemosensitive human neoplasms. Recent reports on induction chemotherapy in locoregionally advanced SCCHN have indicated that OR rates and CR rates approaching 90 %

Table 42.1 Second-line treatment in recurrent/metastatic SCCHN (phase II/III data)

Author (year)	Drug	Prior chemotherapy for R/M-SCCHN	Median PFS (months)	Median OS (months)
Pivot (2001) [11]	MTX	62 %	1.5	3.7
Stewart (2009) [12]	MTX	Unclear	N/A	6.7
Machiels (2011) [13]	BSC (MTX)[a]	83 % (17 %)[b]	1.9	5.2
Numico (2002) [14]	Docetaxel	61 %	4.0 (TTP)	6.0
Zenda (2007) [15]	Docetaxel	Unclear	1.7	4.6
Specenier (2011) [16]	Docetaxel	77 %	1.7	4.1
Argiris (2013) [17]	Docetaxel	Unclear	2.1 (TTP)	6.0

MTX methotrexate, *BSC* best supportive care, *PFS* progression-free survival, *N/A* not assessable, *TTP* time to progression, *OS* overall survival
[a]78 % of the patients received MTX
[b]17 % of the patients relapsed <6 months after chemoradiation

and 60 %, respectively, are achievable [3]. These data are far from what can be reached in the recurrent/metastatic disease setting in which a more unfavorable (resistant) phenotype has emerged. In fact, compiled results from 12 nonrandomized trials showed an OR rate of 50 % and a CR rate of 16 % [18]. Some investigators have indicated that reaching a CR, especially if confirmed histologically, is meaningful for survival benefit [4, 19, 20], while PRs might have much less impact on survival and merely indicate biological effectiveness [4]. This may certainly be so for long-term survival. In the earlier mentioned prognostic factor analysis of the two ECOG studies, ten times more CRs were observed in those alive at 2 years and beyond vs. those with a survival <2 years (37 % vs. 3 %). For OR (CR + PR), these percentages were 78 % vs. 25 %, suggesting that CR might be a surrogate marker for survival.

42.4.1 Single-Agent Chemotherapy

The four most extensively studied single cytotoxic agents in advanced or recurrent disease are bleomycin (average OR 21 %), methotrexate (average OR 31 %), 5-fluorouracil (5-FU) (average OR 15 %), and cisplatin (average OR 28 %). Response rates with these agents, but also with several other conventional agents of different classes [the platinum analog carboplatin (25 %), the alkylating agents ifosfamide (26 %) and cyclophosphamide (36 %), the anthracycline doxorubicin (24 %), and the vinca alkaloid vinblastine (29 %)], are generally in the 15–30 % range, while response duration is generally between 3 and 5 months [7, 21–29]. Similar response rates, mostly observed in phase II studies, were observed with newer agents such as paclitaxel, docetaxel, vinorelbine, irinotecan, edatrexate, pemetrexed, capecitabine, orzel, and S-1 [30–41] (Table 42.2).

As evident from the table, the taxanes, paclitaxel and docetaxel, are among the highest in activity in this disease setting. At the same time, it is clear from the table that there is a wide range of activity in different studies, most likely reflecting variations in patient characteristics. For most of the conventional agents, but also of the newer agents, no direct comparison has been made with the standard palliative agent methotrexate. The few exceptions to this are summarized in Table 42.3.

Table 42.2 New active[a] agents in recurrent/metastatic SCCHN

Drug	Response rates (%)	First author, year [references]
Edatrexate	6–21	Kuebler, 1994 [37]; Schornagel, 1995 [38]
Pemetrexed	26	Pivot, 2001 [32]
Vinorelbine	6–16	Testolin, 1994 [33]; Degardin, 1998 [34]
Irinotecan	21	Murphy, 2005 [36]
Capecitabine	8–24	Colevas, 2006 [3]; Martinez-Trufero, 2010 [35]
Orzel	21	Colevas, 2001 [41]
S-1	27	Park, 2008 [39]
Paclitaxel	20–43	Schrijvers, 2005 [30]; Grau, 2009 [31]
Docetaxel	20–42	Schrijvers, 2005 [30]; Hitt, 2006 [40]

[a]Activity defined as ≥15 % responses

Grose et al. [42] randomized 100 patients to be treated either with methotrexate or cisplatin. OR rates were 16 and 8 %, median durations of response were 18 and 8 weeks, and median durations of survival were 20 and 18 weeks, with methotrexate and cisplatin, respectively. A similar but smaller study was conducted by Hong et al. [25]. They found neither a difference in OR rate nor in median OS. However, mucositis occurred more frequently in the methotrexate group (38 % vs. 0 %; $p=0.001$), while vomiting occurred more frequently in the cisplatin group (87 % vs. 10 %; $p<0.0001$). These two randomized studies demonstrated that in the treatment of recurrent SCCHN, methotrexate and cisplatin are equally effective, although methotrexate appears to be better tolerated. Schornagel et al. [38] reported on an adequately sized European Organization for the Research and Treatment of Cancer (EORTC) trial, in which edatrexate (an analog of methotrexate) was compared with methotrexate. The originally favorable outcome in the phase II part of this protocol could not be confirmed in the phase III final results. There was strikingly more toxicity with edatrexate than with

Table 42.3 Single-agent treatment in recurrent/metastatic SCCHN: randomized trials

Author (year)	No. of patients	Drugs randomized	Response rate (%)	Median OS (months)
Grose (1985) [42]	100	Methotrexate	16	4.6
		Cisplatin	8	4.1
Hong (1983) [25]	38	Methotrexate	23	6.1
		Cisplatin	29	6.3
Schornagel (1995) [38]	264	Methotrexate	16	6.0
		Edatrexate	21	6.0
Vermorken (1999) [43]	95	Methotrexate	16	6.8
		Paclitaxel 3 h (vs. 24 h)	11 (–23)	6.5
Guardiola (2004) [44]	57	Methotrexate	15	3.9
		Docetaxel	27	3.7

OS overall survival

methotrexate (90 % vs. 45 % high-grade toxicity) and similar efficacy. As mentioned above, nonrandomized trials suggested a high activity with the use of taxanes in R/M-SCCHN patients. Direct comparisons were therefore of major interest. Vermorken et al. [43] compared paclitaxel 175 mg/m^2, administered either as a 3-h or a 24-h infusion, with standard-dose methotrexate (40–60 mg/m^2 weekly) in a randomized phase II study. The 24-h infusion regimen was considered too toxic due to a high incidence of febrile neutropenia. However, none of the regimens was superior with respect to response or survival. Weekly schedules of taxanes induce interesting response rates and may have a better therapeutic index than three weekly schedules. Guardiola et al. [44] randomized 57 patients between weekly docetaxel 40 mg/m^2 or weekly methotrexate 40 mg/m^2. The OR rate in this phase II trial was significantly higher with docetaxel (27 % vs. 15 %). However, there was no indication that OS or time to progression was any different between the two treatment arms. It is currently unclear if any of the cytotoxic agents prolongs survival when compared with supportive care alone as an adequately powered randomized controlled trial has never been performed. Only one small study in the past was designed to demonstrate clinical benefit over best supportive care only, using randomized controlled trial methodology. In that trial, 31 patients treated with single-agent cisplatin demonstrated prolonged survival compared with 26 patients treated with supportive measures only [45]. An interesting aspect in this trial was the demonstration that patients who respond do so quickly. Of the 16 responders, 75 % responded after the first cycle and the remaining 25 % after the second cycle [3, 45].

42.4.2 Combination Chemotherapy

42.4.2.1 Standard Platinum-Based Combinations

Combination chemotherapy is very often considered in patients who are young and in a good condition, in particular when favorable prognostic factors for response to chemotherapy are available [4]. The Wayne State University cisplatin/infusional 5-FU (PF) regimen gradually emerged as the most commonly used combination chemotherapy regimen in patients with SCCHN. With that regimen, nonrandomized trials suggested a better outcome than what was observed with single-agent treatment, at least with respect to OR rates and CR rates [18]. However, response rates were notably lower for the subsets of patients who had prior surgery and radiation and those who had metastatic disease [3]. In a number of adequately sized randomized trials performed in the 1990s, this PF regimen was shown to be superior to single-agent regimens, in terms of response rates but not in terms of meaningful survival advantage, and this gain in response rates was obtained at the cost of more toxicity [6, 7, 24] (Table 42.4).

Jacobs et al. [7] compared the PF regimen with either cisplatin alone or 5-FU alone in a randomized phase III trial which included 249 patients. The OR rate to PF (32 %) was superior to that of cisplatin (17 %) or 5-FU (13 %) ($p=0.035$). However, there was neither a difference in median time to progression nor in survival among the three groups. Forastiere et al. [6] randomized 277 patients to PF, carboplatin/5-FU

Table 42.4 Platinum-based combinations vs. single-agent chemotherapy: randomized trials

Author (year)	No. of patients	Agents	Response rate (%)	Median overall survival (months)
Jacobs (1992) [7]	249	PF	32*	5.5
		P	17	5.0
		F	13	6.1
Forastiere (1992) [6]	277	PF	32†	6.6
		CF	21	5.0
		M	10	5.6
Clavel (1994) [24]	382	CABO	34‡	7.3
		PF	31§	
		P	15	
Urba (2012) [49]	795	P + PEM	12	7.3
		P + placebo	8	6.3

P cisplatin, *C* carboplatin, *M* methotrexate, *B* bleomycin, *V* vincristine, *PEM* pemetrexed, *CABO* = P + M + B + V
*$p=0.035$, †$p<0.001$, ‡$p<0.001$, §$p=0.003$

(CF), or standard-dose methotrexate. Hematologic and nonhematologic toxicities were significantly worse with PF than with methotrexate ($p=0.001$). Toxicity with CF was intermediate between the two other regimens. The OR rates were 32 % for PF, 21 % for CF, and 10 % for methotrexate, respectively. The comparison of PF to methotrexate was statistically significant ($p<0.001$), and the comparison of CF to methotrexate was of borderline statistical significance ($p=0.05$). Median response durations and median survival times were similar for all three treatment groups. The CF combination also induced fewer responses than the PF regimen in a randomized phase III trial in the neoadjuvant setting [46]. Moreover, there was no difference in response rate in a randomized comparison of carboplatin plus methotrexate vs. single-agent methotrexate [47]. Taken together, these data clearly suggest that carboplatin is less active than cisplatin in the treatment of SCCHN.

Clavel et al. [48] in a first prospective trial randomized 185 patients between CABO, which consisted of cisplatin, methotrexate, bleomycin, and vincristine, and ABO (CABO without cisplatin). Although the OR rate was higher with CABO (50 % vs. 28 %; $p=0.003$), this did not lead to a better survival. In a next phase III study Clavel et al. [24] compared PF with CABO and with cisplatin alone in 382 patients with R/M-SCCHN. The OR rate was 31 % with PF, 34 % with CABO, and 15 % with cisplatin alone. The two combination regimens were significantly better in that respect than cisplatin alone ($p<0.001$ and 0.003, respectively). In addition, the CR rate with CABO (9.5 %) was higher than with cisplatin alone (2.5 %) ($p=0.02$) or with PF (1.7 %) ($p=0.01$). However, although perhaps expected differently, these higher response rates (and CR rates) did not translate into an improved median survival, which was 7.3 months in all three arms. The median time to progression among the assessable patients was 19 weeks in the CABO arm, 17 weeks in the PF arm, and 12 weeks in the cisplatin arm (log rank $p=0.02$). Both combination regimens were associated with more toxicity.

In the largest phase III trial ever conducted in R/M-SCCHN, 795 patients were randomly assigned to receive either cisplatin plus pemetrexed or cisplatin plus placebo [49] (Table 42.4). For the whole intention-to-treat population, no survival advantage was observed. However, among patients with performance status 0 or 1, a preplanned subgroup analysis revealed a significant increase in OS and PFS with the cisplatin–pemetrexed regimen (8.4 vs. 6.7 months; $p=0.026$; 4.0 vs. 3.0 months; $p=0.044$, respectively). Moreover, the investigators demonstrated efficacy of the cisplatin–pemetrexed combination in patients with oropharyngeal cancers (OS, 9.9 vs. 6.1 months; $p=0.002$; PFS, 4.0 vs. 3.4 months; $p=0.047$) but they did not provide any data on human papillomavirus (HPV) status which could possibly have influenced the results. As expected, the cisplatin–pemetrexed arm exhibited a higher rate of adverse events including drug-related deaths and grades 3–4 hematologic toxicities and fatigue. Taken together, the potential benefit of the doublet therapy is promising in good performance patients and warrants further study.

42.4.2.2 Platinum–Taxane Combinations

Of the newer agents, the taxanes have been studied most extensively in combination chemotherapy regimens [30, 50–54]. More recently, the carboplatin–docetaxel combination was evaluated in a phase II study conducted by the Southwest Oncology Group [53]. Sixty-eight patients were treated with docetaxel 65 mg/m^2 and carboplatin AUC 6 every 21 days. The OR rate was 25 %. Sixty-one percent of the patients experienced grade 3/4 neutropenia. The median PFS was 3.8 months and the median OS 7.4 months.

The paclitaxel plus cisplatin (PP) combination was directly compared to the PF regimen in the Intergroup trial E1395 conducted by ECOG [54]. Patients received either paclitaxel 175 mg/m^2 (over 3 h) and cisplatin 75 mg/m^2, both on day 1, or the classical PF regimen. The OR rate was 26 % with PP and 30 % with PF ($p=0.84$). The overall grade 3/4 toxicity rate was similar between the two groups. However, grade 3/4 mucositis (31 %) was only observed in the PF arm, while the occurrence of neurotoxicity was similar in the two groups. Median OS was 8.7 months in the PF group and 8.1 months in the PP group. Considering the more favorable toxicity profile, PP may be a valuable alternative to PF.

42.4.2.3 Two-Drug and Three-Drug Platinum–Taxane Combinations

The response rates of two-drug or three-drug combinations with paclitaxel or docetaxel in nonrandomized trials are summarized in Table 42.5. With TPF (docetaxel 80 mg/m^2 day 1, cisplatin 40 mg/m^2 days 2 and 3, and 5-FU 1000 mg/m^2 by continuous infusion days 1–3, repeated every 28 days), Janinis et al. [55] observed an OR rate of 44 %, a median time to progression of 7.5 months, and a median OS of 11 months. Despite the use of granulocyte colony-stimulating factor (G-CSF), febrile neutropenia occurred rather frequently

Table 42.5 Platinum–taxane combinations in recurrent/metastatic SCCHN: two vs. three drugs

	Response rates (complete response rates) (%) with	
	Paclitaxel	Docetaxel
Two drugs		
Cisplatin	32–39 (0)	33–52 (9–11)
Carboplatin	33–33 (4–8)	25 (NR)
Three drugs		
Cisplatin/5-FU	31–38 (13)	44 (12)
Cisplatin/ifosfamide	58 (17)	–
Carboplatin/ifosfamide	59 (17)	–

NR not reported
Based on data from refs. [30, 50–52, 54]

(in 15 % of the patients). Benasso et al. [56] treated 47 patients with PPF (paclitaxel 160 mg/m^2 on day 1 and cisplatin 25 mg/m^2/day and 5-FU 250 mg/m^2/day, both on days 1–3), every 3 weeks. The OR rate was 31 % with 13.3 % complete responders. Median PFS and OS were 4.1 months and 7.9 months, respectively. Forty-eight percent of the patients experienced grade 3/4 neutropenia. The TIP and TIC regimens were tested in R/M-SCCHN by Shin et al. [51, 52]. The TIP regimen consisted of paclitaxel 175 mg/m^2 on day 1, ifosfamide 1000 mg/m^2 (by 2-h infusion) on days 1–3, mesna 600 mg/m^2 on days 1–3, and cisplatin 60 mg/m^2 on day 1, repeated on day 22 [51]. Ninety percent of the patients experienced grade 3 or 4 neutropenia, and the rate of febrile neutropenia was unacceptably high (27 %). The OR rate was 58 % with 17 % complete responders. In the TIC regimen, similar doses of paclitaxel and ifosfamide were used as in TIP, but cisplatin was replaced by carboplatin AUC 6 [52]. Also TIC was repeated every 3 weeks. TIC induced febrile neutropenia in 30 % of the patients and one patient died of neutropenic sepsis. The OR rate was 59 % with 17 % complete responders. The median duration of the responses was 3.7 months. Overall, it can be concluded that taxane-containing triplets induce high response rates, also in the recurrent/metastatic disease setting. However, they are associated with substantial hematologic toxicity and a high complication rate. As these triplets have never been directly compared with PF in a randomized phase III study in this setting, they should not be recommended outside clinical trials. Moreover, as none of the combination chemotherapy regimens demonstrated an OS benefit when compared to single-agent methotrexate, cisplatin, or 5-FU, the use of combination chemotherapy preferably is used in younger patients with a good performance status and with symptomatic disease who require prompt symptom relief.

42.4.2.4 Cytotoxic Chemotherapy in R/M-SCCHN: Summary

For patients who are not in the condition to be treated with the more aggressive platinum-based combination chemotherapy regimens, single-agent methotrexate is still a standard palliative therapy.

Platinum-based combinations are superior to single-agent therapies in terms of response rate (at the cost of more toxicity) but do not lead to meaningful survival benefit.

In first-line setting, median survival ranges between 6–9 months and 1-year survival rates vary from 20 to 40 %.

Once platinum resistance occurs, the outlook is very poor.

The reference arm for testing new single cytotoxic agents, preferably in a randomized trial design, is single-agent methotrexate.

There is thus clearly an urgent need of novel anticancer therapies that target the tumor cells specifically while minimizing the toxic side effects, and R/M-SCCHN patients should preferably be invited to participate in phase I/II clinical trials investigating such experimental therapeutics.

42.5 Targeted Therapies in R/M-SCCHN

Several biological therapies have been chosen in head and neck cancer patients because of their different mechanism of action, greater selectivity (target of action is overexpressed as compared to normal tissue), and different toxicity profiles or because they play a role in carcinogenesis [2, 57]. These include drugs that target growth factors and their receptors, signal transduction, cell cycle control, prostaglandin synthesis, protein degradation, hypoxia, and angiogenesis (Fig. 42.1). More recently, EGFR antisense oligonucleotides, antibody-based immunoconjugates, peptides, affibodies, and nanobodies

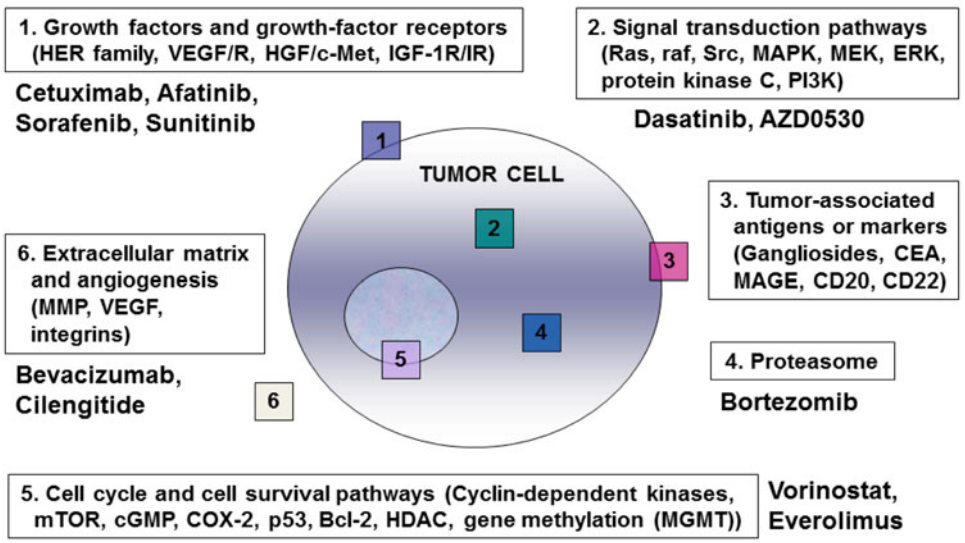

Fig. 42.1 Potential therapeutic targets in SCCHN

have entered preclinical and clinical investigations [58, 59]. Based on practice-changing results in patients with melanoma, immunotherapy targeting specific co-signaling pathways to enhance antitumor immunity represents an interesting approach also in R/M-SCCHN [60]. In this chapter, only those data will be highlighted that have presently some relevance for the treatment of patients with R/M-SCCHN.

42.5.1 Epidermal Growth Factor Receptor and ErbB2

The epidermal growth factor receptor (EGFR, otherwise known as ErbB1 or HER1) inhibitors are of particular interest, because EGFR and its ligand TGF-α (alpha) are overexpressed in the vast majority of cases of SCCHN. In contrast, ErbB2 (HER2/neu) expression in SCCHN ranges between 40 and 60 % [61]. EGFR overexpression and increased EGFR copy number have been related to poor prognosis in patients with SCCHN [62, 63]. Its prognostic role is more specifically related to the treatment received, such as radiotherapy [62, 64] and chemotherapy [65]. Recently, it was found, however, that both EGFR expression by immunohistochemistry and EGFR gene copy number by fluorescence in situ hybridization (FISH) were not predictive for response to anti-EGFR therapy with cetuximab [66, 67].

Two of the potential EGFR-targeting strategies are currently in clinical use: the monoclonal antibodies (MoAbs) directed at the extracellular domain of the receptor and the small molecule and adenosine triphosphate (ATP)-competitive tyrosine kinase inhibitors (TKIs). Table 42.6 is summarizing some important EGFR inhibitors under clinical investigation in R/M-SCCHN. EGFR-activated signaling pathways and the effect of activation on cell proliferation and survival are well documented [68]. Ligand binding to the EGFR is followed by stimulation of a number of different signal transduction cascades, including the mitogen-activated protein kinase (MAPK) pathway and the phosphatidylinositol 3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) pathway. The MoAbs and TKIs act at different points on the pathway to disrupt signaling. However, it is likely that the effects of these agents are not mediated by disruption of EGFR signaling pathways alone. Also, antibody-dependent cellular cytotoxicity (ADCC) is thought to be an important mechanism of action, but for a long time, it was thought that this only referred to immunoglobulin G_1 (IgG1) MoAbs [69, 70]. However, very recently it was discovered that also human IgG2 MoAbs against EGFR effectively trigger ADCC but, in contrast to IgG1, only by cells of the myeloid lineage [71]. The ability of many EGFR inhibitors to enhance the effects of radiation and/or chemotherapy has been demonstrated both in vitro and in vivo [72]. In vitro and in vivo data suggest that the combined use of an EGFR-targeted MoAb and a TKI increases the impact of either agent alone on downstream signaling, apoptosis, proliferation, and tumor (xenograft) growth [73, 74], and this may be of interest for the clinical situation, in particular for the recurrent/metastatic disease setting (see below).

42.5.1.1 Monoclonal Antibodies

Cetuximab

The best-studied monoclonal antibody thus far is cetuximab, which is a human–murine chimeric IgG_1 monoclonal antibody, which competitively binds to the extracellular domain of the EGFR. Cetuximab has been tested in R/M-SCCHN, either in second-line after failure of platinum-based chemotherapy or in first-line in combination with platinum-based chemother-

Table 42.6 Selection of relevant EGFR-targeting agents under clinical investigation in SCCHN

Monoclonal antibodies				Toxicity
Cetuximab	IMC225	Chimeric human–murine	IgG1	Skin
Matuzumab	EMD72000	Humanized mouse	IgG1	Skin
Nimotuzumab	h-R3	Humanized mouse	IgG1	Systemic/hemodynamic
Zalutumumab	2F8	Human	IgG1	Skin
Panitumumab	ABX-EGF	Human	IgG2	Skin

Tyrosine kinase inhibitors				
Gefitinib	ZD1839	Reversible	EGFR	Skin/gastrointestinal (GI)
Erlotinib	OSI-774	Reversible	EGFR	Skin/GI
	PKI-166	Reversible	EGFR/ERbB2	Skin/GI/systemic/hepatic
Lapatinib	GW-572016	Reversible	EGFR/ERbB2	Skin/GI/systemic
Afatinib	BIBW-2992	Irreversible	Pan Her[a]	Skin/GI/systemic
Dacomitinib	PF-00299804	Irreversible	Pan Her[a]	Skin/oral/GI/systemic

Based on data from refs. [57, 59]
[a]EGFR/Her2/Her4

apy. Moreover, it has been tested as part of the combined modality treatment for locoregionally advanced SCCHN. This latter application is beyond the scope of this chapter.

Cetuximab in Second-Line Therapy

Three phase II trials examined the role of cetuximab in platinum-refractory or platinum-resistant disease. All patients received cetuximab intravenously at an initial loading dose of 400 mg/m^2 followed by weekly 250 mg/m^2.

Baselga et al. [75] added weekly cetuximab to platinum-based chemotherapy in 96 patients with truly platinum-refractory SCCHN. The OR rate (primary end point) was 10 %. The DC rate (CR + PR + SD) was 53 %. The median time to progression and OS were 85 and 183 days, respectively.

Herbst et al. [76] studied the combination of cetuximab and chemotherapy in a rather heterogeneous population of 130 patients with R/M-SCCHN. The patients had either SD after two cycles or had progressed under cisplatin-based chemotherapy. After cetuximab was added to the same regimen, 13 % of the patients responded. The DC rate in the patients with progressive disease at study entry was 55 %. Median duration of response was about 4 months in the cohort of patients with progressive disease at study entry and 7.4 months in the cohort of patients with SD at study entry.

Vermorken et al. [77] conducted an open-label, uncontrolled, multicenter phase II study, with a two-phase design. In the first phase, 103 patients with platinum-refractory R/M-SCCHN received single-agent cetuximab. A PR was documented in 13 % of the patients. The DC rate was 46 %. The median duration of response was 126 days. The median time to progression was 70 days. Fifty-three patients (51 %) who experienced progression while receiving single-agent cetuximab continued treatment with cetuximab but then again in combination with a platinum compound. No objective responses were observed in this second phase. Responses in the latter three studies were remarkably similar, irrespective of whether the cetuximab was administered as a single agent or added to a platinum-based regimen. This suggests that the observed responses were attributable to cetuximab alone rather than to the reversal of platinum resistance by cetuximab.

Interestingly, the survival of around 6 months achieved with cetuximab in platinum-refractory disease was found similar to that seen with first-line therapy and represented an increase in survival of 2.5 months compared with platinum-refractory historical controls [10]. Based on these results and particularly considering the fact that about 50 % of the patients showed DC, cetuximab monotherapy seems to be a good option for patients with R/M-SCCHN who have progressed on platinum-based chemotherapy.

Cetuximab in First-Line Therapy

The feasibility of the combination of cetuximab with cisplatin or carboplatin and 5-FU was demonstrated in a phase I/II study [78]. In addition, it was shown that cetuximab could be easily combined with weekly paclitaxel [79] and with the combination of a platinum and a taxane [80]. The second step was to evaluate whether the addition of cetuximab to platinum-based chemotherapy in first-line for recurrent/metastatic disease would benefit patients in terms of survival gain. Up to this moment, this has been studied only in two randomized multicenter phase III trials [81, 82] (Table 42.7).

Burtness et al. [81] assigned 117 patients to cisplatin 100 mg/m^2 every 4 weeks either with weekly cetuximab or with weekly placebo. The primary end point of this study was PFS. The study was designed to detect a difference in median PFS of 2 months, i.e., 2 months with cisplatin plus placebo and 4 months with the experimental arm. However, the observed median PFS in the control arm was longer than expected (2.7 months). The median PFS in the cetuximab arm was 4.2 months and that difference did not reach statistical significance ($p=0.09$). In fact, the actual power to detect a 2-month difference in this situation was only 50 %. The OR rate was 26 % in the experimental arm vs. 10 % in the control arm ($p=0.03$). Median OS was not significantly different (9.2 vs. 8 months, $p=0.21$). Development of cetuximab-related skin toxicity was associated with an improved OS (hazard ratio 0.42, $p=0.01$).

In the EXTREME study [82], 442 patients were randomized to receive either chemotherapy alone (cisplatin 100 mg/m^2 or carboplatin AUC 5 mg/ml/min on day 1 followed by 5-FU 1000 mg/m^2/day for 4 days) or the same regimen com-

Table 42.7 First-line treatment with EGFR inhibitors in recurrent/metastatic SCCHN: randomized trials

Study, author (year)	*N*	Regimen	Response rate (%)	Median PFS (months)	Median OS (months)
ECOG 5397 Burtness (2005) [81]	117	P + cetuximab	26*	4.2	9.2
		P + placebo	10	2.7	8.0
EXTREME Vermorken (2008) [82]	442	PF^1 + cetuximab	36*	5.6*	10.1*
		PF^1	20	3.3	7.4
SPECTRUM Vermorken (2013) [90]	657	PF^2 + panitumumab	36*	5.8*	11.1
		PF^2	25	4.6	9.0

P cisplatin, *PF^1* cisplatin or carboplatin plus 5-fluorouracil, *PF^2* cisplatin plus 5-fluorouracil, *significant differences, *PFS* progression-free survival, *OS* overall survival

bined with weekly cetuximab (initial loading dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2). Cycles were repeated every 3 weeks for a maximum of six cycles. Thereafter, in the combined arm, cetuximab was continued as a single agent until disease progression or unacceptable toxicity whatever came first. No crossover was permitted in this study. Excluded were patients who had received prior chemotherapy except when this had been part of their primary treatment provided this chemotherapy was ended at least 6 months before inclusion in the study. The primary end point was OS. The addition of cetuximab to platinum/5-FU significantly prolonged the median OS from 7.4 months in the chemotherapy-alone group to 10.1 months in the group that received chemotherapy plus cetuximab (hazard ratio for death, 0.80; 95 % confidence interval, 0.64–0.99; $p=0.04$) (Fig. 42.2).

The addition of cetuximab also prolonged the median PFS time from 3.3 to 5.6 months (hazard ratio for progression, 0.54; $p<0.001$) and increased the OR rate from 20 to 36 % ($p<0.001$) with 0.9 % CR in the control arm compared to 6.8 % CR in the investigational arm. The beneficial effect was evident both in the patients treated with cisplatin/5-FU and the patients treated with carboplatin/5-FU, although also in this study response rates with carboplatin/5-FU were below those obtained with cisplatin/5-FU independent from the treatment arm (Fig. 42.3). Moreover, protocol-defined subgroup analyses showed that the beneficial effects of adding cetuximab to platinum/5-FU chemotherapy on OS and PFS were evident in nearly all subgroups analyzed. The most common grade 3 or 4 adverse events in the chemotherapy-alone and cetuximab groups were anemia (19 and 13 %, respectively), neutropenia (23 and 22 %), and thrombocytopenia (11 % in both groups). Sepsis occurred in nine patients in the cetuximab group and in one patient in the chemotherapy-alone group ($p=0.02$). There were 11 cases of grade 3 or 4 hypomagnesemia in the cetuximab group,

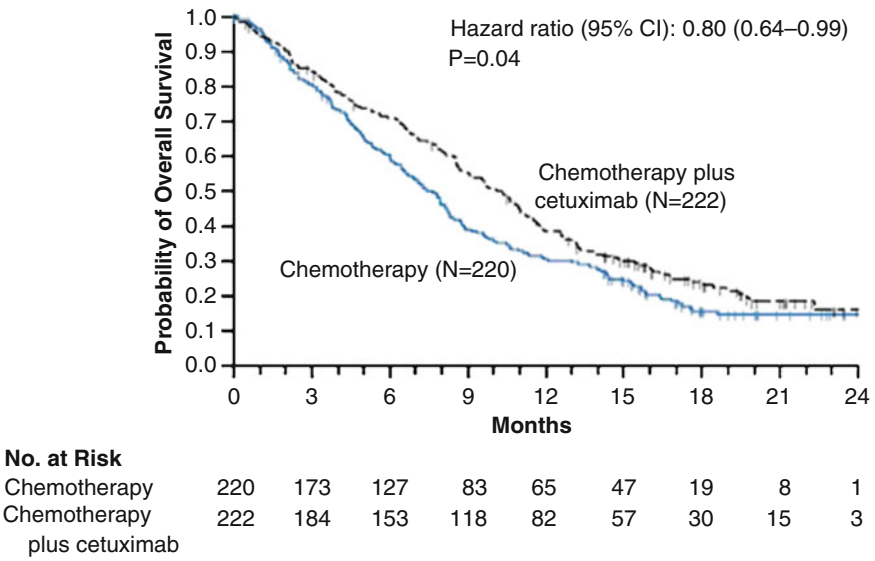

Fig. 42.2 Overall survival with platinum/5-FU combination chemotherapy with or without cetuximab (reprinted from Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008;359:1116–27. Copyright 2008 Massachusetts Medical Society. All rights reserved)

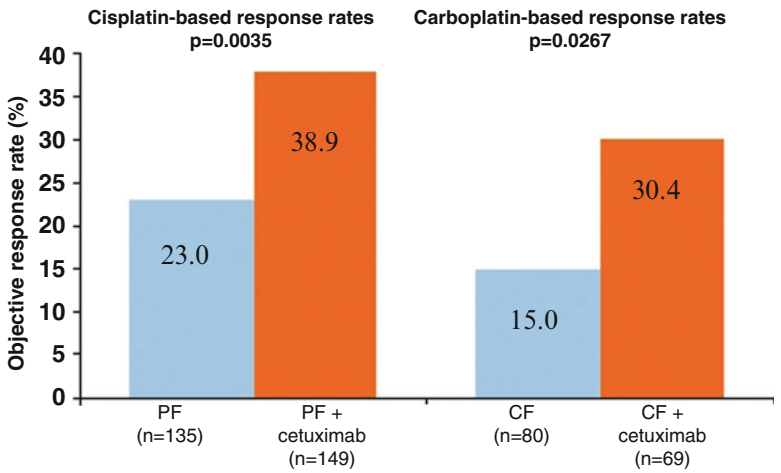

Fig. 42.3 Response rates: cisplatin/5-FU (PF)-based therapy vs. carboplatin/5-FU (CF)-based therapy

as compared with three cases in the chemotherapy-alone group ($p=0.05$). Of the 219 patients receiving cetuximab, 9 % had grade 3 skin reactions and 3 % had grade 3 or 4 infusion-related reactions. There were no cetuximab-related deaths. The long-term follow-up data of this study were presented in 2014 [83]. Thirty-one (14 %) patients in the cetuximab arm and 25 (11 %) in the chemotherapy arm of the intention-to-treat population lived more than 2 years. At 5 years, 8 patients (6 and 2, in both arms, respectively) were still known to be alive. During the cetuximab maintenance period, the frequency of grade 3–4 toxicity decreased from 81 to 49 % when compared with the initial treatment period with platinum-based regimen plus cetuximab. Despite the markedly low 5-year survival figures, the long-term benefit with the addition of cetuximab has been confirmed.

This is the first time in over 30 years that superiority (in terms of survival) of a new regimen over standard platinum-based combination chemotherapy has been observed. Cetuximab and platinum-based chemotherapy is now considered as a new standard for the treatment of R/M-SCCHN for those who are able to tolerate platinum-based combination chemotherapy regimens [84].

Based on the results of several phase II studies with taxane/cetuximab combinations demonstrating OR rates above 50 % and manageable toxicity, future randomized trials should further explore the promising role of taxanes and their intriguing interaction with cetuximab [79, 80, 85] (Table 42.8). This, in fact, is taking place with the regimen that was originally reported by Guigay et al. in 2012 [85]. That so-called TPEx regimen (supported by G-CSF) induced in phase II an OR rate of 54 % in 54 R/M-SCCHN patients, a median PFS of 7.1 months and a median OS of 15.3 months. After four 3-weekly cycles of this TPEx combination (docetaxel 75 mg/m^2 day 1, cisplatin 75 mg/m^2 day 1 every 21 days, and weekly cetuximab), maintenance therapy was applied with biweekly single-agent cetuximab which was continued until disease progression or unacceptable toxicity. Since 2014, the GORTEC 2014-01 trial is ongoing in France, Germany, and Spain. This study compares the cisplatin/5-FU plus cetuximab regimen from the EXTREME trial with the TPEx regimen mentioned above. The primary end point is OS. Ancillary studies will provide data on QoL, cost-effectiveness, and HPV/p16 tumor status.

In contrast, disappointing results were obtained with a pemetrexed/cisplatin/cetuximab combination in 66 R/M-SCCHN patients out of which 35 had received prior cytotoxic chemotherapy [86]. In this phase II study, a relationship between the higher-than-expected rate of deaths (7.6 %), due to frequent grade 4 neutropenia (10.4 %) and pemetrexed, was suspected, thus hampering efforts to further develop this regimen in patients with R/M-SCCHN.

Panitumumab

Panitumumab (ABX-EGF) is a fully human IgG2 antibody with a very strong binding to the receptor [57, 87]. It blocks ligand binding and induces internalization of the receptor but no receptor degradation. Side effects include pruritus, skin rash, dyspnea, fatigue, abdominal pain, asthenia, and diarrhea. Panitumumab at a weekly dose of 2.5 mg/kg has an acceptable tolerability and encouraging clinical activity in patients with a variety of tumor types. Its pharmacokinetic profile allows a more convenient three weekly administration (9 mg/kg). Three studies with panitumumab in the recurrent/metastatic disease setting are of interest, i.e., the PRISM study, the PARTNER study, and the SPECTRUM study. The PRISM study is a phase II study with single-agent panitumumab in the second-line setting that enrolled 52 patients. Primary efficacy results showed a 4 % PR rate and a 39 % DC rate [88].The PARTNER study is a randomized phase II study in the first-line setting studying docetaxel plus cisplatin with or without panitumumab [89]. Data, although not statistically significant, indicated longer median PFS and higher OR rate (6.9 vs. 5.5 months and 44 % vs. 37 %, respectively) but shorter median OS (12.9 vs. 13.8 months) in the panitumumab arm. The interpretation of the decreased OS with the addition of panitumumab is hampered by crossover trial design allow-

Table 42.8 Chemotherapy plus cetuximab in recurrent/metastatic SCCHN showing promising results with taxane-based regimens

Author (year)	Phase	*N*	Regimen	Response rate (%)	Median PFS (months)	Median OS (months)
Burtness (2005) [81]	III	117	P + cetuximab	26*	4.2	9.2
			P + placebo	10	2.7	8.0
Vermorken (2008) [82]	III	442	PF^{l} + cetuximab	36*	5.6*	10.1*
			PF^{l}	20	3.3	7.4
Buentzel (2007) [80]	II	23	Paclitaxel + Carboplatin + cetuximab	56	5.0 (TTP)	8.0
Hitt (2012) [79]	II	46	Paclitaxel + cetuximab	54	4.2	8.1
Guigay (2012) [85]	II	54	Docetaxel + P + cetuximab	54	7.1	15.3

P cisplatin, *PF^{l}* cisplatin or carboplatin plus 5-fluorouracil, *significant differences, *PFS* progression-free survival, *TTP* time to progression, *OS* overall survival

ing patients who initially received docetaxel plus cisplatin to switch to panitumumab monotherapy upon disease progression. In the panitumumab arm, increments in PFS and OR rate were noted in the overall population and also in the p16-positive and p16-negative subgroups. The SPECTRUM trial is a phase III trial in which patients in the first-line recurrent/metastatic disease setting were randomized to be treated with cisplatin/5-FU with or without panitumumab [90]. Differences with the EXTREME trial included: being a global versus a European trial, not allowing carboplatin/5-FU to start with, not allowing performance status 2 patients to start with, and no compulsory maintenance therapy. Activity of panitumumab in this trial was observed in terms of an improved OR rate (36 % vs. 25 %; $p=0.0065$) and an improved PFS (5.8 vs. 4.6 months, $p=0.0036$). However, this did not translate into a significant OS benefit, albeit that there was a 2.1 months' benefit in median OS over a 9.0 months' median survival in the control arm (Table 42.7). The planned subanalysis of this study by p16 status will be described below.

Zalutumumab

Zalutumumab [57] is also a fully human IgG1 EGFR-directed monoclonal antibody. The frequency of acneiform rashes with this compound increases with the dose administered. Zalutumumab so far is the only anti-EGFR MoAb that has been tested in a phase III trial in the second-line setting in patients who failed standard platinum-based chemotherapy vs. best supportive care (BSC) alone [13] (Table 42.9). Patients in the BSC arm were allowed to receive single-agent methotrexate, if so wished by the investigator or patient. Despite significantly enhanced PFS with the zalutumumab regimen and the fact that the tail of the survival curve suggested that at 12 months a double amount of patients was alive in the zalutumumab arm, no significant impact on OS was found. Frequent grade 3–4 side effects were as follows: rash (21 % vs. 0 % in the zalutumumab vs. control arm, respectively), anemia (6 % vs. 5 %), and pneumonia (5 % vs. 2 %). Tumor hemorrhage (nine cases), pneumonia (five cases), and lung abscess (two cases) led most commonly to zalutumumab withdrawal.

Matuzumab

Matuzumab is a humanized IgG1 monoclonal antibody that in a phase I dose escalation study in stage III/IV larynx and hypopharynx cancer showed that fever and transient elevations of liver enzymes were the most frequently observed treatment-related adverse events [91]. A weekly dose of 200 mg, based on pharmacokinetic findings, was selected for further studies. No data of randomized trials in R/M-SCCHN are available.

Nimotuzumab

Nimotuzumab [57] is also a humanized IgG1 mouse antibody. Preliminary data suggest that therapeutic levels of nimotuzumab can be achieved without eliciting skin toxicity, which is the most common side effect of the other anti-EGFR-directed antibodies. Nimotuzumab has a lower receptor affinity than, e.g., panitumumab, cetuximab, or matuzumab, and there seems to be a relationship between receptor affinities and incidence of acneiform rash for anti-EGFR MoAbs [92]. It has been hypothesized that higher binding and internalization of MoAbs in the tumor together with a lower level of internalization in noncancerous tissues is obtained with intermediate affinity constant (K_d) values between 10^{-9} and 10^{-8} M, as is the case for nimotuzumab. Moreover, recent experimental observations have demonstrated that in contrast to other anti-EGFR antibodies, the intrinsic properties of nimotuzumab requires bivalent binding for stable attachment to cellular surfaces, which leads to a greater selectivity of nimotuzumab to bind to cells that express moderate to high EGFR levels, such as in SCCHN. At present, there is no clinical evidence that higher affinity to the receptor leads to greater efficacy, though stronger binding clearly leads to higher toxicities. A phase IIB clinical study in Indian patients with SCCHN showed very few skin reactions, including urticaria and pruritus, but did show some headache, hypertension, and fluctuation in blood pres-

Table 42.9 Second-line treatment with EGFR inhibitors in recurrent/metastatic SCCHN: randomized trials

Study, author (year)	*N*	Regimen	Response rate (%)	Median PFS (months)	Median OS (months)
IMEX Stewart (2009) [12]	486	Gefitinib (250 mg)	2.7	ND	5.6
		Gefitinib (500 mg)	7.6	ND	6.0
		MTX	3.9	ND	6.7
ECOG 1302 Argiris (2013) [17]	270	D + Gefitinib	12.5	3.5 (TTP)	7.3
		D + placebo	6.2	2.1 (TTP)	6.0
ZALUTE Machiels (2011) [13]	286	Z + BSC	6.3	2.3*	6.7
		BSC (optional MTX)	1.1	1.9	5.2
LUX-Head & Neck 1 Machiels (2015) [102]	483	Afatinib	10.2	2.6*	6.8
		MTX	5.6	1.7	6.0

MTX methotrexate, *D* docetaxel, *Z* zalutumumab, *BSC* best supportive care, *PFS* progression-free survival, *ND* no data, *TTP* time to progression, *significant differences, *OS* overall survival

sure [93]. Nimotuzumab is presently approved for use in SCCHN, glioma, and nasopharyngeal cancer in various countries and is granted orphan drug status for glioma in the USA and for glioma and pancreatic cancer in Europe.

42.5.1.2 Tyrosine Kinase Inhibitors

The TKIs compete with ATP for the cytoplasmatic catalytic domain of EGFR. Gefitinib and erlotinib are reversible specific EGFR TKIs and belong to the group of quinazoline TKIs. This group also comprises PD153035 and GW 572016 (lapatinib), which are reversible dual EGFR/HER-2 inhibitors; EKB-569, which irreversibly inhibits the EGFR and HER-2 tyrosine kinase; and the irreversible pan-ErbB TKIs BIBW-2992 (afatinib) and PF-00299804 (dacomitinib) (see Table 42.6). PKI-166 (dual EGFR/ErbB-2) belongs to the pyrrolotriazine TKIs, which also include AEE788 (dual EGFR/ErbB-2) and BMS 599626. ARRY-334543 (dual EGFR/ErbB-2) and PD1578 belong to the pyridopyrimidine TKIs [57].

Single-Agent Use

Until very recently, the results with reversible oral TKIs have been disappointing [12, 94–98] (Table 42.10). Single-agent trials with reversible TKIs published in peer-reviewed journals showed OR rates ranging from 0 to 11 % and a median PFS of approximately 2.5 months [94–98]. Drug toxicity was generally mild, consisting of skin rash and diarrhea, more frequent at higher dosages. It has been suggested, based on some of these single-arm studies, that outcome might not only be related to the occurrence and severity of the skin reaction but also related to the dose used. This latter aspect was tested in a large phase III trial (1839 IL/0704; IMEX) in which 482 patients with R/M-SCCHN, unresponsive to platinum or unfit for platinum, were randomized in a three-armed study to receive either gefitinib 250 or 500 mg/day or methotrexate 40 mg/m^2 intravenously weekly [12]. Neither gefitinib 250 nor 500 mg/day improved survival compared with single-agent methotrexate. OR rates were 2.7, 7.6, and 3.9 %, respectively, and median OS was 5.6, 6, and 6.7 months, respectively (see also Table 42.9). Tumor bleeding was observed more frequently in patients treated with gefitinib than with methotrexate. Single-agent lapatinib (1500 mg/day) was associated with disappointing activity (no objective responses) in a phase II study in 42 patients with recurrent and/or metastatic disease, 15 of whom had previously received treatment with an EGFR inhibitor [98]. Cohen et al. [99] reviewed individual patient data from five clinical trials of erlotinib, lapatinib, or gefitinib to determine if there are clinical characteristics that are associated with clinical benefit. Performance status ($p=0.04$), older age ($p=0.02$), and development of rash ($p<0.01$), diarrhea ($p=0.03$), or oral side effects ($p=0.02$) were independently associated with clinical benefit. Older age, better performance status, and development of rash were associated with longer PFS and OS. EGFR mechanistic toxicities that developed during therapy were also highly associated with benefit and suggest a relationship between drug exposure and outcome.

To date, the only TKI that so far has shown activity comparable to that of cetuximab is afatinib, an irreversible HER family blocker. This was shown in a randomized phase II study in patients failing previous platinum therapy [100]. Dacomitinib showed comparable activity (13 %) but in a non-randomized study in patients without prior platinum [101]. Very recently afatinib was compared with methotrexate in a phase III trial (LUX-HN1) in patients failing first-line platinum-based chemotherapy [102] (Table 42.9). Patients were randomized 2:1 to 40 mg/day afatinib or 40 mg/m^2/week methotrexate. The primary end point of PFS and secondary end point of delayed deterioration in global health status, pain, and swallowing were met in favor of the afatinib arm. Of particular interest was the observation in the p16-negative cohort. However, neither response nor OS was significantly improved.

Combinations with Chemotherapy

A phase I/II trial of erlotinib and cisplatin performed by the Princess Margaret Hospital phase II consortium and the National Cancer Institute of Canada Clinical Trials Group in a population of platinum-sensitive R/M-SCCHN patients revealed an OR rate of 21 % and a median OS of 7.9 months [103]. These data are similar to those reported by Burtness et al. [81] with the combination of cisplatin and cetuximab

Table 42.10 TKIs inhibiting EGFR in recurrent/metastatic SCCHN: data from peer-reviewed journals

Drug	Author (year)	Phase	Prior palliative chemotherapy	Response rate (%)
Erlotinib	Soulieres (2004) [94]	II	0–1 lines	4
Gefitinib	Cohen (2003) [95]	II	0–1 lines	11
	Cohen (2005) [96]	II	0–5 lines	1
	Kirby (2006) [97]	II	0–1 lines	9
	Stewart (2009) [12]	III	P+/P–	3–8
Lapatinib	De Souza (2012) [98]	II	Unclear	0
Afatinib	Seiwert (2014) [100]	II	Prior P	16[a]/8[b]
Dacomitinib	Abdul Razak (2013) [101]	II	No prior P	13

P platinum-based regimen
[a]By investigator review
[b]By independent central review

in similar patients, albeit that these latter data were obtained in a randomized trial setting. Combinations of the TKIs with cisplatin plus docetaxel (in Europe with gefitinib, in the USA with erlotinib) have shown interesting results in small groups of patients and did not cause more hematologic toxicity than normally observed with cisplatin plus docetaxel alone [104, 105]. However, ECOG [17] conducted a randomized, placebo-controlled trial of docetaxel 35 mg/m^2 on days 1, 8, and 15 every 28 days, with or without gefitinib 250 mg/day in R/M-SCCHN patients. Although the combination was well tolerated and improved the time to progression from 2.0 to 3.5 months ($p=0.03$), this did not translate into an improved OS (see Table 42.9). Based on preliminary data, the combination of lapatinib and capecitabine yielded a 24 % OR rate in the early report of 34 evaluable patients, which corresponds with that reported for capecitabine alone [35, 106]. No data on OS were available in that latter study.

42.5.1.3 Overcoming Resistance to Anti-EGFR Therapy

Due to the existence of various receptor signaling pathways consisting of mesenchymal–epithelial transition factor (c-Met), PI3K-Akt, ErbB2/HER2, or ErbB3/HER3, aurora A kinase, phosphorylated signal transducer and activator of transcription 3 (STAT3), vascular endothelial growth factor (VEGF), primary or acquired resistance to cetuximab will usually develop. Apart from various combination regimens with either classic cytotoxic drugs or targeted agents, novel promising approaches include dual targeting MoAbs, mixture of MoAbs, and therapeutics blocking multiple HER receptors. The latter group comprises lapatinib, afatinib, or dacomitinib which were mentioned earlier [58, 59, 107]. An example of dual targeting MoAbs is the IgG1 antibody MEHD7945A which simultaneously inhibits both EGFR and HER3 and also regulates ADCC in vitro and in vivo. A 2014 randomized phase II study of MEHD7945A vs. cetuximab in second-line treatment of R/M-SCCHN failed to demonstrate any significant survival or response differences [108]. Catumaxomab (anti-EpCAM and anti-CD3) and ertumaxomab (anti-HER2/neu and anti-CD3) further expand the armamentarium of dual targeting MoAbs. Finally, Sym004 represents a mixture of two MoAbs aiming at nonoverlapping epitopes on the EGFR [109].

42.5.2 Vascular Endothelial Growth Factor and Vascular Endothelial Growth Factor Receptor

Activation of the VEGF–VEGFR axis triggers a cascade of signaling processes that promote tumor angiogenesis and lymphangiogenesis. The majority of the studies, although not all, examining the prognostic significance of VEGF expression did observe a worse outcome in patients with SCCHN expressing VEGF and VEGFR-2 [110, 111]. Anti-VEGF strategies include neutralizing antibodies to VEGF or VEGFR and VEGFR TKIs.

42.5.2.1 Bevacizumab

Bevacizumab is a humanized VEGF-A-directed antibody that is in clinical development in a wide variety of tumors including non-small cell lung cancer, breast cancer, ovarian cancer, prostate cancer, and brain tumors. Seiwert et al. [112] integrated bevacizumab 10 mg/kg every 2 weeks into an alternating regimen of infusional 5-FU, hydroxyurea, and daily radiation as treatment for newly diagnosed or recurrent SCCHN requiring local control. Because of neutropenia, the originally planned chemotherapy doses (5-FU 800 mg/m^2, hydroxyurea 1000 mg/m^2) needed to be decreased (5-FU 600 mg/m^2, hydroxyurea 500 mg/m^2). Three thrombotic events and two fatal bleedings as well as late complications including five patients with fistula formation (11.6 %) and four with ulceration/tissue necrosis (9.3 %) were observed, for which a relation to bevacizumab was suspected. A phase II study demonstrated activity of a combination of bevacizumab and pemetrexed in first-line treatment of R/M-SCCHN [113]. In fact, the authors reported an OR rate of 30 % and a median OS of 11 months among 37 evaluable patients. However, bleeding complications were relatively high, with four grade 3 and two fatal bleeding events. Currently, a phase III trial (NCT00588770) investigating the role of a platinum doublet with or without bevacizumab in R/M-SCCHN is ongoing.

42.5.2.2 Tyrosine Kinase Inhibitors and Other Anti-angiogenic Agents

The complications mentioned above are regularly reported in different studies, not only with bevacizumab but also with the TKIs [57]. Early data on semaxanib (a small molecule TKI that interferes with angiogenesis by selectively inhibiting the VEGFR-2 receptor) and the multikinase inhibitor sorafenib [which is both an inhibitor of Raf-1 and B-Raf kinases and protein tyrosine kinases associated with VEGFR-2 and VEGFR-3 as well as the platelet-derived growth factor receptor B (PDGFR-B)] are summarized in two recent reviews, showing only modest activity and a higher-than-expected thromboembolic events [57, 72]. Recently, a high incidence of fatal and nonfatal hemorrhagic complications and fistulization in R/M-SCCHN was reported with sunitinib, a multitargeted TKI of REarranged during Transfection (RET), VEGFR, PDGFR, and c-KIT [114]. The severity of these complications highlights the importance of improved patient selection for future studies with these compounds in head and neck cancer. Use outside clinical trials is not recommended. In contrast, promising results were achieved with sorafenib, a multikinase Raf, VEGFR, and PDGFR inhibitor, combined with carboplatin and paclitaxel in a phase II study [115]. In that study, a DC rate of 84 % was reported, while PFS and OS were 8.5 and 22.6 months,

respectively. Despite favorable preclinical data and clinical phase I results, the addition of the selective integrin inhibitor cilengitide did not add any survival advantage when combined with the cisplatin/5-FU/cetuximab (as in EXTREME) regimen in a randomized phase II study [116].

42.5.3 Combined Targeting of EGFR and VEGFR

Based on preclinical data, combined targeting seems of interest and may be particularly of interest for patients with R/M-SCCHN when tolerance of such an approach proves to be good. Cohen et al. [117] combined erlotinib 150 mg/day and bevacizumab in patients with R/M-SCCHN. In the phase I portion of the study, no dose-limiting toxic effects were observed at the highest dose level of bevacizumab (15 mg/kg every 3 weeks). Forty-eight patients were treated at that dose level. The most common toxic effects were rash and diarrhea. Three patients had serious bleeding events of grade 3 or higher. The OR rate was 14.6 % with 8.3 % CR. The median time of OS and PFS was 7.1 months (95 % confidence interval 5.7–9.0) and 4.1 months (2.8–4.4), respectively. Argiris et al. [118] presented data on the combined treatment with weekly cetuximab and bevacizumab 15 mg/kg every 3 weeks in patients with R/M-SCCHN. Best response in 45 evaluable patients was 16 % PR and 58 % SD. The median PFS was 2.8 months and median OS 7.5 months. Toxicity was manageable. Only rarely serious toxicities were observed.

42.5.4 Other Targets Including Immunotherapy

Other targets, such as those along the EGFR downstream pathways (RAS-RAF-MAPK, PI3K-Akt-mTOR, STAT, phospholipase-C gamma, and protein kinase-C), aurora A, insulin-like growth factor-1 receptor (IGF-1R), proteasome, histone deacetylases (HDACs), toll-like receptor 8, epithelial cellular adhesion molecule (Ep-CAM), and cyclooxygenase-2, are all of interest but not being at the level of having relevance for daily practice, as yet [58, 59, 119] (Table 42.11). Similarly, immunotherapy represents an emerging field of research interest but also without any randomized clinical data available so far. In addition, clinical implementation of immunotherapy is hampered by the fact that the host immune response to the tumor in its immediate microenvironment is highly complex and remains poorly understood [120]. Notwithstanding this limitation, there is a rapidly evolving subset of MoAbs targeting T-cell immune checkpoint molecules like cytotoxic T-lymphocyte antigen 4 (CTLA4), programmed death-1 (PD-1), and its ligand PD-L1. Currently, the largest body of clinical evidence exists for metastatic melanoma, albeit antitumor properties of the T-cell checkpoint inhibitors have been demonstrated in a variety of malignancies including renal cell carcinoma and non-small cell lung cancer [121]. In SCCHN, a gene expression signature study revealed a T-cell-inflamed microenvironment similar to melanoma in 33–47 % of the examined samples. PD-L1 expression and the presence of tumor-infiltrating lymphocytes were strongly correlated with mesenchymal phenotype of SCCHN, thus indicating a potential benefit from immunotherapy [122]. According to the recently presented, preliminary results from a phase Ib study, pembrolizumab (anti-PD-1 MoAb) produced a 20 % OR rate in 56 evaluable patients with R/M-SCCHN. Subgroup analysis based on HPV status found similar OR rates, while median PFS and OS were longer in HPV-positive than HPV-negative patients (17.2 vs. 8.1 weeks and median OS not reached vs. 9.5 months, respectively). The most frequent drug-related toxicities observed were fatigue (18 %), pruritus (10 %),

Table 42.11 Overview of promising immunotherapies in SCCHN

Targeting tumor antigens: tumor antigen-specific monoclonal antibodies – Cetuximab[a], panitumumab, nimotuzumab, onartuzumab, AV-203, MM-121, cixutumumab
Enhancing ADCC to tumor antigen-specific monoclonal antibodies – e.g., IL-12, VTX-2337
Restoring STAT1/STAT3 signaling balance – Ruxolitinib, SAR302503, BMS911543, pegylated interferon-γ
Targeting immunosuppressive cytokines – Bevacizumab, ficlatuzumab, rilotumumab (AMG 102), siltuximab
T-cell checkpoint inhibitors – Ipilimumab, tremelimumab, MED14736, MPDL5280A, BMS-936558, nivolumab, pembrolizumab
Therapeutic cancer vaccines – HPV 16 E6 and E7 peptide vaccine, MAGE-3 and HPV-16 vaccine, HPV pNGVL4a-CRT/E7 (Detox) DNA vaccine, TG4001 vaccine, Lm-LLO-E7 vaccine, multi-epitope p53 vaccine

ADCC antibody-dependent cellular cytotoxicity, *STAT* signal transducer and activator of transcription, *HPV* human papillomavirus, *MAGE-3* melanoma-associated antigen 3, *DNA* deoxyribonucleic acid
Based on data from ref. [119]
[a]FDA approved for SCCHN

and nausea (8 %) [123, 124]. A prospective phase III trial of pembrolizumab vs. standard treatment (methotrexate, docetaxel, or cetuximab) in platinum-resistant R/M-SCCHN (NCT02252042) is ongoing.

42.5.5 Targeted Therapy in R/M-SCCHN: Summary

After decades without real progress, a recent randomized trial showed that adding cetuximab, the first clinically available EGFR-directed monoclonal antibody, to a standard chemotherapy regimen (platinum/5-FU) led to an important survival benefit in patients with R/M-SCCHN, and this has changed practice. So far, the data on the monoclonal antibodies against EGFR seem to be more promising in their interaction with cytotoxic agents than the small molecule TKIs. However, combined targeting either with different anti-EGFR approaches or with both anti-EGFR and anti-VEGF(R) approaches seems an interesting field of research. There is a plethora of targeted therapies in various stages of preclinical and clinical development. The next challenges will be to sort out which of those agents have clinically meaningful activity and to find out how to incorporate them into the existing treatment strategies for those suffering from this devastating disease. The most promising but also demanding approach is to identify reliable prognostic and predictive biomarkers which successfully pass prospective validation in a phase III trial setting. HPV and p16 status may become a stratification element for future randomized trial design [89, 100, 125–128] (Table 42.12 and Fig. 42.4). HPV may be of particular interest when testing single-agent activity of newer targeted therapies [100, 108].

Table 42.12 Relationship between human papillomavirus (HPV)/p16 status and treatment outcomes in recurrent/metastatic SCCHN

Study group	Phase	Drugs	HPV/p16	
			Prognostic	Predictive
EXTREME [82, 125]	III	PF ± cetuximab	Yes	No
SPECTRUM [90, 126]	III	PF ± panitumumab	Yes	Yes
ECOG 1395 [54, 127]	III	PF vs. PP	Yes	NR
ECOG 3301 [127, 128]	II	Irinotecan + docetaxel	Yes	NR
PARTNER [89]	II	Docetaxel + cisplatin ± panitumumab	Yes ?	No
PoC 1200.28 [100]	II	Afatinib vs. cetuximab	NR	Yes

PF platinum plus 5-fluorouracil in EXTREME, cisplatin plus 5-fluorouracil in SPECTRUM and ECOG 1395, *PP* paclitaxel plus cisplatin, *NR* not reported

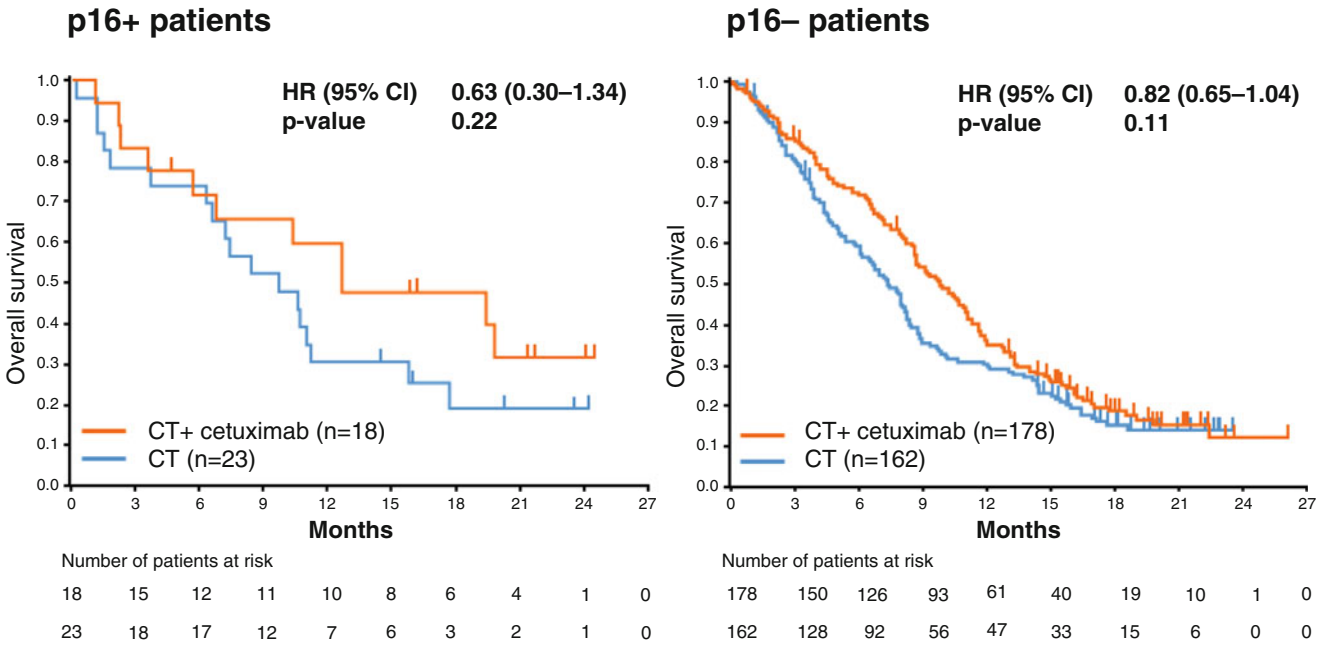

Fig. 42.4 Overall survival in the EXTREME trial by p16 status (presented by Vermorken JB at the 4th International Conference on Innovative Approaches in Head and Neck Oncology (ICHNO), Barcelona, Spain, February 7–9, 2013 (abstract SP-006)) (courtesy of Jan B. Vermorken)

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Phase I Study Methodology in Head and Neck Oncology

43

Aaron Hansen and Christophe Le Tourneau

Abstract

Phase I trials evaluating anticancer treatments in locoregionally advanced or recurrent metastatic head and neck squamous cell carcinomas (HNSCC) require disease-specific considerations. In the locoregionally advanced setting, trials are often conducted in combination with radiation (RT) in patients with a curative diagnosis. Both safety and efficacy are relevant factors in their design and conduct. Preclinical evidence of safety, as well as appropriate biological justification of antitumor activity, should be available to rationalize the incorporation of new agents in the combination treatment regime. Trials enrolling patients with recurrent and/or metastatic HNSCC have been transformed by the advent of molecularly targeted agents and immune checkpoint inhibitors. Several challenges are faced by these studies which include patient enrichment, measurement of efficacy, and determining the optimal biological dose. Regardless of the disease stage, innovative clinical trial designs; identification of predictive, therapeutic, and toxicity biomarkers; and detection of early signals of antitumor activity are urgently needed to expedite the development of safe and effective combination regimes in HNSCC.

Keywords

Phase I trial • Dose escalation • Dose-limiting toxicity • Novel agents • Radiotherapy

43.1 Introduction

Phase I clinical trials aim to establish the recommended dose or schedule of a new intervention. In oncology, these trials have primarily been designed to evaluate the safety of new cytotoxic anticancer agents in successive cohorts of cancer patients treated with increasing doses until dose-limiting toxicity (DLT) is observed in a prespecified proportion of accrued subjects. The design and methodology of phase I trials comprise many components including the choice of the starting dose, target toxicity level, number of patients per dose level, dose escalation method, specification of DLT, and definition of the maximum tolerated dose and recommended phase II dose.

As efficacy is usually not the primary endpoint of phase I cancer clinical trials, these studies are often performed in unselected tumor types. However, phase I trials specific for patients with head and neck squamous cell carcinomas (HNSCCs) emerged in the 1990s for several treatment-, tumor-, and patient-related reasons (Table 43.1). While these studies typically investigated novel radiosensitizers in patients with locoregionally advanced HNSCC, more recently phase I trials have been designed for patients with recurrent, metastatic HNSCC. This trend has largely been driven by an enriched understanding of the molecular and immune landscape of HNSCC [1–3] and the impact this may have on treatment response and toxicity to either molecular-targeted agents

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Table 43.1 Reasons to conduct phase I trials specifically in the HNSCC

Treatment related
• HNSCC treatment involves complex multidisciplinary strategies (e.g., radiotherapy, chemotherapy, and or molecularly targeted agents), which may produce unexpected treatment-related toxicities due to interactive effects that need to be exclusively assessed in the HNSCC population
• Localized or locoregionally advanced nonmetastatic HNSCC is curable with radiation with or without chemotherapy or biological treatment. As such, the evaluation of efficacy in addition to toxicity is of relevance when combining RT with new drugs
• Late and delayed toxicities are important in HNSCC as they are frequently associated with functional impairment of vital organs
Patient related
• Prevalence of comorbidities in some HNSCC patients may hamper the delivery of a new intervention using dosing schedules defined for other malignancies
• Adverse effects on mucosa and skin rendered by new interventions may be unacceptably exacerbated in patients suffering from locoregional recurrence of HNSCC due to potential prior therapy with surgery and/or radiation
Tumor related
• HNSCC have a diverse mutational profile and specific patterns of immune cell infiltration. These molecular and immune landscapes are disease specific, and the resultant antitumor activity of molecularly targeted agents or immune therapies may be unique to HNSCC

or immune therapies. Furthermore these types of trials are providing go/no-go decisions for drug testing in this distinct patient population to facilitate a more efficient and economical evaluation of experimental therapies.

The development of new therapies in HNSCC continues to evolve and needs to be evaluated for safety and tolerability in phase I trials before being compared against existent standard treatments for efficacy. Phase I trials in the locoregionally advanced HNSCC setting face a different set of issues compared with studies involving recurrent metastatic disease, and thus they will be addressed separately in this chapter.

43.2 Phase I Trials in Locoregionally Advanced HNSCC

The design of phase I trials combining RT with anticancer agents in locoregionally advanced HNSCC has a unique set of considerations (Fig. 43.1 and Table 43.2). In clinical trials enrolling this curable patient population, efficacy considerations are as critical as safety issues. Trials investigating

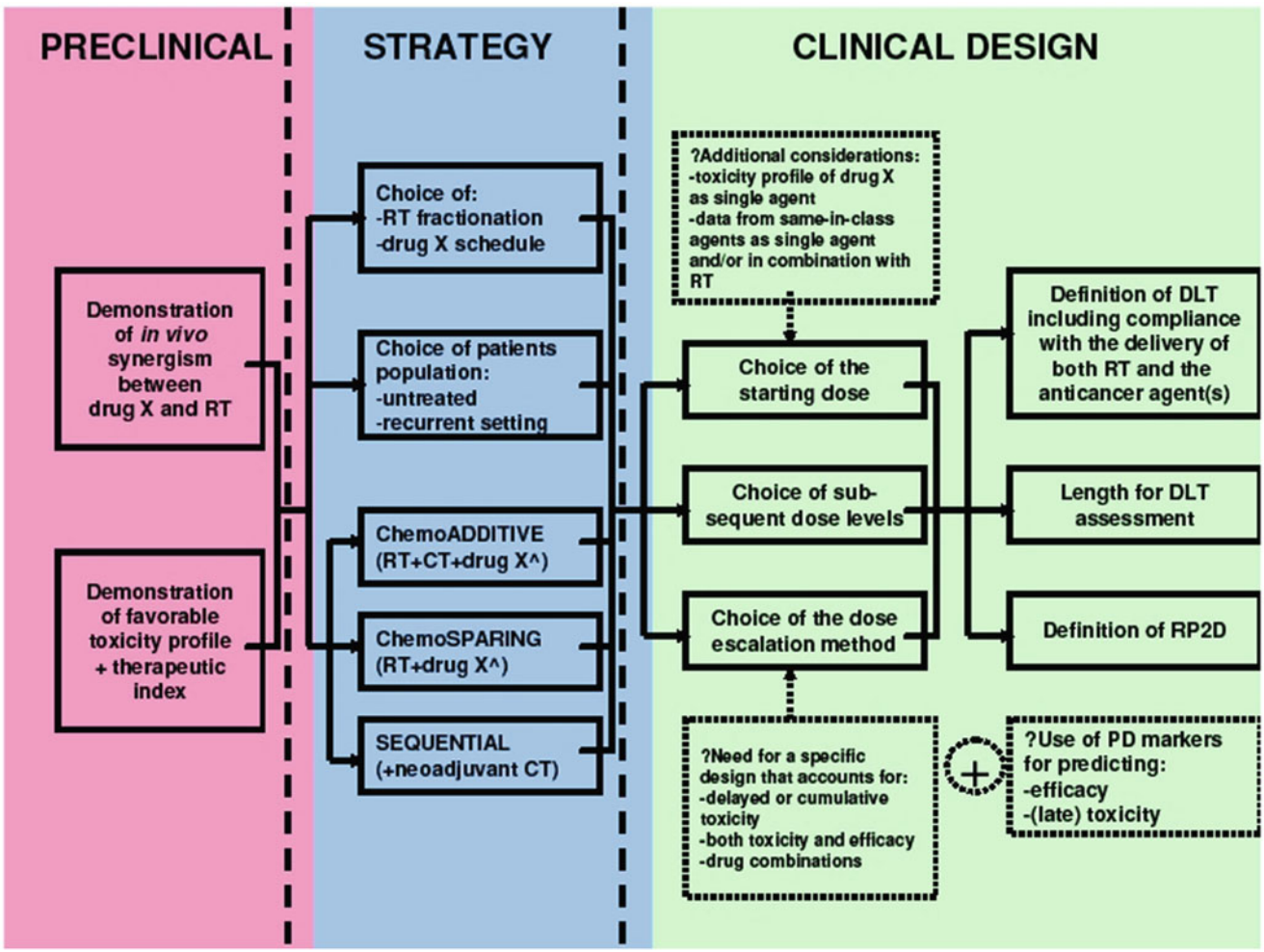

Table 43.2 Considerations for phase I trials combining radiation with anticancer agents in HNSCC

Specific considerations	Issues
Locoregionally advanced HNSCC	
Methodologic considerations	• Dose escalation methods: rule based (e.g., standard 3+3 design) or model based (e.g., Bayesian design) • "Dose-intensity escalation" with escalation of dose of drug and/or number of drug administrations
Safety considerations	• Use of preclinical models to predict safety; limitations such as the availability of appropriate models, cross species specificity; extent to which these evaluations need to be completed prior to initiation of human phase I trial • Choice of starting dose of anticancer agent to be combined with radiation • Optimal length for observation for DLT including acute and late toxicity • Novel phase I trial designs to enable late toxicity assessment without causing delay in dose escalation • Predictive markers of late toxicity
Efficacy considerations	• Use of preclinical models to predict efficacy; limitations such as the availability of appropriate models, cross species specificity; extent to which these evaluations need to be completed prior to initiation of human phase I trial • Efficacy of anticancer agent to be combined with radiation • Maintenance of radiation dose intensity in phase I trial • Compliance of anticancer agent and of radiation therapy • Novel phase I trial designs to account for efficacy in addition to toxicity • Identification of surrogate markers of efficacy
Special considerations	• Challenges for drug combinations to add to definitive radiation therapy • Possibility of development of platinum-free radiation combinations with new drugs • Phase I trials with a neoadjuvant chemotherapy component to add to chemoradiation as sequential therapy
Recurrent metastatic HNSCC	
Special considerations	• Enrichment strategies involve enrolling only patients with HNSCC or patients with HNSCC and a specific molecular abnormality • Efficacy issues in phase I trials: delayed response of immune checkpoint inhibitors and immune-related RECIST criteria • Optimal biological dosing • Dose escalation designs for combination regimens

multiple drug combinations as well as those involving a neoadjuvant chemotherapy component raise specific methodological concerns and thus will also be discussed in this section.

43.2.1 Methodologic Considerations

43.2.1.1 Dose Escalation Methods in Phase I Trials Combining Radiation with Anticancer Agents

Most phase I dose escalation methods in oncology have been designed under the assumption that both efficacy and toxicity increase monotonically with dose. As such, the recommended phase II dose has traditionally been established as the highest safe dose, based on a prespecified acceptable level of DLT. The most commonly used dose escalation method for phase I trials remains the traditional 3+3 dose escalation method, for which dose levels are prespecified, and dose increments often become smaller as the dose increases. The 3+3 method is a rule-based method that proceeds as follows: if none of the first three patients enrolled in a cohort experiences a DLT, then another three patients will be treated at the next higher dose level. However, if one of the first three patients encounters a DLT, then up to three more patients will be added to the same dose level. If the target toxicity level has been preset at 33 % or less, then dose escalation would stop if two or more patients among a cohort of 3–6 patients experience DLT. Besides the 3+3 method, other dose escalation methods such as Bayesian designs (e.g., modified continual reassessment method) which are model based have been developed but underutilized for trials involving anticancer agents without RT [4]. Bayesian models require an initial estimate of the prior distribution of the dose–toxicity relationship, and then toxicity data obtained from patients enrolled in each dose level provide additional information for the statistical model to produce the posterior distribution. The latter is then used to help identify the dose closest to the target toxicity level.

While no specific dose escalation method is recommended for trials of anticancer agents given in combination with RT, the traditional 3+3 method is often used. Guidelines for early phase development of radiosensitizers from the National Cancer Institute Radiation Therapy Oncology Group (NCI-RTOG) have suggested that conservative dose escalation should be performed when the drug

Fig. 43.1 Selected key considerations for the design of a phase I clinical trial of drug X in combination with RT in head and neck cancer. *CT* chemotherapy, *RT* radiotherapy, *DLT* dose-limiting toxicity, *RP2D* recommended phase II dose, *PD* pharmacodynamic. ^if drug X is noncytotoxic

is known to have significant toxicity in the organ irradiated [5]. Conversely, rapid dose escalation can be used for stereotactic radiosurgery or stereotactic radiation combined with a minimally toxic biological agent. Although the dose of an anticancer agent to be combined with RT would usually be escalated if tolerable to its full monotherapy recommended phase II dose, the optimal dose to combine with RT remains elusive, especially for some molecularly targeted agents which do not exhibit dose-dependent antitumor activity.

43.2.2 Safety Considerations

Toxicity evaluation is a crucial reason to perform tumor-specific phase I trials of radiation combined with systemic therapy. For example, the side effect profile for gemcitabine, an antimetabolite chemotherapy, is similar across most tumor types. However when combined with radiation, this regimen produces dose-limiting toxicities dependent on the organ irradiated. In a phase I trial of patients with locoregionally advanced pancreas cancer, gemcitabine and radiation produced severe nausea and vomiting in addition to neutropenia and thrombocytopenia [6], whereas in HNSCC this combination produced severe pharyngeal scarring and stenosis [7].

43.2.2.1 Safety Issues in Phase I Trials Combining Radiation with Anticancer Agents

RT and anticancer agents are combined to optimize the therapeutic index in locoregionally advanced HNSCC. Therapeutic index is a ratio that takes into account treatment efficacy and toxicity. Efficacy in the treatment of locoregionally advanced HNSCC is measured by the prevention of locoregional recurrence and of distant metastasis. From the perspective of toxicity, combining RT with anticancer agents not only increases acute toxicity compared to RT alone but may also produce chronic toxicity due to delayed or cumulative adverse effects on normal tissues. Therefore, specific safety issues that warrant careful consideration in these trials include the maintenance of the standard RT dose, the choice of a safe starting dose and of subsequent dose levels for the anticancer agent, and the assessment for delayed or cumulative toxicity for the combined modality therapy.

43.2.2.2 Use of Preclinical Models to Predict Safety

No specific recommendations have been published on preclinical in vitro and in vivo models that reliably predict the safety of combination of RT and anticancer agents in humans. Observations in preclinical models are not always corroborated in clinical trials because the complex tumor microenvironment and diverse molecular landscape [8, 9], in addition, the interaction between the tumor and host immune system, are difficult to replicate in vitro and in vivo. Strategies to improve the translation of preclinical tests include using multiple cell lines or animal models, orthotopic xenograft models, genetically engineered mouse models, and patient-derived xenografts. Preclinical studies may provide some useful safety data to guide dosing, such as therapeutic index of the RT–anticancer agent combination. However, preclinical data must be interpreted with caution due to their limited cross species predictability. Radiation in-field toxicity in the head and neck region that may be exacerbated by the addition of a new anticancer agent is of particular significance in HNSCC. Therefore, it would seem prudent to perform preclinical toxicity evaluations of RT and new drug combinations on mucosal, salivary gland, and neural tissues [10]. The extent to which these preclinical evaluations should be completed prior to the initiation of human phase I trials remains unclear.

While not yet established, immune checkpoint inhibitors may have a future role as radiosensitizers. Predicting human toxicities of immune checkpoint inhibitors from animal models is challenging due to interspecies differences in immune response and immune-mediated adverse events. Furthermore for other types of biopharmaceutical derived products (BDPs) such as monoclonal antibodies or fusion proteins, preclinical testing is often confined to a single species due to lack of target homology between species. These toxicology evaluations are limited in terms of identifying idiosyncratic toxicities. While availability of a pharmacologically relevant species generally allows detection of target-mediated toxicities of BPDs, preclinical evaluations of these agents are limited in terms of identifying idiosyncratic or immune-mediated adverse events that may occur in humans.

43.2.2.3 Choice of the Starting Dose of Anticancer Agent to Combine with RT and Dose of RT in Phase I Trials

Once a new RT–anticancer agent combination is thought to be safe to enter human testing, based on properly conducted preclinical studies, the choice of the starting dose of the anticancer agent and subsequent dose escalation are key elements of the phase I trial design. While there is guidance on the choice of the starting dose of a novel anticancer agent entering phase I evaluation as monotherapy [11], no recommendations have been established to determine the starting dose of an anticancer agent to be combined with RT. Generally, the toxicity profiles of anticancer agents intended to be combined with RT would already have been described as single agents. The therapeutic index of a new combination evaluated in preclinical models should help identify a safe starting dose and schedule, along with subsequent dose escalation for phase I trials. If preclinical data indicated a wide therapeutic index for the combination, it is reasonable to use a higher starting dose along with greater dose increments between dose levels for the anticancer agent, whereas a narrow therapeutic index would stipulate a

more conservative strategy. Nevertheless, the translation of available preclinical data to the clinic may not be straightforward. This was illustrated in a phase I trial that combined RT with weekly gemcitabine in locoregionally advanced HNSCC [12]. Although the starting dose was selected based on preclinical data showing safe and potent radiosensitization at concentrations well below cytotoxic levels, only 1/30 of the initial starting dose of gemcitabine was ultimately deemed to be safe without causing excessive early as well as delayed toxicities.

43.2.2.4 Optimal Length for DLT Assessment

A safe dose for an anticancer agent to be combined with RT is a dose that does not produce excessive acute, delayed, and cumulative toxicity. Normal tissue recovery from RT is the main determinant of delayed or cumulative toxicity. Delayed or cumulative toxicities are of concern in situations where patients are treated with a curative intent, and many survive to suffer from such adverse effects in the long term. Preclinical studies may help identify delayed or cumulative toxicities from RT by observing the animal hosts for a sufficient time to assess for expected or unexpected adverse effects. However, the risk of toxicity exacerbation by the addition of a systemic agent may not be reliably predicted by preclinical models and needs to be carefully considered in the design of phase I trials [10]. In clinical practice, the duration of time allocated for assessment and clearance of dose-limiting toxicities to enable dose escalation or de-escalation decisions differs between phase I trials of systemic agents with or without RT. The Cancer Therapy Evaluation Program (CTEP) and the Radiation Research Program (RRP) of the National Cancer Institute suggested that toxicity assessment for dose-limiting events spans the entire RT period and up to 30 days after completion of RT [13]. Radiation-induced toxicities can be biphasic with early side effects occurring within 2 weeks to 3 months of starting treatment and late side effects occurring months to years after RT completion. It would be impractical from a dose escalation perspective to wait for the late-phase toxicities because it would detrimentally slow patient accrual. Furthermore, it is expected that at the end of a phase I trial of novel agent and RT, all adverse events including those that occurred outside of the assessment window for DLT will be reviewed, to derive at a safe recommended phase II dose for subsequent evaluation.

43.2.2.5 Accounting for Delayed or Cumulative Toxicity in the Dose Escalation

The suggested assessment period for toxicity of 30 days after completion of RT in phase I trials combining RT with anticancer agents results in prolonged delays between cohort openings and closures. To avoid this limitation, several model-based dose escalation designs have been proposed that do not mandate trial suspension while patients are being observed. These designs use time-to-event end points. Cheung and Chappell developed a Bayesian-based method, known as the time-to-event continual reassessment method or TITE–CRM, which incorporates the time to the event (the event being toxicity) for each patient [14]. Simulations suggest that for treatments with late-onset toxicity, the TITE–CRM is more efficient than the traditional 3+3 design or the standard continual reassessment method for determining the maximum tolerated dose and leads to shorter trial durations [15]. Nevertheless, in two clinical trials combining RT with an anticancer agent in pancreatic cancer, this design led to the accrual of more patients to dose levels below the recommended phase II dose than was expected with the traditional 3+3 design [16, 17]. A variation of the TITE–CRM has been proposed in which accrual is temporarily suspended if the risk of toxicity at proposed doses for future patients is unacceptably high [18]. Although these methods may theoretically shorten trial duration in case of delayed or cumulative toxicities, they need to be optimized for successful practical application in phase I clinical trials combining RT with anticancer agents.

The "rolling trial" strategy has been proposed to expedite the investigation of novel agent–RT combinations while allowing sufficient time to observe for potential delayed or cumulative toxicity. This strategy simultaneously activates several novel agent–RT combination trials such that while one trial is undergoing its mandatory waiting period to clear DLT, another trial can actively recruit to fill its next cohort. This approach is particularly attractive if multiple anticancer agents are available to be combined with RT and can be evaluated by the same group of experienced investigators in the disease site of interest. A similar type of design that allows multiple regimens to be tested sequentially is the "ping-pong" method [19]. Patients are accrued on two separate cohorts in an alternating fashion. These cohorts test different novel agent–RT regimens. Once the first cohort has completed accrual, the patients are monitored for DLTs, while the alternative cohort commences accrual. The purpose of this design is to shorten the duration of a phase I study and thus improve its efficiency.

43.2.2.6 Predictive Markers of Late Toxicity

The identification of clinical and laboratory predictive markers for delayed or cumulative toxicity may help prevent or reduce the risk of delayed or cumulative toxicity in patients receiving RT in combination with an anticancer agent. A retrospective analysis of three chemoradiation trials performed by the Radiation Therapy Oncology Group (RTOG) found that older age, advanced T stage, larynx or hypopharynx primary site, and neck dissection were associated with an increased risk of late toxicities defined as chronic grade 3 or 4 pharyngeal/laryngeal toxicity, and/or requirement for a feeding tube >2 years after study registration and/or treatment-related death within 3 years [20].

Besides these clinical predictive markers of chronic toxicity, there are also research efforts in progress aiming to identify laboratory-based predictive biomarkers [21]. A predictor of acute radiation toxicity has been identified in a study of 183 head and neck cancer patients undergoing radiotherapy with or without chemotherapy, where 22 polymorphisms in 17 genes were analyzed [22]. Single nucleotide polymorphisms of the DNA repair gene *NBN* were found to be predictive of radiation-induced oral mucositis. Currently there are no predictive markers of late toxicity in HNSCC reported in the literature. However, in postoperative RT for breast cancer, Li et al. showed that high levels of pretreatment circulating transforming growth factor-β (TGF-β), a potent fibrogenic cytokine, are associated with an increased risk of adverse effects [23]. Similar results were observed in patients receiving thoracic RT [24]. Yuan et al. also showed that specific genotypes of the TGF-β gene were associated with lower risk of radiation pneumonitis in patients with non-small cell lung cancer treated with definitive radio(chemo)therapy [25]. However, none of these clinical or biological factors are being used in clinical practice for therapeutic decisions to select patients or to change treatment regimen, probably because of their low specificity.

43.2.3 Efficacy Considerations

43.2.3.1 Efficacy Issues in Phase I Trials Combining Radiation with Anticancer Agents

Historically, the rationale for combining RT with anticancer agents has mainly been driven by pragmatic approaches rather than based on preclinical scientific evidence [26]. For most drugs given in combination with RT for HNSCC, synergism in preclinical models has usually been observed [27–29]. An example of consistency between preclinical and clinical studies includes EGFR inhibitors that have shown in both preclinical and clinical studies to produce greater activity when combined with accelerated over standard fractionation RT [28, 30]. However, some preclinical data have not been validated in the clinical setting. For example, although some preclinical studies have shown that lower doses of cisplatin tend to produce increased radiosensitization than higher doses [29, 31], the FDA-approved regimen in locoregionally advanced HNSCC involves high-dose cisplatin because of the lack of randomized trial comparing low versus high doses of cisplatin in combination with RT. As patients are often being treated with a curative intent, it is essential to minimize the likelihood of compromising their outcome while evaluating new chemoradiation combinations. The pragmatic approach is certainly not optimal, and preclinical results are now expected before launching a new RT–anticancer agent combination in the clinic.

43.2.3.2 Use of Preclinical Models to Predict Efficacy

In order to maximize safe and efficient investigations of new drugs in combination with RT, the CTEP and the RRP of the National Cancer Institute have provided guidelines regarding required preclinical studies before launching new chemoradiation combinations in the clinic [13]. They recommend the demonstration of in vivo synergy with fractionated RT, with little or no radiosensitization of normal tissues in two different tumor models. Additivity or synergy between RT and anticancer agents may be achieved by the modulation of the classical 5 Rs, which comprise *r*adiosensitivity, DNA damage *r*epair, cellular *r*epopulation and proliferation, *r*eoxygenation of hypoxic tumor cells, and *r*edistribution from more resistant to more sensitive phases of the cell cycle. Three decades ago, Steel and Peckham proposed a method to study drug–RT interactions based on the isoeffect concept reflected via the construction of isobolograms [32]. The central concept in the isobologram method is the determination of the envelope of additivity delineated by boundaries within which all responses are deemed to be purely additive. These boundaries are determined by the addition of responses to each agent applied alone. Preclinical studies to evaluate tumor control or growth delay at biologically relevant doses of the anticancer agent and fractionated RT should be performed under controlled conditions [10] (i.e., using RT alone and drug alone). The testing of multiple dosing schedules of drug and RT administration can help bring the most optimal schedules of combination to clinical trials.

43.2.3.3 Efficacy of Anticancer Agent to Be Combined with RT

It is unclear whether new drugs should display a minimum threshold of clinical efficacy as a single agent in recurrent and/or metastatic HNSCC before being tested in combination with RT for locoregionally advanced disease. Anticancer agents commonly used in combination with RT for locoregionally advanced HNSCC, including cisplatin, carboplatin, 5-FU and cetuximab, have demonstrated single-agent efficacy in HNSCC patients. However, some new drugs are being studied in combination with RT despite lacking single-agent activity. For instance, raltitrexed, an antimetabolite agent, was studied in combination with RT [33], although it was shown to display minimal antitumor activity as single agent in the inoperable setting [34]. Similarly, lapatinib, a dual EGFR and HER-2 inhibitor, was studied in combination with RT and cisplatin [35], even though no clinical activity had been observed as a single agent in recurrent and/or metastatic HNSCC [36]. These two agents have only been tested in single-arm phase II trials in combination with RT. Randomized controlled trials are needed to determine if these agents can improve patient's outcome when combined with RT despite minimal single-agent activity in the recurrent and/or metastatic setting.

Regardless of the properties of the anticancer agent to be combined, it is imperative that the dose of RT is not compromised to allow greater tolerance of the drug. Given that locoregionally advanced HNSCC is a curative disease, the delivery of definitive dosages of RT is critical to ensure therapeutic efficacy is not affected by the systemic agent being added as an adjunct. Hence, compliance with the delivery of both RT and of the anticancer agent needs to be considered in the definition of dose-limiting toxicities of a combination regimen.

43.2.3.4 Accounting for Efficacy in the Dose Escalation

In phase I cancer clinical trials of novel anticancer agents, efficacy is generally not the primary end point. However, in trials where patients are treated with a curative intent, the evaluation of efficacy in addition to safety is relevant. Novel trial designs have therefore emerged attempting to define a safe recommended phase II dose while simultaneously taking into consideration antitumor activity. Bayesian-based methods have been developed that incorporate both toxicity and efficacy in their designs. These methods have been originally designed for anticancer drugs used without RT but can readily be applied to drugs in combination with RT. The EffTox method defines an acceptable dose combination based on trade-offs between the probabilities of treatment efficacy and toxicity [37]. The TriCRM is another Bayesian-based method that considers three categories [38] (no efficacy and no toxicity, efficacy only, and toxicity only). Some investigators have proposed methods for drug combination studies that use both toxicity and efficacy as end points. In the design proposed by Yin et al., patients are randomly assigned among several combinations that are selected by a statistical model to determine the most effective and least toxic combination [39]. The main issue with these methods is that they assume response can be accurately and rapidly assessed with standard response criteria or with surrogate end points in order to maintain a short assessment period. For instance, the use of time-to-event end points such as progression-free survival at 6 months would obviously lead to unacceptably long trial delays and closures. On the other hand, the use of objective response according to RECIST criteria after completion of chemoradiation may not be relevant, as most patients usually respond to treatment. The use of complete response is not a valid marker of overall survival in locoregionally advanced HNSCC, since the absence of radiological complete response does not necessarily implicate the presence of residual disease but may be due to treatment effects or scar tissues [40]. The search for validated markers or end points of efficacy in this patient population is therefore of paramount importance before implementing these methods in clinical practice.

43.2.4 Special Considerations

43.2.4.1 Clinical Development Challenges

In the past, locoregionally advanced HNSCC was managed primarily with RT and/or surgery. Chemotherapy has only been used in the metastatic setting or if recurrences were not amenable to surgery or re-irradiation. Since the publication of the MACH–NC meta-analysis, the benefit of concomitant platinum-based chemoradiation over RT alone has been established in this patient population [41, 42]. Recently, the anti-EGFR monoclonal antibody cetuximab was approved in combination with RT in locoregionally advanced HNSCC [30], based on a large randomized trial that compared this strategy against RT alone, which represented standard of care at the time the trial was designed. With the shift of platinum-based chemoradiation as the current standard of care, three potential strategies can be perceived to further improve therapeutic index and clinical outcome. The first is a chemo-additive strategy by adding another drug to cisplatin. However, this strategy might lead to unacceptable toxicity even when drugs without overlapping toxicities are combined with cisplatin, as illustrated in a phase II trial combining concomitant boost RT with high-dose cisplatin and cetuximab [43]. The second strategy is a chemo-sparing strategy which investigates platinum-free RT combinations with new drugs. The last strategy involves the addition of a neoadjuvant component prior to the delivery of chemoradiation.

43.2.4.2 Challenges for Drug Combinations

In situations where multiple systemic agents are combined with RT, the dose escalation can be challenging and raises specific issues in the design of phase I trials. If full doses of all agents cannot be delivered safely, the selection of appropriate dose combinations and schedules of systemic agents to combine with RT is not always straightforward. Most phase I trials evaluating several anticancer agents in combination with RT escalate the dose of only one agent, keeping fixed the doses of the other(s). However, it may not be always possible to administer all drugs at their recommended phase II doses as single agents. For example, while the weekly recommended phase II doses for cisplatin and docetaxel given as single agents in combination with RT are 40 and 15 mg/m^2, respectively [44], the combination of the two drugs with hyperfractionated RT showed that they could only be administered at the doses of 15 and 10 mg/m^2, respectively [45]. Hence, the decision of which drug to be administered at its full dose can be challenging. Several Bayesian-based designs specific for combination trials have been developed in an attempt to minimize this uncertainty [39, 46–48]. These designs do not require any prior assumption about the best dose combination and aim to guide the dose escalation of the agents based on all toxicities observed. The ultimate goal is

to determine the most active drug combination among those deemed to be safe. These methods may determine several maximum tolerated doses, and the investigator may then choose the one with the best therapeutic index as the recommended phase II dose.

Immune checkpoint inhibitors combined with RT present a challenge due to their overlapping toxicities. In non-small cell lung cancer, immune checkpoint inhibitors have a 10–15 % risk of pseudoprogression in the first 2 months. Pseudoprogression is an observed response to immune checkpoint inhibitors whereby tumor size initially increases due to inflammation, only to subsequently decline in size as the inflammation subsides. Given the location of HNSCC tumors, such response patterns could produce potential airway compromise or esophageal obstruction. This is particularly relevant if these immunotherapies are used in combination or in the neoadjuvant setting with RT, which could exacerbate this immune reaction. Strategies to mitigate these problems will be important to ensure that such combinations are safe and do not cause patients with curable disease to suffer with unacceptable toxicities that may compromise their ability to receive treatment and thus their chance of being cured.

43.2.4.3 Development of Platinum-Free RT Combinations with New Drugs

The investigation of platinum-free combinations with RT in locoregionally advanced HNSCC is appealing since the platins are associated with substantial acute and long-term toxicity. However, since platinum-based regimens remain the standard of care in this curative setting, the aim to develop non-platinum-based regimens to combine with RT can be challenging. Four approaches may be taken to develop new platinum-free chemoradiation combinations without compromising efficacy.

The first approach involves the initial evaluation of new agents in combination with RT in the recurrent setting where therapeutic options remain limited. One drawback might be the difficulty to reliably extrapolate the safety profile of the investigational drug(s) from an advanced to a localized disease setting, as the latter group of patients are generally in better physical condition. This was illustrated in a phase I trial evaluating concomitant chemoradiation with bevacizumab, a monoclonal antibody targeting the vascular endothelial growth factor, in previously irradiated patients with locoregionally recurrent disease [49]. Five of 26 patients treated in the expansion cohort died, two of them from stroke and hemorrhage possibly related to bevacizumab. In contrast, chemoradiation with bevacizumab seemed to be well tolerated when used in untreated patients [50]. Furthermore, the potentially higher rate of adverse events in a heavily pretreated patient population may lead to a lower recommended phase II dose of the new agent than one that could be safely administered in untreated patients. This issue was highlighted in a phase I trial that evaluated concomitant pemetrexed and cetuximab in combination with RT in two different cohorts, depending on whether patients had received previous RT or not [51]. The recommended phase II dose for pemetrexed differed in the two cohorts, suggesting that previously irradiated patients may not tolerate the same dose intensity of concomitant systemic therapy than treatment-naïve patients.

The second approach utilizes the delivery of platinum-free regimens with a curative intent concomitantly with altered fractionation instead of standard fractionation RT. This approach assumes that the incorporation of a more intensified RT schedule would compensate for any potential loss of benefit due to the administration of a platinum-free regimen. Evidence in support of this approach includes the MARCH meta-analysis which reported a survival benefit with the use of altered fractionation RT schemes compared to standard fractionation RT [52]. Furthermore, a subgroup analysis of the trial by Bonner et al. showed that the addition of cetuximab was more effective when combined with altered fractionation than standard fractionation RT [30]. In another trial, the small molecule EGFR tyrosine kinase inhibitor gefitinib was designed to combine with altered fractionation RT using a concomitant boost scheme [53].

The third approach evaluates platinum-free combinations in the context of intolerance or contraindication to platinum compounds, such as in patients over 70 years of age who do not appear to derive benefit from the addition of concomitant platinum to definitive RT [42]. However, the accrual of these selected patient populations to complete large randomized trials may be difficult due to their relative infrequent incidences in clinical practice. As well, the incorporation of new agents may be compromised in patients with renal dysfunction. Lastly, the results that can be generated by these trials would guide management for these subgroups but are not generalizable to patients who can tolerate platinum-based regimens.

Finally, testing platinum-free combinations in patients with a highly favorable prognosis with radiation-only treatment would be another potential approach. Patients with human papillomavirus (HPV)-driven tumors have been shown to have excellent survival with either standard or accelerated fractionation radiotherapy, with 3-year survival rates over 90 % in those with a light-smoking history [54]. Phase I trials evaluating non-platinum RT regimens could preferentially select patients with oropharyngeal HPV-positive disease without compromising clinical outcomes.

43.2.4.4 Phase I Trials with a Neoadjuvant Chemotherapy Component

A survival benefit has been shown by the addition of a taxane to neoadjuvant chemotherapy with cisplatin and 5-FU, compared to cisplatin and 5-FU alone, before delivering defini-

tive RT-based treatment for locoregionally advanced HNSCC [55, 56]. Phase I clinical trials evaluating these so-called sequential strategies, which consist of neoadjuvant chemotherapy plus concurrent chemoradiotherapy, were prevalent. However, several randomized phase III studies have demonstrated that neoadjuvant chemotherapy does not have a survival advantage over standard concurrent chemoradiotherapy [57, 58]. Future phase I trials of neoadjuvant chemotherapy regimens will have to account for the potential of cumulative toxicities, the impact this may have on starting or the intensity of concurrent treatment, the dose escalation designs and the definition of DLT.

43.3 Phase I Trials in Recurrent, Metastatic HNSCC

Traditionally phase I trial methodology for systemic anticancer treatment is similar across all solid tumor types. However over the last decade, molecular-targeted agents and immune checkpoint inhibitors have transformed phase I trial design (Table 43.2). Given the putative pharmacological action of these agents, it may be hypothesized a priori which subpopulation of patients would have the largest clinical benefit and antitumor response. As a result some phase I trials have adopted an enrichment approach to enroll or identify certain patient groups that have either a particular molecular aberration or tumor type, to permit an earlier evaluation of antitumor activity of a novel compound. The technological process of identifying these genomic abnormalities is termed molecular profiling and will be discussed in Sect. 43.3.1. Establishing efficacy in a small group of patients is challenging, and these types of end points must be carefully chosen and interpreted. Finally given these agents may not have a monotonic dose–toxicity curve, selecting a recommended dose using nontoxicity parameters represents an alternative to the historical method of dose determination. While these aspects may not be unique to any one tumor type, this section will discuss how they can impact phase I trials in recurrent and/or metastatic HNSCC.

43.3.1 Enrichment Strategies

Enrichment strategies preferentially enroll patients of certain tumor types into phase I trials. Typically this approach is supported by compelling preclinical data in the prespecified tumor type that demonstrates significant antitumor effect of a drug or therapeutic combination. While not often used in first in human phase I studies, this type of patient enrolment can be utilized for dose escalation phase Ib trials or to explore further the safety and tolerability of an investigational regimen in a dose expansion cohort. The phase Ib trial of the oral phosphatidylinositol 3-kinase inhibitor BYL-719 and the epidermal growth factor receptor inhibitor cetuximab in patients with recurrent metastatic HNSCC (NCT01602315) was based on strong in vivo and in vitro data indicating synergistic antitumor activity of this combination in xenografts and cell lines, respectively [59]. The objective of the study was to determine the recommended dose of BYL-719 and cetuximab and characterize the toxicity profile in patients with recurrent metastatic HNSCC who had progressed on platinum-based first-line chemotherapy. This trial is also notable for the dose escalation design which fixed the dose of cetuximab to its recommended dose and utilized two dose levels for BYL-719, 300 and 400 mg. Furthermore in an effort to account for swallowing difficulties that HNSCC patients often have, BYL-719 administration in both tablet and suspension form was tested in separate cohorts to define pharmacokinetic profiles.

Molecular selection of patients with specific genomic or immune aberrations is another type of enrichment strategy, which is often adopted in "basket" trials. In these studies patients of any tumor histology are enrolled and treated with the same study drug(s), provided they have the requisite molecular aberration such as a somatic mutation or particular level of protein expression. This type of strategy has been enabled by advances in next-generation sequencing which has permitted patients' tumors to be profiled for somatic mutations or gene copy number in a timely and cost-effective manner. The rationale for this approach is that these molecular abnormalities act as oncogenic drivers, and as a consequence alteration of these dysregulated cellular pathways by investigational agents may produce tumor responses. The genomic and immune landscape is distinct for HNSCC as demonstrated by whole exome sequencing studies and immune infiltrate analysis of head and neck tumors [1–3]. In a phase I trial of select tumor types which included metastatic HNSCC (NCT01848834), patients with a tumor that expressed programmed death ligand-1 receptor (PD-L1) were eligible for treatment with the programmed death-1 monoclonal antibody pembrolizumab [60]. This study tested archived tissue or fresh tumor biopsies with immunohistochemistry for PD-L1 expression, and patients were enrolled if the stroma or ≥1 % of tumor cells stained positive. The rate of PD-L1 expression in head and neck cancer samples was 78 % (81/104), which consequently provided little barrier to patient accrual. However it should be noted that other trials use different PD-L1 assays and subsequently have different cutoffs to define PD-L1-positive tumors. Some limitations with molecular selection are the lack of sufficient tissue for testing given most patients may only have a diagnostic biopsy available, the impact of clonal evolution when testing archived tumor samples, the barriers to fresh tumor procurement such as safety and patient's reluctance to undergo a biopsy, and the low-frequency aberrations.

43.3.2 Efficacy Issues

Choosing appropriate end points and evaluation criteria to measure efficacy is important to assess the therapeutic risk benefit of investigational regimens. Response rate is the traditional end point used to evaluate antitumor activity in a phase I/II study. Overall response rates for single-agent and combination chemotherapy or biological treatment ranges from 10 to 43 %, and typically responses are seen within the first two cycles of treatment [61]. Different response patterns have been observed with immune checkpoint inhibitor clinical trials in patients with metastatic melanoma [62, 63], which may challenge clinical benefit assessment with a response rate end point. Antitumor activity with immune checkpoint inhibitors can include regression of all baseline lesions, steady decline in overall tumor volume, tumor response after initial volume increase, and reduction in tumor volume despite appearance of new lesions. It is not known if such patterns will be observed in HNSCC patients; however, they should at least be accounted for when designing immune checkpoint inhibitor studies in this population. Immune-related response criteria have been developed to properly characterize these response patterns to immunotherapy, and while these cannot replace standard RECIST version 1.1 criteria, they should be incorporated as part of tumor assessment [64]. In addition, time-to-event end points such as 6-month progression-free survival may provide supporting data to assist in determining clinical benefit, which may have utility in the treatment-naïve or second-line setting. The applicability of such parameters in those who have been heavily pretreated with multiple lines of systemic therapy is not known, although it is unlikely to be useful.

43.3.3 Optimal Biological Dosing

Optimal biological dose (OBD) of a drug is based on predefined nontoxicity end points that establish plasma drug concentration, target-drug saturation, and or maximal alteration of a target-mediated pathway. Pharmacokinetic (PK), pharmacodynamic (PD), or functional imaging parameters that measure these effects are typically used to derive the OBD. Testing PD and functional imaging end points in HNSCC patients are relevant given differential expression of drug targets between tumor types and between tumor and normal tissue. PD markers are usually measured in tumor tissue and are often included as secondary or exploratory objectives in phase I clinical trials. However, to date, no agent approved for use in solid tumors has had its recommended dose based solely on a PD end point. There are several challenges facing PD markers: obtaining sufficient fresh tumor tissue for testing, availability of a robust companion diagnostic, determining the predefined threshold of target inhibition, and having an appropriate patient sample size. In a trial of the pan-phosphoinositide 3-kinase inhibitor BKM-120 (buparlisib) with cetuximab in patients with recurrent metastatic HNSCC (NCT01816984), a PD end point is being measured to define OBD. The co-primary end points of this study are the level of phosphorylated epidermal growth factor receptor (EGFR) in snap frozen tumor tissue samples as quantified by the PamGene kinase array platform (PamGene International B.V., Hertogenbosch Netherlands) and a traditional maximum tolerated dose as defined by the incidence of DLTs. The correlation between these end points may identify the pharmacologically active dose of the study combination.

43.3.4 Dose Escalation Designs for Combination Regimens

Single agent treatments in the recurrent metastatic setting are unlikely to produce significant prolonged benefit. This approach typically fails because of the development of drug resistance or minimal activity of the drug. Combination regimens therefore aim to improve patient outcomes by inducing a greater antitumor response and circumventing acquired drug resistance. Prior to testing of the combined treatment, safety data of each individual agent would be known. However PK and PD interactions between multiple agents may have an impact on the dose–toxicity relationship, and thus phase I testing of novel multi-agent regimens in tumor-specific populations is necessary.

No one specific dose escalation method can be applied to all combinations, but pharmacology information from preclinical and clinical studies can guide the design of such trials [64]. There are various modifications that have been proposed to both rule- and model-based designs to account for multi-agent treatments [65]. In general rule-based methods are most commonly used, which is in spite of simulation studies that have reported that model-based designs have more favorable operating characteristics where more patients are treated at levels closer to the eventual recommended dose [66, 67]. Barriers to implementing Bayesian-adaptive designs include the required statistical expertise, the quality of preclinical information, and the investigator familiarity with model-based methods. Beyond dose escalation, another challenge facing multi-agent regimens is the attribution of toxicity. The use of each patient as his or her own control involves patients being initially treated with one drug and then in the subsequent cycle being treated with both agents. This would help distinguish which agent in the combination is the cause of an adverse event.

43.4 Conclusions

The addition of novel anticancer agents to RT-based treatment in locoregionally advanced HNSCC aims to optimize the therapeutic index. Additionally in patients with recurrent metastatic HNSCC, phase I trials may provide an early signal that a particular agent or combination has promising antitumor activity. In both settings, innovative trial designs may facilitate the development of more effective therapies for patients with HNSCC. However in order to achieve this, multiple issues need to be addressed such as patient selection, biomarker validation, acute and chronic toxicity monitoring, efficacy assessment, and determination of the most active dose. Advances in preclinical testing may contribute important information for the evaluation of new combinations or agents. The unique aspects of these phase I trials provide a strong impetus for the development and implementation of novel phase I trials designs in HNSCC.

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Treatment of the Elderly Head and Neck Cancer Patient

44

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Abstract

Elderly patients represent from 40 to 60 % of head and neck squamous cell carcinoma (HNSCC). These patients often receive inadequate treatment, either exceeding their tolerance capability or exposing them to a lesser chance of cure because of undertreatment. Customizing treatment to the individual patient is the key for avoiding such pitfalls. This paper analyzes the literature on optimal management of elderly patients with HNSCC, from the diagnostic procedures with a comprehensive geriatric assessment (CGA) of comorbidities to the specific recommendations for surgery, radiotherapy, and chemotherapy.

Keywords

Head and neck • Cancer • Elderly • Geriatric • Diagnostic • Treatment • Surgery • Radiotherapy • Chemotherapy

44.1 Introduction

The concept of elderly patients is highly questionable and definitely not closely linked to civil age. The median age for diagnosis of invasive head and neck cancers is of about 60 years. More than 40 and up to 60 % of head and neck cancers occur in patients older than 65 years [1]. Hence, the management of the so-called "elderly" patients with head and neck cancer represents a very common situation in our daily practice. This incidence of elderly people with head and neck cancer squamous cell carcinoma (HNSCC) will further grow in the next decades due to several independent parameters: the constant increase of life expectancy in most industrialized countries, the limited efficacy of tobacco and alcohol prevention campaigns and growing female incidence, and finally the medical awareness to provide a better quality of care to the geriatric population. Unfortunately, as for other cancer types, until recently most research trials have been using an upper age limit excluding patients over 65 or 70 years of age, thus leaving us with no evidence-based guidelines and a few often ill-defined recommendations for older patient age groups. This lack of evidence stresses the need for prospective studies with reliable assessment of patient's comorbidities aiming at well-defined treatment schedules including individually customized variations according to patient's condition.

Several conflicting facts need some clarification: it seems logical to accept the statement that the number and severity of comorbidities increase with age and interfere with the choice of treatment and disease outcome. Thus every year, more reports claim that head and neck cancer patients should be treated regardless of age when their general condition is satisfactory. Unfortunately there is an epidemiologic evidence that most elderly patients do not benefit of the same chance of access to proper oncologic management as younger patients.

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44.2 The Specificity of the Elderly Head and Neck Cancer Patient

By definition, the elderly patient with head and neck squamous cell carcinoma (HNSCC) has been exposed for a longer time to the main epidemiological features of such diseases: heavy tobacco and/or alcohol addictions with resulting comorbidities, chronic obstructive pulmonary disease, infection, various degrees or cardiorespiratory insufficiencies, liver steatosis and cirrhosis, poor oral hygiene and dental condition, fungal infections, malnutrition, weight loss, frailty, low performance status, Wernicke's encephalopathy, and associated neurological disorders. However the degree of severity and combinations of comorbidities widely differ from a patient to another. They should not constitute a contraindication to curative treatment unless they would expose the patient to a shorter life expectancy than the spontaneous evolution of the malignant tumor. Moreover, a number of these comorbidities are either ignored or insufficiently controlled at the time of the diagnosis of cancer. The identification, systematic evaluation, and, whenever possible, correction of such conditions should be done before starting the treatment of the head and neck malignancies to give the patient the best chance for tolerance and ultimate benefit.

Sometimes, however, the elderly head and neck cancer patient may just present with a perfect general condition and be biologically younger than most people in the same age group. Such patients should also be clearly identified and offered the same management as for younger patients.

44.3 Upper Age and Outcome in Curatively Treated Head and Neck Cancer Patients

The more solid data come from prospective research trials including patients older than 65 years with reliable data on acute and late morbidity as well as disease outcome, compared per age group. Under those conditions, the eligible patient population presents with a similar range of patient's health conditions and disease stages and management. In 1996, Pignon et al. [2] reported 1589 patients with head and neck cancers enrolled in EORTC trials with follow-up on radiotherapy toxicity and survival. Patients over 65 years represented more than 20 % of the sample. Survival and toxicity were examined in different age ranging from 50 to 75 years and over. There was no significant difference in survival between age groups. A trend test was performed to assess correlation between age and acute toxicity. There was no significant difference in acute objective mucosal reactions ($p=0.1$) and in weight loss >10 % ($p=0.4$). In contrast, older patients had more severe (grade 3 and 4) functional acute toxicity ($p<0.001$) than younger patients. The probability of late toxicity occurrence in relation to time was evaluated with the Kaplan–Meier method and the log-rank test. Eighteen percent of patients were free of late effects at 5 years, the log-rank test showing no significant difference between ages ($p=0.9$). In conclusion, chronological age was considered irrelevant for therapeutic decisions. As a consequence the recommendation was made to delete upper age limit from eligibility criteria in every EORTC on-going and new protocol of radiotherapy in head and neck cancer.

In 2004 a report on the compliance to this recommendation in subsequent protocols was made by Horiot [3] during the 2004 SIOG (International Society of Geriatric Oncology) meeting in San Francisco and later published [4]. Six EORTC head and neck trials (including 574 patients) were activated after 1996. Two had an upper limit at ≤75 years and 4 no upper age limit (EORTC protocols 22954, 24954, 22962, 24001). Only 15 % of these 574 patients were aged 65 or more: Unfortunately only one patient was older than 75. Despite a satisfactory compliance of protocol writers, the actual recruitment of older patients was disappointing. The reasons for that low recruitment are probably multifactorial: resistance to change, insufficient information of doctors and patients, and need for specific protocol design for adequate selection of elderly patients. Another issue probably relates to the increasing number of treatment schedules involving concomitant radiochemotherapy regimens, obviously more toxic than radiotherapy alone.

Literature reports on the outcome of treatment for head and neck cancer patients aged ≥80 years were very rare up until a few years ago. Several reports on this upper age group were recently published. Similar prognosis regardless of age after radiotherapy of head and neck cancers, including small subsets of patients over 80 years of age have been reported by Metges [5], Schofield [6], and Zachariah [7]. Italiano [8] reports a series of 316 patients treated by surgery and/or radiotherapy and concludes that the outcome is the same than in younger patients. However this is a historical retrospective analysis of a regional database with selection biases and wide treatment variations. Ortholan [9] reports 260 patients over 80 years of age with oropharyngeal cancers. Two hundred patients received a locoregional treatment with a curative intent (surgery and/or radiotherapy), 29 with a palliative intent, and 31 did not receive an LR treatment. The median disease-specific survival was 29 months. In multivariate analysis, the independent prognostic factors for DSS were stage (HR = 0.42 [0.24–0.72]), age (HR = 0.43 [0.24–0.75]), and performance status (HR = 0.50 [0.27–0.95]). The median overall survival (OS) was 14 months. In multivariate analysis, the independent prognostic factors for OS were age (HR = 0.52 [0.35–0.79]), stage (HR = 0.56 [0.38–0.84]), tumor differentiation (HR = 0.60 [0.33–0.93]), and performance status (HR = 0.6 [0.37–0.97]). In patients treated with a curative intent, treatment adapted to age was not associated with a decreased overall survival or

disease-specific survival as compared with the standard treatment. However, prophylactic lymph node treatment in stages I–II tumors decreased the rate of nodal recurrence from 38 to 6 % ($p=0.01$).

The impact of age at diagnosis on prognosis and treatment in laryngeal cancer was recently reviewed in 945 patients with laryngeal cancer treated from 1978 to 2004 in the Uppsala–Orebro region in Sweden [10]: There were no significant differences in the clinical features between age groups. Overall survival (OS) and disease-specific survival (DSS) were worse among the oldest, although a significant proportion was cured. Relapse risk was lower among the oldest (12 %) compared with the youngest (23 %). However, the risk of never becoming tumor-free was 25 % among the oldest versus 7 % in the youngest. The authors conclude that although elderly patients with laryngeal carcinoma cope well with treatment, undertreatment may determine outcome more than age.

Although specific prospective trials are still badly missing, recent literature reports all stress that older age groups are of increasing relevance in HNSCC and need reliable and comprehensive pretreatment evaluations. This patient population also requires the activation of prospective trials on adapted strategies and dose reductions whenever justified by risk factors induced by comorbidities.

44.4 Multidisciplinary Diagnosis and Pretreatment Assessment in Geriatric Patients

44.4.1 Definitions, Geriatric Scales, and Geriatric Evaluation Focused on Head and Neck Cancer Patients. Selection of Patients for Radical Treatment

The inclusion of a specific geriatric assessment in the multidisciplinary work-up of the cancer patient is a prerequisite to give the best chance to the well-fit patient to receive the same treatment as a younger patient and to plan the appropriate changes in treatment strategies for patients with comorbidities. The comprehensive geriatric assessment (CGA) [11, 12] is a multidisciplinary evaluation of functional, cognitive, and psychological status, comorbidities, nutritional status and medications, and family, relatives, and social support. Functional status explores patient's ability to fulfill usual daily activities. Objective performance measurements include the "timed up and go" test and the 6-min walk and grip test. Optimally, the geriatrician coordinates these evaluations and collects the data needed to complete the scoring scale. CGA is now a well-documented tool to predict morbidity and mortality in elderly patients with cancer [13–15]. Repeated measurements during treatment and follow-up can reliably quantify changes of patient's condition with time.

Practical algorithms have been published to assist clinicians in selecting patients for standard treatment versus modified schemes [15]. The severity of a single comorbidity is of more relevance than the number of comorbidities. The weight of such combinations is taken into account in the Adult Comorbidity Evaluation 27 (ACE-27) [16].

Nutritional evaluation, ultrasound screening of carotid arteries, identification of tobacco and alcohol addictions and assistance for stopping it, detection and treatment of depression, and assessment of renal function measured by isotopic clearance methods are part of the pretreatment assessment of elderly head and neck cancer patients. Fatigue is a very common symptom, often of multifactorial origin. Its causes must be understood and whenever possible corrected before treatment starts since the deterioration of general condition and exhaustion of patient resources are the major reasons for non compliance and/or early treatment interruption in curative management of elderly cancer patients.

There are however practical obstacles to organize a full-scale multidisciplinary CGA: Sometimes by lack of expertise or availability in some of the involved disciplines (including the geriatrician!) but mostly by the absence of coordination to ensure a smooth and timely planning of the consultations and specific work-up of each consultant and, later, to centralize the various findings, taking them into account to customize the treatment strategy. Obviously, multidisciplinary hospitals and/or cancer institutes usually offer the best conditions to setup this rather heavy multidisciplinary work-up and management of the elderly cancer patient.

Recently, several attempts were made to evaluate the usefulness of CGA to identify yet unrecognized health problems and demonstrate its effectiveness in influencing treatment decisions and/or to modify treatment prescriptions [17–19]. The review of these reports [17] concludes that a large number of abnormalities and comorbidities are detected by CGA that most often allowed to predict mortality and chemotoxicity. These findings influenced 21–49 % of treatment decisions. Moreover, a single report [18] analyzed a sample of head and neck cancers only (100 patients), finding significant scores of malnutrition in 47 %, cognitive impairment (22 %), depression (20 %), comorbidities (69 %), and vulnerability (75 %). Overall, only three randomized published studies evaluated the effectiveness of CGA-like interventions, thus stressing the need for further research to improve the effectiveness of the CGA in providing a better treatment and outcome to cancer patients.

The EORTC has recently decided that a screening tool called G-8 should be used to evaluate which patients need a CGA and which ones might do well with the standard treatment. The tool is easy to administer, as it takes only a few minutes to fill in [20] (see Fig. 44.1).

Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	0 = severe decrease 1 = moderate decrease 3 = no decrease
Weight loss during the last 3 months?	0 = > 3kg; 1 = does not know 2 = between 1 and 3 kg 3 = none
Mobility?	0 = bed or chair bound; 1 = able to get out of bed or chair but does not go out; 2 = goes out
Neuropsychological problems?	0 = severe dementia /depression 1 = mild dementia 2 = no psychological problems
BMI (weight in kg/height in m^2)	0 = BMI <19; 1 = BMI 19 to <21 2 = BMI 21 to <23; 3 = BMI ≥ 23
Takes more than 3 prescription drugs per day?	0 = yes; 1 = no
In comparison with other people of the same age, how does the patient consider his health status?	0 = not as good; 0.5 = does not know; 1 = as good; 2 = better
Age	0 = >85 yr; 1 = 80-85 yr; 2 = <80 yr
Total score	**0-17**

Fig. 44.1 G-8 geriatric screening tool (reprinted from Bellera CA, Rainfray M, Mathoulin-Pélissier S, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Oncol. 2012;23(8):2166–72. With permission from Oxford University Press)

44.4.2 Preparation of the Patient to Treatment

Denutrition or malnutrition is present in at least 20 % of cancer patients. This figure is probably underestimated in geriatric head and neck cancer patients due to a reduced oral intake because of pain, difficulty in swallowing, and inappetence. Moreover, elderly people often do not complain of loss of appetite. Fluid intake is frequently suboptimal resulting in various degrees of dehydration and electrolyte imbalance often associated with impaired renal function. The nutritional status of all and elderly patients should be systematically evaluated [21] at the time of the initial work-up since rapid deterioration may occur early in the course of radiotherapy and is a common observation when delivering concomitant radiochemotherapy. Missing this point would expose the patient to a high risk of poor treatment tolerance, treatment interruption, and/or dose reduction with a loss of chance of cure. Minor denutrition conditions should be dealt with dietetic counseling, oral nutritional supplements, and regular follow-up of oral intake during and after treatment. Artificial nutrition should be planned before treatment when oral intake is of less than 60 % of needs and/or when severe mucosal and general side effects of treatment are expected. Percutaneous endoscopic gastrostomy (PEG) should be preferred to nasogastric feeding tubes which may become a cause of discomfort upon the appearance of severe acute mucosal reactions. With proper prospective management, the need for parenteral nutrition remains rare, except for situations of severe malnutrition with poor digestive function, preexisting to cancer diagnosis.

A systematic evaluation of the denture and periodontal tissues is mandatory in every head and neck patient. It is even more important in the elderly patient in whom the probability of deterioration of dental condition is usually higher than in the younger patients. The clinical and radiological dental work-up should take place as early as possible to allow healing of dental extractions when needed without increasing the delay between diagnosis and treatment.

When radiation therapy is planned, teeth in good condition will be preserved. Daily fluoride topical applications and oral hygiene will prevent post-radiation dental caries [22]. Customized dental gutters will be manufactured to enable lifetime daily topical fluoride gel applications. Oral hygiene recommendations and compliance to fluoride applications should be initiated and checked during radiotherapy. The use of very high fluoride toothpaste contents (about 1300 ppm) is an alternative method when customized gutters are poorly tolerated, e.g., when acute mucosal reactions occur. Keeping good dental status and hygiene is an essential component of maintaining a good nutritional intake. Edentulous patients also need to be evaluated to detect the presence of hidden risks (sharp extractions edges, residual roots, impacted wisdom teeth, etc.) and to check the condition of removable dental prosthesis.

Elderly patients are often left alone to deal with the constraints of disease diagnostic and therapeutic procedures. This may sometimes result in inappropriate patient understanding and adhesion to therapeutic recommendations, thus leading to refusal or poor compliance to treatment. Adequate management of the elderly cancer patient, including specific advice and support on head and neck cancer treatment, must be organized in the frame of the geriatric oncology team, with, whenever needed, the availability of psychosocial workers and psycho-oncologists. This includes the information of patients and relatives as well as the assistance for proper organization of patient venues (transportation, timing) for the duration of ambulatory treatments.

44.5 Management of the Elderly Cancer Patient

44.5.1 Curative Aim

44.5.1.1 Surgical Management of the Elderly Patient

Predictive factors for complications in surgically treated elderly patients with HNSCC have been analyzed by Sanabria [23] in 242 patients over 70 years of age. Comorbidities were present in 87.6 % of patients, and 56.6 % presented with complications (44.6 % local and 28.5 % systemic). Male sex, bilateral neck dissection, the presence of two or more comorbidities, reconstruction procedures, and clinical stage IV were associated with a high risk of postoperative complications. The authors propose a predictive index based upon preoperative variables which, in their series, show an 84 % sensitivity and 41 % specificity.

As expected, the main limitation to surgical indications in the elderly cancer patients is the number and severities of comorbidities, interfering with the risks of general anesthesia and perioperative period. In most cases, mild cardiovascular comorbidities can be corrected and should not interfere with the treatment choice. Conservative surgical techniques should be preferred whenever possible. Reconstructive surgery with flaps is seldom considered in older patients since higher complication rates are reported in patients of more than 70 years of age [24]. Moreover, older patients are known to be less compliant to feeding and phonatory rehabilitation procedures than younger patients [25]. Radiotherapy alone or radiochemotherapy when feasible should be preferred to mutilating surgery in moderately advanced and advanced laryngeal and hypopharyngeal carcinomas. Conservative surgical procedures either by cervicotomy or by transoral resections [26] can be considered in the management of limited carcinomas of the oral cavity, oropharynx, and larynx especially when the need for postoperative radiotherapy is unlikely. Early vocal cord cancers can be either treated surgically (usually by microsurgical carbon dioxide laser techniques) or by radiotherapy alone although the quality of voice seems superior with radiotherapy. Difficult access to radiotherapy facilities and shorter treatment with surgery may be good arguments in favor of surgery. Functional neck nodes surgery, whenever indicated, can be usually performed regardless of age except for major medical contraindications.

Recommendations on the surgical management of elderly patients with cancer have been issued by experts of the International Society of Geriatric Oncology [27], and the relationship of comorbidities and age and surgery have been reviewed recently [28].

In most cases, however, surgery will be combined to radiation therapy, mostly postoperatively. The quality of surgical techniques and pathology report are essential to optimal radiotherapy planning and to reduce the risk of late complications from combined treatment.

With modern radio-surgical techniques, the risk of carotid artery rupture has become very low. However the risk of carotid stenosis and cerebrovascular stroke is not negligible after neck dissection and radiotherapy, reported sometimes as high as 30–40 % [29]. An effective prevention of such risk is made by identifying and treating patients with risk factors (tobacco addiction, hypertension, dyslipidemia, ultrasound screening of carotid arteries before and after treatment). Modern radiotherapy techniques have almost eliminated the dose hot spots that could result, for instance, from overlapping the upper and lower neck nodal target volumes.

44.5.1.2 Radiotherapy

The consistency of geriatric assessment recommendations for patients receiving radiotherapy was discussed by Falandry [30]. However although general statements apply to HNSCC patients, no comments are made regarding the specificity of head and neck radiotherapy. By definition radiotherapy to HNSCC is a locoregional treatment. Small tumors from almost any head and neck site, adequately irradiated with well-controlled target volumes to the primary site and first nodal level, produce moderate mucosal side effects and provide high cure rates. Hence age should not interfere at all with the indication of curative radiotherapy. Larger primary tumors, usually associated with various degrees of nodal spread, will need a more aggressive treatment on larger tumor and nodal target volumes with more toxic mucosal acute side effects that will interfere with patient nutrition and treatment tolerance. The difficulties met with radiotherapy to elderly patients will be increased in these moderately advanced and advanced HNSCC.

In head and neck cancers, most local regional failures occur within the first 2 years. Thus, reducing total dose and/or target volume is not a valid option when delivering curative radiotherapy to elderly patients since it would invariably result in higher local regional failures as shown by Ortholan [9] reporting that the omission of node treatment for T1–T2 N0 oral cavity cancer in patients aged >80 years induces a high risk of node recurrence.

Techniques of external megavoltage radiotherapy have considerably progressed over the past decade allowing high accuracy to conform target volumes to effectively irradiated volumes and enable a better sparing of normal tissues. Intensity-modulated radiation therapy (IMRT) is now the reference radiotherapy technique to treat head and neck cancers. Brachytherapy also benefited from imaging progress but remains less frequently used probably because it requires a more specific expertise and is performed under general anesthesia.

As a result, acute tolerance has markedly improved, while the incidence and severity of late normal tissue damage decreased. The benefit from innovative radiotherapy techniques is essential to offer head and neck cancer geriatric patients the best chance of a good tolerance to curative radiotherapy.

Acute tolerance is improved by minimizing skin and mucosal reactions. The main benefit seems however to arise from the reduction of the incidence and severity of late effects, mainly fibrosis (by multiplication of portals) and xerostomia by sparing whenever possible the contralateral salivary glands [31]. Nowadays, IMRT is feasible with all modern linear accelerators and should be available in every radiotherapy department. Unfortunately, not all patients can benefit from it for reasons of cost, availability and experience. The geriatric population may be excluded from their use, either by the absence of specific protocol recommendations or worst, as being considered as a low priority. Most of the literature on radiotherapy toxicity in elderly patients is gathered from reports of series treated with "standard radiotherapy" which still provide a biased message to contraindicate radiotherapy or lower total doses, thus reducing the chance of cure of these patients.

The next step in high-precision radiotherapy, stereotactic body radiotherapy (SBRT), can also become an innovative approach to treat elderly patients with medically inoperable cancers. In well-selected cases (localized tumors with none or limited nodal spread), SBRT allows the delivery of a tumoricidal dose in a few fractions, e.g., 40–45 Gy in 5–6 fractions on alternative days over 1–2 weeks. Early results show encouraging local control and survival while maintaining a good quality of life [32, 33].

Socioeconomic and psychological issues may interfere with the medical decision as well as the patient's acceptance or refusal to radiotherapy. The distance between patient's home and treatment site may not be consistent with a protracted ambulatory treatment. Access to local hosting facilities for elderly people for the duration of their treatment is rare and sometimes unaffordable. Hospital admission may be either impossible because of priorities given to other patients or refused by the patient. Daily transportation for long distances may generate psychological lassitude and physical fatigue that may jeopardize treatment delivery and outcome by early stopping or increased overall treatment time. In some cases, a dose/fractionation compromise is proposed to patients, by reducing the number of fractions and increasing the dose per fraction. This concept called hypofractionation, when equivalent biological tumor doses are delivered, always results in increased late normal tissue damage, sequelae, and complications. Head and neck hypofractionated radiotherapy with a lower biological tumor dose exposes the patient to a poorer outcome and should be reserved for palliation only.

Prevention of nutritional deterioration is essential when irradiating large volumes of oral cavity and oropharyngeal and hypopharyngeal mucosa. As said earlier, a percutaneous endoscopic gastrostomy should be performed before starting treatment and be progressively used to compensate reduced oral intake due to the progression of mucosal reactions. Oral hygiene recommendations, preventive treatment of bacterial and fungal infections, should almost systematically be activated.

44.5.1.3 Radiotherapy and Chemotherapy

Up until the advent of platinum compounds, there was no or little interest in combining radiotherapy and chemotherapy in head and neck cancers. The additional toxicity of chemotherapy was then a major argument to contraindicate its use in frail and/or elderly patients. The results of randomized trials and meta-analyses [34] then demonstrated that cisplatinum-based schemes and radiotherapy could significantly improve the outcome compared to radiotherapy alone, the main benefit being observed after concomitant radiochemotherapy at the cost of an increased (mostly acute) toxicity. Postoperative concomitant radiochemotherapy has become the standard management of moderately advanced and advanced head and neck cancers carrying a significant locoregional failure risk [35]. Of course these randomized trials excluded almost all frail and elderly patients. The revival of the interest of induction chemotherapy was raised by trials on laryngeal preservations [36, 37] and more recently by the locoregional and survival benefit of neoadjuvant taxanes [38]. Moreover, a noncytotoxic molecular-targeted therapy (anti-EGFR receptor cetuximab) combined with radiotherapy also produced a significant locoregional and survival benefit in moderately advanced head and neck cancers. These progresses, although not applicable in all patients, have urged to reconsider the indications of chemotherapy in the elderly patient.

The main severe toxicities of cisplatinum-based chemotherapy consist of renal failure with potassium and magnesium losses, nausea and vomiting, peripheral neuropathies, and hearing impairment. Adequate hydration is not always feasible in older patients. Dose reductions based only on the patient's age should not be done when the treatment is given with a curative aim. Attention should be given about the results provided by the Cockroft–Gault method to calculate creatinine clearance which often underestimates renal function in elderly [39]. Combined platinum-based chemoradiotherapy regimens, used in healthy non-elderly patients substantially increase the incidence of severe acute [40, 41] and late adverse events [42–44]. Hence they should be prescribed with care in fit elderly patients only. Cisplatin is the preferred platinum agent and is associated with higher tumor response rates than carboplatin [45], which, because of a better toxicity profile, is often reserved for patients unable to tolerate cisplatin.

The usefulness of the addition of 5-FU to platinum compounds is still debated in younger patients because its advantages are not obvious while inconveniences (cardiotoxicity, increased mucosal toxicity) are well documented. Hence although it can be safely delivered to elderly patients in good general condition [45], it is preferable in most cases to prescribe a single platinum compound.

Taxane (paclitaxel and docetaxel) metabolism can be affected in patients with impaired liver function, a significant decrease in total paclitaxel clearance being observed with increasing age [46]. This may contraindicate the use of taxanes in patients with severe alcoholic-induced liver dysfunction. The sequential combinations of cisplatin and taxanes

increase the incidence and severity of peripheral neuropathies. Combinations of cisplatin, fluorouracil, and taxanes, now widely used for induction chemotherapy, can produce a large range of acute severe toxicities: Grade 4 neutropenia and febrile agranulocytosis, sepsis, and severe mucositis. Thus the combination of these three therapies must be avoided or prescribed only to elderly patients without any comorbidity. Careful patient selection of elderly patients allows induction chemotherapy with cisplatin and docetaxel as shown in 44 patients over 65 years of age with stage III and IV head and neck cancers using a 3-week course [47]: The overall response rate was 88 %, with grade 3–4 neutropenia in 75 %, and febrile neutropenia in 4 %.

44.5.1.4 Radiotherapy and Molecular-Targeted Therapies

About 90 % head and neck cancer cells overexpress the epidermal growth factor receptor (EGFR) which correlates to the malignant phenotype leading to reduced apoptosis, high proliferation rate, angiogenesis, and metastatic invasiveness. Agents blocking this malignant phenotype have a lower toxicity than most cytotoxic drugs and seem an attractive alternative combination with radiotherapy in older and/or frail patients. The first randomized trial comparing radiotherapy and cetuximab to radiotherapy alone [48] concluded to a 30 % reduction in the risk of disease progression and 11 % increase in the 3-year PFS rate survival in favor of the experimental arm. There was no upper age limit in the eligibility criteria. Acute mucosal reactions were similar in both arms. The main acute cetuximab toxicity consists of acneiform rash (17 %) occurring predominantly in the facial and cervical areas. Of interest this rapidly reversible side effect seems associated with a better chance for improved survival, grade 2–4 acne/rash being associated with a 51 % reduction in the risk of death compared to that of patients with a 0–1 grade of acne/rash [49]. This rather acceptable toxicity profile seems attractive for including cetuximab in the radiotherapy management of elderly head and neck cancer patients. In the original randomized trial, the median age was 57, suggesting a very low percentage of elderly patients entered in this study. Although not formally established on a nonselected elderly population, the addition of cetuximab to curative radiotherapy for elderly patients seems safe [50].

44.5.1.5 Radiotherapy, Chemotherapy, and Molecular-Targeted Therapies

The EXTREME phase III trial [51] undertaken in recurrent and/or metastatic head and neck cancers, adding cetuximab to standard first-line platinum-based chemotherapy produced statistically and clinically significant benefits, in terms of prolonged survival and improved tumor response, compared with the traditional approach of combination chemotherapy. Of interest, 77 pts (10 % of the whole sample) were over 65 years of age. The next logical step in healthy patients was to investigate the role of cetuximab in combination with definitive chemoradiotherapy in locally advanced disease. The phase III RTOG 0522 trial, comparing a chemoradiotherapy regimen of accelerated concurrent radiotherapy plus cisplatin with the same chemoradiotherapy regimen plus cetuximab, failed to show a benefit of cetuximab with this approach. However with other radiation schemes, it remains a valid approach [52].

An extensive list of references on the multidisciplinary approach of head and neck cancer in the elderly can be found in the recent review of Mountzios [53].

Recommendations

- Elderly head and neck cancer patients should benefit from the same diagnostic investigations and multidisciplinary decision process as younger patients.
- G-8 screened elderly patients with a poor score should be offered a CGA (comprehensive geriatric assessment) to identify, quantify, and whenever possible treat comorbidities.
- Elderly patients should be exposed to more intensive management than they are currently receiving. This management should be closer to that currently received by younger patients.
- Patients should receive the most appropriate treatment thought to be safe and effective according to their biological age and comorbidities.
- The aim should be to maximize overall survival while minimizing toxicity to achieve the greatest patient benefit.
- Socioeconomic and psychological issues should be dealt with to facilitate access, acceptance, and compliance to treatment.
- The maintenance of a proper dietary input and balance should be planned and controlled before, during, and after treatment using preferably percutaneous endoscopic gastrostomy whenever an insufficient oral intake is foreseen.
- Lighter radiotherapy (and chemotherapy) schedules should be preferred to supportive care only, unless survival expectancy is very short.
- The inclusion of fit elderly patients in research protocols should be encouraged regardless of age.
- Specific protocols should be designed for elderly patients with comorbidities in order to collect evidence-based data on optimal management of these patients
- G-8 screening and CGA should be part of the trial design and clinical practice to document how to tailor treatment to a patient population of growing incidence.

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Normal Tissue Complications and Protection in Head and Neck Cancer Patients

45

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Abstract

It has been long recognized that radiotherapy, surgery, and chemotherapy for head and neck (H&N) cancer cause a wide range of acute and late morbidities. These effects impact general and H&N-specific symptoms, quality of life, and critical functions. The increasing use of altered fractionation and chemoradiation has led to a substantial increase in both acute and late toxicity. Countering this is the growing use of intensity-modulated radiation which has lowered dry mouth-related issues and targeted agents which are associated with less complex/lower burden toxicity profiles. In this chapter, we discuss issues in toxicity measures and reporting methods. We also discuss the management of mucositis, swallowing disorders, and osteonecrosis.

Keywords

Toxicity • Morbidity • Complications • Side effects • Adverse effects • Adverse events • Quality of life • CTCAE

45.1 Introduction

It has been long recognized that radiotherapy, surgery, and chemotherapy cause a wide range of acute and late morbidities. These effects impact general and H&N-specific quality of life (QOL) measures and functional outcomes. The increasing use of altered fractionation and chemoradiation has led to a substantial increase in both acute and late toxicity. Due to variations in data collection and reporting methods, it is difficult to quantify the magnitude of these changes, which in turn constrains efforts to reduce morbidity or interpret therapeutic gain. In this chapter, we discuss issues in toxicity measures, reporting methods, and interventions to reduce toxicity. There is no single gold standard for defining or measuring the adverse effects of cancer treatment. The measures selected must be based on the specific focus of the trial or study objectives [1].

45.1.1 Toxicity, Adverse Events, QOL, and Function

Although often used interchangeably in everyday oncology vernacular, the terms toxicity, morbidity, QOL, and adverse events have specific definitions that arise from their focus or purpose. There is overlap and potentially complex interactions between these terms and concepts. For example, a mild degree of physiologic change or impairment may be noted on expert examination or specific testing (barium swallow), but may or may not create a clinical consequence (e.g., aspiration pneumonia), be perceived by the patient, or be rated as problematic by some patients, and not others, thus having lesser impact on measured QOL. Social, environmental, or comorbidity factors as well as compensatory responses may be operative.

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Toxicity may be applied broadly to changes in tissue or symptoms *related to cancer treatment*. Also, known as morbidity, these events are the focus of measurement efforts and interventions to reduce incidence or severity. On a practical level, use of the Common Terminology Criteria for Adverse Events (CTCAE) terms is considered "toxicity reporting" or adverse event reporting. In this respect, most, but not all, adverse events are generally viewed as a consequence of cancer treatment.

"Adverse event" is a regulatory term applied to any "unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure" [2]. This distinction is important since one may be unable to determine the underlying cause of an event: while most are from cancer therapy, some events are from comorbid illnesses, some are related to the cancer itself, and some are multifactorial in etiology.

"Quality of life" is also used broadly to indicate changes in the state of health as related to the cancer diagnosis or treatment. More specifically, QOL is the patient's perception of changes in symptoms and health state and are thus determined by the patient alone, without interpretation or grading by a clinician or observer. More recently these endpoints have been referred to as "patient-reported outcomes" or PROs. There is a current effort to develop CTCAE-based PRO tools, essentially converting a patient-reported symptom or event into a CTCAE grading scale [1].

Function endpoints for the head and neck (H&N) patient refer to activities, such as speech, eating (oral and swallowing phases), vision, hearing, smell, and taste. This chapter focuses on the most bothersome and long-lasting issues affecting the QOL of H&N patients: eating/swallowing and dry mouth. QOL tools for these issues will be briefly reviewed. Objective testing of swallowing, salivary function, taste, and smell are beyond the scope of this chapter.

45.1.2 Acute and Late Effects

Examples of acute adverse event rates from modern trials are listed in Table 45.1, comparing three cycles of concurrent cisplatin (from RTOG 0129 conducted between 2002 and 2005) and from radiation and concurrent cetuximab (conducted between 1999 and 2002) [3, 4]. Both trials utilized 2D radiotherapy. In general, there are significant pitfalls in comparing event rates between two trials. The specific rates of adverse events (or changes in QOL) must be considered in the context of a specific clinical trial and are dependent on the specific tools used, methods, frequency, and general rigor of data collection. However, the toxicity profiles of concurrent cisplatin versus concurrent cetuximab are strikingly different. Notably, cetuximab carries significantly lower acute toxicity than cisplatin: early death (0 % vs. 3.3 %), auditory (<10 % vs. 21 %), grades 3–4 febrile neutropenia (0 % vs. 10 %), pain (28 % vs. 53 %), and renal (0 % vs. 4 %). Rates of high-grade mucositis appear similar (33 % vs. 26 %). However, cetuximab carries high out-of-field dermatologic effects (acneform rash, 87 % vs. 2 %). The cetuximab trial did not separately score the combined effects of radiation and cetuximab on in-field dermatitis, which is generally more intense due to the presence of both the drug rash and radiation. The Bonner cetuximab trial did not report late effects.

Table 45.1 Acute effects from conventional radiation and concurrent cisplatin versus concurrent cetuximab in 2D era

	RTOG 0129 cisplatin (%)	Bonner cetuximab trial (%)
Early or toxic death	3.3	0
Febrile neutropenia grades 3–4	10.0	0
Auditory grades 1–3	21	<10
Renal grades 3–4	3.6	0
Mucositis grades 3–4	33	26
Other GI/nausea	52	49
Skin grades 3–4 in-field	10	23
Skin out-field (grades 1–4)	2	87
Pain grades 1–3	53	28

Based on data from [3, 4]

Table 45.2 Late effects from conventional radiation and concurrent cisplatin in 2D era (from RTOG 0129)

Events	70 Gy plus cisplatin x3 (%)
Worst overall grades 1–2	64
Worst overall grades 3–4	21
Feeding tube at 1 year	29
Mucositis grades 3–4	1
Esophagus	4
Skin grades 3–4	1
Osteonecrosis	3
Subcutaneous fibrosis	3
Soft tissue or bone grades 1–3	10

Based on data from [4]

Late effects from RTOG 0129 for three cycles of cisplatin and conventional radiation are shown in Table 45.2. The median follow-up was 4.8 years. For multiple reasons (e.g., competing risk of death, challenges in recognition and grading, or late injuries which may be mostly subjective), the rates of late injuries may be considered as somewhat under-reported.

45.1.3 Predictors of Toxicity and Function

Several factors have been identified that may predict for worse QOL outcomes, including older age, advanced T-stage, and larynx/hypopharynx primary site and neck dissection [5]. Additional factors include the presence of a feeding

tube, comorbid disease, tracheotomy, site, and stage. Data correlating QOL with functional outcome and symptom burden or specific CTCAE terms and grades are inconsistent. This may due to methodological issues, patient adaptation, patient prioritization of symptoms in relation to other dimensions of QOL, or issues in study design.

45.2 Adverse Event Reporting

45.2.1 Evolution of Toxicity Reporting

The methods for reporting adverse events (AEs) in oncology have evolved in response to new treatments and the needs of end users [1, 2]. Previous terminology and grading systems include WHO (1979), CTC for chemotherapy (1983), RTOG for radiotherapy acute and late effects (1984), and the LENT-SOMA late effects system (1995). While some of these systems are still in use, the NCI-CTC system was revised in 2003 (NCI-CTCAE) to provide a comprehensive grading system for all modalities and includes terminology to cover both acute and late effects. The CTCAE system is designed for broad capture of adverse events such as secondary endpoints in clinical trials. While the individual terms and descriptive language have evolved and have been used for many decades, the individual terms and grading parameters have not been validated for reliability or sensitivity, nor were they intended to be used as primary endpoints in clinical trials. Trials with a toxicity focus generally require multiple tools and morbidity endpoints including patient-reported outcome instruments (PROs), objective testing of function to more fully characterize the degree, and impact of a given injury.

45.2.2 CTCAE Terminology and Grading System

In late 2009, the fourth revision of CTCAE was released [6]. The main purpose of the revision was to reconcile and map CTCAE terms to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, the official regulatory terminology standard used across all medical areas. CTCAE v 4.0 includes approximately 800 AE terms. Each AE term is associated with a five-point severity scale using specific language for each grade. The AE terms useful in H&N cancer are dispersed among many organ system categories (i.e., there is no "H&N" section of the CTCAE).

Table 45.3 (CTCAE v 4.0 terms relevant to H&N cancer) provides a compilation of CTCAE 4.0 terms that are most commonly applied in H&N cancer trials. The shaded scales are useful for late effects reporting, but may also be applied as descriptors of earlier effects. As noted in 2003, a time-related designation sharply dividing acute from late effects no longer makes sense in an era of complex and protracted multimodality treatments. However, as a general rule, events developing or present 90 days after completion of cancer therapy (usually from the completion of radiotherapy) are generally considered late effects. The grading terms and descriptors should not be considered modality specific since many injuries may be caused by more than one modality or are from the interaction of multiple modalities, cancer response, or comorbidities.

45.2.3 Adverse Event Reporting Methods

The analysis and publication of toxicity data from clinical trials is a key component of outcomes reporting. Enormous amounts of adverse event data collected on clinical trials require methods to condense this information into digestible summaries. There are no regulatory or cooperative group standards for such analysis or presentation, resulting in wide variations in reporting and hampering the comparison of trials outcomes [7]. The most common approach uses a tabular display showing the incidence of various terms commonly known as a "safety" or "toxicity profile" table. One method to summarize such data is the "worst grade summary method" (WGSM) [8]. The WGSM provides an overall incidence rate, summarized by severity grade, consolidating adverse event data among organ and tissue categories. However, patients receiving multimodality therapy often experience multiple coincident (and/or sequential) adverse events during or after the delivery of treatment. Since each patient may contribute only one event to the summary, the more events one tries to summarize using the worst grade method, the more data are excluded, resulting in systematic under-reporting of toxicity. An alternative method for summarizing complex toxicity data has been proposed, but requires further testing and is not considered a routine reporting method at this time [8].

45.2.4 Late Effects Reporting

Accurately recognizing, collecting, and reporting late effects have been a thorny issue haunting radiotherapy studies since late effects were first recognized. Challenges include the need for long-term follow-up, data loss due to competing risks, the need for reliable grading scales, difficulty in the clinical recognition of the features and variations of the injury, the overall small number of recorded events, and need for standardized methods of analysis and presentation.

Two common methods used to summarize late effects reporting have been reviewed [9]. Actuarial estimates using Kaplan–Meier calculations are designed to adjust for incomplete follow-up either because the patient was still alive and without the relevant adverse effect when last seen or because the patient died of cancer or unrelated causes without having

Table 45.3 CTCAE v 4.0 terms commonly applicable to H&N trials

Pain (select site) (pain)	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling
Mucositis oral definition: a disorder characterized by inflammation of the oral mucosal	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated
Oral pain definition: a disorder characterized by a sensation of marked discomfort in the mouth, tongue, or lips	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	–
Facial pain definition: a disorder characterized by a sensation of marked discomfort in the face	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	–
Pain definition: a disorder characterized by the sensation of marked discomfort, distress, or agony	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	–
Fatigue definition: a disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self-care ADL	–
Myelitis definition: a disorder characterized by inflammation involving the spinal cord. Symptoms include weakness, paresthesia, sensory loss, marked discomfort, and incontinence	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
Peripheral motor neuropathy definition: a disorder characterized by inflammation or degeneration of the peripheral motor nerves	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated
Peripheral sensory neuropathy definition: a disorder characterized by inflammation or degeneration of the peripheral sensory nerves	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
Hearing impaired definition: a disorder characterized by partial or complete loss of the ability to detect or understand sounds resulting from damage to ear structures	Adults enrolled on a monitoring program (a 1, 2, 3, 4, 6, and 8 kHz audiogram): threshold shift of 15–25 dB averaged at 2 contiguous test frequencies in at least one ear or subjective change in the absence of a grade 1 threshold shift Pediatrics (a 1, 2, 3, 4, 6, and 8 kHz audiogram): >20 dB at any frequency tested and does not meet criteria for >grade 2	Adults enrolled in monitoring program (a 1, 2, 3, 4, 6, and 8 kHz audiogram): threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear Adults not enrolled in monitoring program: hearing loss but hearing aid or intervention not indicated; limiting instrumental ADL Pediatrics (a 1, 2, 3, 4, 6, and 8 kHz audiogram): >20 dB at >4 kHz	Adults enrolled in monitoring program (a 1, 2, 3, 4, 6, and 8 kHz audiogram): threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear; therapeutic intervention indicated Adults not enrolled in monitoring program: hearing loss with hearing aid or intervention indicated; limiting self-care ADL Pediatrics (a 1, 2, 3, 4, 6, and 8 kHz audiogram): hearing loss sufficient to indicate therapeutic intervention, including hearing aids; >20 dB at 3 kHz and above in one ear; additional speech–language-related services indicated	Adults: profound bilateral hearing loss (>80 dB at 2 kHz and above); nonserviceable hearing Pediatrics: audiologic indication for cochlear implant and additional speech–language-related services indicated
Tinnitus definition: a disorder characterized by noise in the ears, such as ringing, buzzing, roaring, or clicking	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	

Neck edema definition: a disorder characterized by swelling due to an accumulation of excessive fluid in the neck	Asymptomatic localized neck edema	Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL	Generalized neck edema (e.g., difficulty in turning neck); limiting self-care ADL	
Hoarseness definition: a disorder characterized by harsh and raspy voice arising from or spreading to the larynx	Mild or intermittent voice change; fully understandable; self-resolves	Moderate or persistent voice changes; may require occasional repetition but understandable on telephone; medical evaluation indicated	Severe voice changes including predominantly whispered speech	
Laryngeal inflammation definition: a disorder characterized by an inflammation involving the larynx	Mild sore throat; raspy voice	Moderate sore throat; analgesics indicated	Severe throat pain; endoscopic intervention indicated	
Voice alteration definition: a disorder characterized by a change in the sound and/or speed of the voice	Mild or intermittent change from normal voice	Moderate or persistent change from normal voice; still understandable	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; may require assistive technology	
Laryngeal edema definition: a disorder characterized by swelling due to an excessive accumulation of fluid in the larynx	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., dexamethasone, epinephrine, antihistamines)	Stridor; respiratory distress; hospitalization indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
Esophageal stenosis definition: a disorder characterized by a narrowing of the lumen of the esophagus	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Laryngeal stenosis definition: a disorder characterized by a narrowing of the laryngeal airway	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Limiting self-care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated
Pharyngeal stenosis definition: a disorder characterized by a narrowing of the pharyngeal airway	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids); limiting instrumental ADL	Limiting self-care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
Tracheal stenosis definition: a disorder characterized by a narrowing of the trachea	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Stridor or respiratory distress limiting self-care ADL; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
Dental caries	One or more dental caries not involving the root	Dental caries involving the root	Dental caries resulting in pulpitis or periapical abscess or resulting in tooth loss	
Periodontal disease	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	
Dysgeusia (taste alteration)	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste		

(continued)

Table 45.3 (continued)

Pain (select site) (pain)	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling
Salivary duct inflammation definition: a disorder characterized by inflammation of the salivary duct. *Formerly salivary gland changes/saliva (a common acute effect—thick mucus)*	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms; limiting instrumental ADL	Acute salivary gland necrosis; severe secretion-induced symptoms (e.g., thick saliva/oral secretions or gagging); tube feeding or TPN indicated; limiting self-care ADL; disabling	Life-threatening consequences; urgent intervention indicated
Dry mouth	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1–0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min	
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Mucositis laryngeal definition: a disorder characterized by an inflammation involving the mucous membrane of the larynx	Endoscopic findings only; mild discomfort with normal intake	Moderate discomfort; altered oral intake	Severe pain; severely altered eating/swallowing; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
Mucositis oral definition: a disorder characterized by inflammation of the oral mucosal	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated
Pharyngeal mucositis definition: a disorder characterized by an inflammation involving the mucous membrane of the pharynx	Endoscopic findings only; minimal symptoms with normal oral intake; mild pain but analgesics not indicated	Moderate pain and analgesics indicated; altered oral intake; limiting instrumental ADL	Severe pain; unable to adequately aliment or hydrate orally; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
Tracheal mucositis definition: a disorder characterized by an inflammation involving the mucous membrane of the trachea	Endoscopic findings only; minimal hemoptysis, pain, or respiratory symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe pain; hemorrhage or respiratory symptoms; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
Dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full-thickness dermis; spontaneous bleeding from involved site; skin graft indicated
Radiation recall reaction (dermatologic)	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full-thickness dermis; spontaneous bleeding from involved site; skin graft indicated
Skin induration	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration, unable to slide or pinch skin; limiting joint movement or orifice (e.g., mouth, anus); limiting self-care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding

Superficial soft tissue fibrosis	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g., mouth, anus); limiting self-care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding
Fibrosis deep connective tissue	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g., mouth, anus); limiting self-care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding
Trismus	Decreased ROM (range of motion) without impaired eating	Decreased ROM requiring small bites, soft foods, or purees	Decreased ROM with inability to adequately aliment or hydrate orally	
Head region soft tissue necrosis definition: a disorder characterized by a necrotic process occurring in the soft tissues of the head	–	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated
Neck region soft tissue necrosis definition: a disorder characterized by a necrotic process occurring in the soft tissues of the neck	–	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated
Esophageal (mucosal–submucosal) necrosis definition: a disorder characterized by a necrotic process occurring in the esophageal wall	–	–	Inability to aliment adequately by GI tract; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Pharyngeal (mucosal–submucosal) necrosis definition: a disorder characterized by a necrotic process occurring in the pharynx	–	–	Inability to aliment adequately by GI tract; tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Skin ulceration definition: a disorder characterized by circumscribed, inflammatory, and necrotic erosive lesion on the skin	Combined area of ulcers <1 cm; nonblanchable erythema of intact skin with associated warmth or edema	Combined area of ulcers 1–2 cm; partial thickness skin loss involving skin or subcutaneous fat	Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia	Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full-thickness skin loss
Periodontal disease	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	–
Osteonecrosis of jaw	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Severe symptoms; limiting self-care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Hypothyroidism definition: a disorder characterized by a decrease in production of thyroid hormone by the thyroid gland	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated

Yellow-shaded scales are useful for late effects (generally occurring >3 months after completion of treatment)

expressed the adverse effect. Actuarial rates provide an estimate of the cumulative incidence of late events that become clinically manifest in long-term survivors and thus may reflect the level of biologic injury. However, it is also informative to estimate prevalence as a function of time, since some late events are resolved by medical intervention or spontaneously improve with time. The latter aspect will become even more important with improved methods to mitigate or manage late injuries. Both actuarial and prevalence estimates are much more relevant than crude incidence rates (responders divided by number of patients), with each providing different information on the occurrence of late toxicity and its time evolution.

45.2.5 "Quality of Life" Measures

QOL for H&N patients has become an increasingly important consideration in selecting cancer therapy and for clinical trials reporting. Strictly speaking, QOL is a global and multidimensional construct reported by patients without assistance or interpretation by others. A range of tools are available including broad measures of the health state as well as tools which measure specific areas of H&N function or injury, such as mucositis, swallowing, or xerostomia [10–12]. A number of well-developed QOL tools for use in H&N studies have been compiled by J. Ringash (Table 45.4).

In general, broad measures of QOL for a group will decline during therapy, and the average values return to baseline by 1 year. However, specific testing of individual symptoms (single-item questions on dry mouth and swallowing) may persist for many years. Several factors have been identified that may predict for worse QOL outcomes including the presence of a feeding tube, comorbid disease, tracheotomy, site, and stage. Data correlating QOL with functional outcome and symptom burden or specific CTCAE terms and grades are inconsistent. This may be due to methodological issues, patient adaptation, patient prioritization of symptoms in relation to other dimensions of QOL, or issues in study design.

45.3 Protection of Normal Tissues

45.3.1 Medical Prevention of Mucosal Injury and Xerostomia

One of the most common toxicities noted during radiotherapy is mucositis or injury to the epithelial-lined mucosal surfaces of the H&N. With the increased use of concomitant chemotherapy and accelerated radiotherapy, mucositis may appear earlier in onset, be more severe, and be of longer duration. Ulceration lasting more than 3 months after treatment may be difficult to distinguish from soft tissue necrosis. Several medical strategies have been investigated to alter the onset and course of mucositis.

Fibroblast growth factor-7 is an epithelial-specific growth factor. The recombinant human form is called keratinocyte growth factor (KGF). In 2005, the FDA approved KGF to reduce oral mucositis in the stem cell transplant setting based on the results of a phase III trial in patients with hematological malignancies undergoing total body irradiation with high-dose chemotherapy [20]. The incidence and duration of severe oral mucositis were significantly reduced.

In the H&N cancer setting, a randomized phase II study evaluated palifermin weekly for 10 doses with concurrent cisplatin-/5-fluorouracil-based chemotherapy [21]. Although the drug was well tolerated, the results were inconclusive and the dose of KGF (60 μg/kg) was felt to be suboptimal. This has led to two large phase III industry-sponsored trials evaluating KGF at higher dose levels, one in the resected and one in the unresected setting. In 2008, the preliminary results of these trials have been reported [22]. Patients were treated with platinum-based chemoradiation, and in both trials the incidence of severe mucositis was significantly reduced compared with placebo with no difference in survival. Long-term follow-up is needed to assess any differences in cancer control or long-term toxicity.

Amifostine (Ethyol) is a thioorganic compound originally developed as a radioprotector against radiation-induced toxicity in the event of nuclear war. The active metabolite, WR-1065, accumulates in many epithelial tissues, including the salivary glands. Once inside the cell, the agent scavenges

Table 45.4 QOL and PRO tools

Focus	Reference	Instrument	Items	Reporter	Others
QOL	[13]	EORTC QLQ-C30/HN37	65	Self	Modular
	[14]	UW-QOL	13	Self	Surgical focus
	[15]	FACT-H&N	37[a]	Self	Modular
Performance status	[16]	PSS-HN	3	Clinician	Speech, diet, and public eating
Symptoms	[17]	MDASI-HN	22	Self	Modular
Xerostomia	[11]	UM-XQ	8	Self	Interview; no formal validation
	[18]	LASA	6	Self	No formal validation
Voice	[19]	VHI	30	Self	
Swallowing	[10]	MDADI	20	Self	

[a]Two additional items are not scored

radiation-induced reactive oxygen species which may confer radioprotection in normal tissue injuries.

A landmark clinical trial in the prevention of normal tissue injury involved the use of amifostine in H&N cancer. Patients were randomized to receive once daily radiation therapy for 5–7 weeks (total dose 50–70 Gy) or open label amifostine at 200 mg/m^2 i.v. 15–30 min before each fraction of radiation [21]. Amifostine was associated with a reduced incidence of RTOG grade ≥ 2 xerostomia over 2 years of follow-up, an increase in the proportion of patients with meaningful unstimulated saliva production at 24 months, and reductions in mouth dryness scores on a patient benefit questionnaire at 24 months, leading to the FDA approval for use in postoperative radiotherapy.

Despite these results, the role of amifostine in the treatment of carcinomas of the H&N is not without controversy. Current data do not support the routine use of amifostine with chemoradiotherapy for H&N cancer. Data are also insufficient to recommend amifostine to prevent mucositis associated with radiation therapy for H&N cancer [22].

Intravenous amifostine administration carries substantial risks of acute side effects consisting of allergic reaction, hypotension, emesis, and fatigue. In an effort to decrease toxicity and improve convenient delivery of the drug, subcutaneous administration of amifostine has been studied. The preliminary results of Groupe Oncologie Radiotherapie Tête et Cou (GORTEC) 2000–02 were reported comparing amifostine delivery via subcutaneous versus i.v. administration [23]. Although compliance was better with delivery subcutaneously, the rate of compliance was still only 80 %, and insufficient data on efficacy were reported.

The role of amifostine in the current era of concurrent chemoradiation and intensity-modulated radiation therapy (IMRT) is not clear. Technology which physically spares the parotid submandibular glands from higher dose radiation has been shown in several trials to reduce xerostomia, as described below. The potential benefit of amifostine in conjunction with IMRT and strict dose-volume constraints to critical organs is unknown. This coupled with concerns regarding amifostine-related toxicities may explain the far from universal use of amifostine in the treatment of H&N cancer in recent years.

45.3.2 Physical Protection of Normal Tissues

There is growing body of evidence demonstrating significant reductions in late toxicity through the use of IMRT in H&N cancer. Several single-institution trials have demonstrated a reduction in dose to the parotid glands and an associated reduction in xerostomia using IMRT technology [11, 26, 27]. More recently, three phase III randomized trials have been reported, two from Hong Kong and one from the UK (Table 45.5).

Pow et al. compared conventional radiotherapy to treatment with IMRT in nasopharynx cancer [28]. There was a significant improvement in both salivary flow and in QOL parameters. The study by Kam et al. showed improved observer-rated xerostomia at 1 year, but the subjective sensation of xerostomia showed no significant difference in patient-reported outcome between the two arms [29]. The relationship between salivary gland output and subjective sensation of dry mouth is complex and may carry low correlation. The parotid glands generate the serous/watery component of saliva and function to supplement saliva volume during eating. Lack of parotid saliva may still leave one with a baseline sensation of dryness or sticky saliva. Current investigations are evaluating contributions from the submandibular and minor salivary glands that provide mucinous saliva and are thought to be important for lubrication and sensation of baseline oral moisture.

Preliminary findings of the PARSPORT phase III trial from the UK were reported at ASCO in 2009 for patients with oropharynx and hypopharynx cancers [30]. Randomization was to conventional 2D (two-dimensional) parallel opposed fields or parotid-sparing IMRT. Mean doses to ipsilateral parotid glands were 57–60 Gy with 2D versus 26–27 Gy with IMRT. The incidence of LENT-SOMA $\geq$ grade 2 xerostomia 1 year after treatment was 74 % in the 2D arm versus 40 % of patients in the IMRT arm. QOL and salivary flow data are pending.

While the benefit of salivary gland sparing is widely accepted, there are no results yet reported on the potential of IMRT to improve cancer control through radiation dose escalation. The GORTEC is conducting a multicenter phase III trial comparing IMRT (75 Gy) with cisplatin versus conventional radiation (70 Gy) with cisplatin in stage III/IV H&N SCC of the oral cavity, oropharynx, or hypopharynx (personal communication J. Bourhis). The main endpoints are locoregional control and the rate of xerostomia at 2 years.

With the use of IMRT, there has been rising interest in sparing critical structures in addition to the parotid gland. The submandibular glands, larynx, oral cavity, cochlea, brachial plexus, trachea, esophagus, and pharyngeal constrictors are all subjects of ongoing research to determine the optimal dose-volume constraints [31–35].

Dysphagia and associated aspiration have emerged in recent years as major late sequelae of intensive chemo-RT [36].

Table 45.5 Phase III trials of IMRT to reduce xerostomia

First author	Site	No. of patients	Primary endpoint	Outcome
Pow [28]	Nasopharynx	51	Stimulated whole salivary flow	50 % vs. 4.8 % at 1 year ($p<0.05$)
Kam [29]	Nasopharynx	60	RTOG/EORTC xerostomia	39 % vs. 82 % at 1 year ($p<0.001$)
Nutting [30]	Oropharynx/hypopharynx	94	LENT-SOMA $\geq$ grade 2 xerostomia	39 % vs. 74 % at 1 year ($p=0.004$)

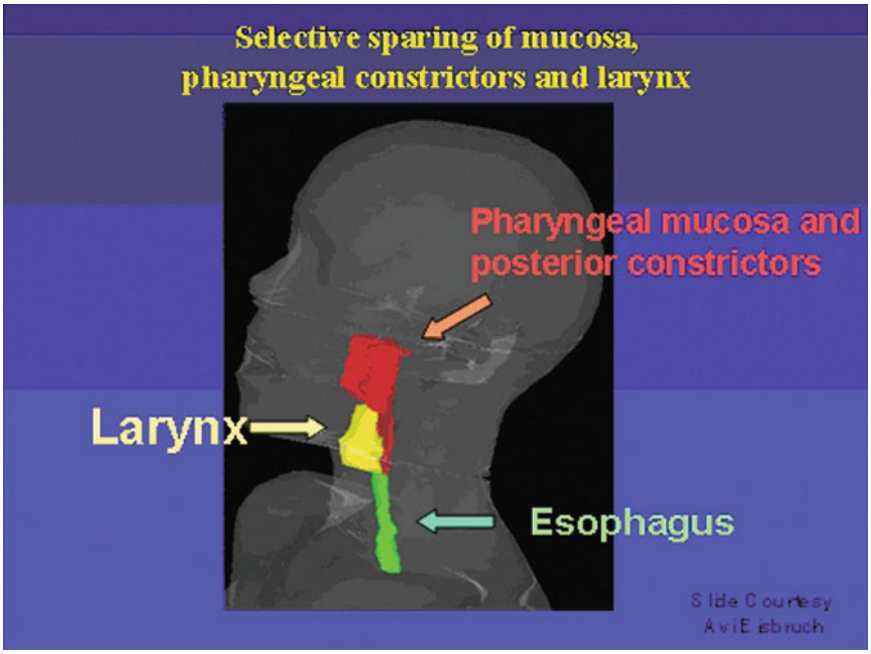

Fig. 45.1 Anatomic location of pharyngeal constrictors and larynx. Slide courtesy Avi Eisbruch

Dysphagia represents a multiorgan dysfunction; however, clinical research in recent years demonstrated several major anatomical structures in which damage is the likely cause of dysphagia: the pharyngeal constrictors (Fig. 45.1), glottic and supraglottic larynx, and esophagus. Significant dose-volume–effect relationships between each of these organs, and various measures of dysphagia, have been published during the past 3 years and recently summarized [37]. These dose–effect relationships remain significant even after correcting for clinical factors such as tumor stage [37, 38].

In general, a mean dose of less than 50 Gy to at least some portion of the pharyngeal constrictors and less than 40 Gy to larynx serves as a general dosimetric guideline to minimize the risk of chronic dysphagia. Reducing the doses to the glottic larynx and part of the inferior constrictors may best be achieved by split-field IMRT, treating the low neck with an anterior field containing a laryngeal block [39]; however, whole-field IMRT in which sparing the glottis is given a high weight may achieve similar results [40]. The need for whole-field IMRT is common in oropharyngeal cancer patients with significant mid-/low-neck lymphadenopathy or with gross involvement of the vallecula, where an anterior beam containing a laryngeal block may shield potential subclinical disease and in which whole-field IMRT may provide better target dose distributions. Efforts to spare noninvolved pharyngeal constrictors and larynx by whole-field IMRT concurrent with full-dose chemotherapy resulted in no recurrences in the vicinity of these structures and only mild worsening of dysphagia compared with pretherapy [38].

Reducing the intensity of the concurrent chemotherapy regimen may also reduce the prevalence of late dysphagia. A study of MRI before and after chemo-RT demonstrated both thickening and increase in T2 sequences in the pharyngeal constrictors (PCs) and larynx 3 months after therapy compared with pretherapy, suggesting that tissue edema is the most likely explanation to the changes occurring in the subacute posttherapy period [41]. These radiologic changes were dose dependent and were most prominent in PCs and larynxes in which the mean dose given was >50 Gy. In contrast, similar changes were not noted in any other muscle, including those receiving high doses. The likely reason these edema-like changes were noted only in the PCs and larynx is the fact that these organs are submucosal and were affected by the acute inflammatory processes occurring during RT, while all other swallowing-related organs, which are not submucosal, were not affected by moderate RT doses. Thus, long-term dysphagia seems to be consequential to acute mucositis (notwithstanding the lack in most patients of the severe, nonhealing mucositis causing chronic ulcers, which underlies a common description of "consequential" late sequelae).

45.3.3 Importance of Peer Review to IMRT Plan Quality and Toxicity

The use of IMRT permits wider variations in targeting and dose distribution, suggesting that normal tissue contouring and cancer targeting may be extremely crucial to IMRT outcomes. Das et al. examined variations in IMRT planning and delivery at five different medical institutions to assess variability in patient care. They reviewed 803 patients who were treated with IMRT 2004–2006 for brain (12 %), H&N (26 %), or prostate (62 %). Forty-six percent of the patients received a maximum dose that was more than 10 %

higher than the prescribed dose, and 63 % of the patients received a dose that was more than 10 % lower than the prescribed dose. H&N cancer cases had the largest variation. This study suggests the need for national and/or international guidelines for dose prescription, planning, and reporting in IMRT. More specific guidance in H&N cancer has recently become available from ASTRO [42].

The importance of careful patient examination and accurate disease localization in relation to selecting cancer targets has also become more critical with IMRT. Rosenthal et al. collected prospective data on 134 consecutive patients with preliminary radiation therapy (RT) plans. Peer review was performed that included H&N examination and imaging review to confirm target localization [43]. Peer review led to changes in treatment plans for 66 % of patients. Most changes were minor, but 11 % of changes were major and thought to be of a magnitude that could potentially affect therapeutic outcome or normal tissue toxicity. Most changes involved target delineation based on physical findings.

IMRT beams traverse nontarget normal structures that were not traditionally exposed during 2D RT for H&N cancer. Dose-volume histograms (DVH) were used in one study to evaluate radiation dose to the lip, cochlea, brainstem, occipital scalp, and segments of the mandible [44]. One hundred and sixty patients were evaluated for toxicity. Thirty percent of IMRT patients had headaches, and 40 % had occipital scalp alopecia. A total of 76 and 38 % of patients treated with IMRT alone had nausea and vomiting, compared with 99 and 68 %, respectively, of those with concurrent cisplatin. IMRT had a markedly distinct toxicity profile from 2D or 3D cases. Scalp alopecia and anterior mucositis were associated with reconstructed mean brainstem dose >36 Gy, occipital scalp dose >30 Gy, and anterior mandible dose >34 Gy, respectively. Thus, dose reduction to specified structures (salivary glands) during IMRT implies an increased beam path dose to alternate nontarget structures that may result in clinical toxicities that were uncommon with previous, less conformal approaches.

While there are no current outcome data regarding the quality of targeting from the current IMRT era, a recent report from the 2D era is a sobering reminder of the importance of peer review in RT quality assurance. The Trans-Tasman Radiation Oncology Group (TROG) reported outcomes from a randomized phase III trial studying radiation and cisplatin with or without tirapazamine. The trial used traditional 2D radiation fields and techniques and was conducted under 89 centers in 16 countries, some with limited experience in radiotherapy clinical trials [45]. Noncompliant radiation planning occurred in 25 % of cases; 47 % of noncompliant cases (12 % overall) had deficiencies expected to have a major adverse impact on tumor control. Major deficiencies were highly correlated with number of patients enrolled at the treating center ($p<0.0001$), with poorer outcomes at less experienced centers. In patients who received at least 60 Gy, those cases with major deficiencies had a markedly inferior outcome compared to those whose treatment was protocol compliant (*overall survival* 50 % vs. 70 %; HR = 1.99, $p<0.001$).

45.3.4 Protons

Proton beam irradiation carries significant dosimetric advantages compared to photon irradiation in H&N cancer. Protons have the potential for therapeutic gain through superior conformality near critical structures (base of skull) and may permit cancer target dose escalation. However, with better conformality and steep dose gradients, target volume delineation becomes paramount to reduce the risk of a marginal miss. Additionally, physics quality assurance, beam modeling, and setup uncertainty play increasing roles.

The technology and delivery methods of proton beam irradiation have been relatively slow to evolve compared to photons. There are currently less than ten operating centers in the USA, but more are expected by 2010 [46–48]. Most centers currently use flat (unmodulated) protons associated with protracted treatment times, often limiting treatments to one field per day. A few centers can routinely deliver 3D proton plans. Figure 45.2 shows excellent conformality and normal tissue sparing using 3D protons. No US centers are routinely delivering intensity-modulated protons (IMPT) at this time, although trials are expected to begin in near future.

Chan et al. have published their experience in the treatment of sino-nasal malignancies with proton irradiation. The main benefit of using protons in this location is to protect the optic structures. Between 1991 and 2002, 102 patients were treated to a median dose of 71.6 Gy. The 5-year local control was 86 % [47].

Protons have also been utilized in the treatment of newly diagnosed or recurrent nasopharyngeal (NPX) carcinoma in an attempt to reduce the volume of irradiated normal tissue. Between 1990 and 2002, 17 patients with T4 tumors were treated at MGH with combined photon and proton irradiation. The median dose prescribed was 73.6 Gy and only one patient developed local recurrence. Loma Linda University Medical Center (LL) has reported their results of reirradiation of the NPX with doses between 50.4 and 70.2 Gy. The local control rates at 2 years have been promising at 50 % [47].

There is less data for the use of protons in the treatment of oropharyngeal carcinoma. Loma Linda has conducted a trial of hyperfractionation in stages II–IV oropharyngeal carcinoma with mixed photon/proton beam irradiation [47]. 25.5 Gy was delivered with protons with the rest given with opposed lateral technique. The results of this trial show locoregional control rates of 93 % at 2 years and late RTOG grade 3 toxicity of 16 %.

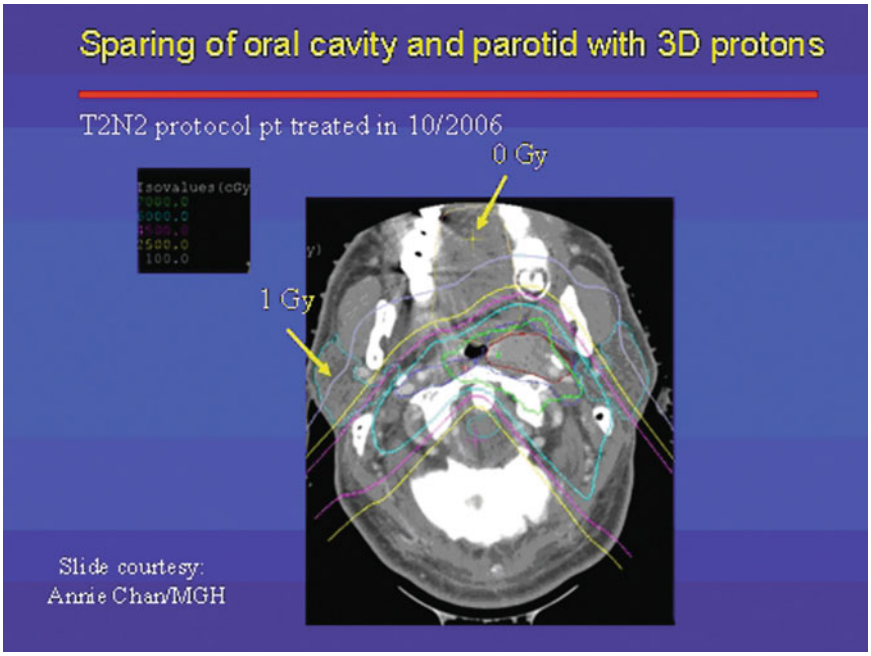

Fig. 45.2 3D protons in the treatment of pharyngeal tumor. Slide courtesy Annie Chan/MGH

In summary, proton beam irradiation carries potentially important dosimetric advantages. This technology is rapidly evolving and more centers are coming on line. Multicenter trials using 3D protons or IMPT are needed in larger patient numbers and in more homogenous populations (e.g., oropharynx cancers) in order to better document the clinical outcomes of this technology.

45.4 Management of Adverse Effects

45.4.1 Management of Mucositis

The increased use of altered fractionation radiotherapy and concomitant chemotherapy, while resulting in significant improvements in survival and decreased progression rates, has also led to a marked increase in the rates of mucosal and skin reactions. Thus, strategies to prevent and manage mucositis have become more critical in recent years. Our methods are summarized in more detail in a recent publication and will be briefly covered here [49].

It is extremely important to appropriately match therapeutic options to the stage and risk of cancer failure. We support NCCN treatment guidelines which permit tailoring of treatment based on a patient's stage, comorbidities, and preferences of the patient and H&N care team [50]. Therapy can thus be individualized in order to maximize tumor control and minimize toxicity. For example, early carcinoma of the tonsil and base of tongue (T1–2, N0–N1) does not require multimodality therapy to achieve excellent outcomes [50].

MASCC and NCCN guidelines and a National Cancer Institute report recommend "basic oral care" as a standard practice to prevent infections and to alleviate mucosal symptoms. However, despite these recommendations there is little evidence that these interventions decrease the incidence or severity of mucositis.

Basic oral care during radiation involves brushing with a soft brush in a nontraumatic way, frequent rinsing with normal saline sodium bicarbonate (1 l of water with 1/2 teaspoon baking soda and 1/2 teaspoon salt), using moisturizing agents as necessary, periodic dental evaluations and cleanings, and the lifelong use of daily dental fluoride prophylaxis.

Pain is the most important aspect of symptom control during radiation therapy to the H&N. Narcotic medications are needed in most patients and must be monitored frequently for total dose, route, frequency, and duration. Long-acting narcotics or fentanyl patches may be used with short-acting narcotics for breakthrough pain. These medications may cause constipation, and thus prophylactic stool softeners or other bowel regimens should be considered. Additionally, viscous lidocaine may provide topical relief in anticipation of meals.

"Magic mouthwash" consisting of some combination of antacids, diphenhydramine, nystatin, viscous lidocaine, and steroids is frequently used in an attempt at analgesia and for antifungal properties. These agents are frequently used; however, they have never undergone formal testing to ascertain their utility.

MASCC and the Cochrane groups have not found sufficient evidence to support the use of oral sucralfate to prevent mucositis. The FDA currently supports the following swish and spit products to decrease mucositis symptoms: Gelclair, MuGard, Mucatrol, and Caphosol. The latter product is currently the subject of a multicenter prospective trial to evaluate its symptom profiles and patient satisfaction in radiation-related mucositis.

45.4.2 Swallowing Disorders

The use of more aggressive chemoradiation treatments has resulted in higher rates of swallowing dysfunction [51]. This has prompted initiatives to prevent or rehabilitate swallowing dysfunction, including systematic use of IMRT, judicious use of feeding tube support, and swallowing exercises [36].

Radiation-induced xerostomia plays an important role in swallowing [52]. Single-center results of IMRT for salivary gland sparing also report low rates of feeding tube dependence [53]. Eisbruch has published detailed methods for minimizing dose to pharyngeal constrictors with excellent results [54]. There are no large multicenter trials with mature data from the "IMRT trials era" (~2005 forward) that have reported swallowing outcomes (check BC/SC tables). Thus, it is too early to know whether IMRT, which spares parotid function and employs smaller volume of high-dose tumor targets (compared with 2D), has had any broad impact on rates of swallowing dysfunction.

Swallowing ability after treatment represents a combination of pretreatment tumor-related dysfunction, treatment-related dysfunction, and the patient's ability to compensate spontaneously or with therapy. Patients' perceptions of their swallowing function may be inconsistent with objectively measured swallowing testing. These findings underscore the importance of swallowing evaluation before, during, and after treatment [55].

There is controversy about the potential benefits of prophylactic versus therapeutic feeding tube (FT) placement [56, 57]. Decision to place a feeding tube is dependent on the degree of pretreatment dysfunction and weight loss, location and target volume of the primary site tumor, use of IMRT and structure sparing techniques, clinician and patient preference, access to feeding tube procedures, and availability of swallowing therapists. The once widespread use of prophylactic feeding tubes seems to be declining in recent years [58].

There are no large, multi-institution, prospective, controlled studies of early swallowing therapy or interventions. Rather, most data are from retrospective, single-institution series. Nonetheless, most larger centers perform baseline swallowing evaluation in at-risk patients and often employ early prevention strategies including swallowing exercises during and after therapy. Nothing-by-mouth (NPO) intervals as short as 2 weeks have been shown to predict poor swallowing outcomes. Recovery of swallowing function may require between 6 months and 2 years in chemoradiation patients [12]. Since 6-month rates seem to predict longer term function, it seems reasonable to aim for maximal swallowing recovery by 6 months post-CRT.

Rosenthal and Lewin recommend that patients swallow as large a volume of maximally tolerated food viscosity as frequently as possible during and after treatment, even if they have a FT, for swallowing exercise. Patients who aspirate or who are at risk for aspiration can be taught to protect their airway. They also recommend specific swallowing exercises that have been demonstrated to improve swallowing ability [36]. There are no current prospective, randomized data to support the use of electrical stimulation of swallowing muscles.

Future directions to reduce swallowing dysfunction include judicious use of aggressive concurrent chemoradiation patients, systematic sparing of pharyngeal constrictors via IMRT, and reducing radiation dose in favorable risk HPV-related cancers.

45.5 Osteoradionecrosis

Osteoradionecrosis (ORN) is an uncommon event after standard dose and fractionation radiotherapy for H&N cancer with an incidence reported between 5 and 15 % [59–64].

With the use of modern radiotherapy techniques, the rates of bone necrosis appear to be on the decline in part due to better homogeneity and high-dose target volume reduction associated with IMRT. Eisbruch et al. reported no cases of ORN between 1996 and 2005 with strict prophylactic dental care and IMRT with a maximum mandible dose constraint <72 Gy [62].

The range of clinical ORN varies from small areas of exposed bone to large open wounds showing necrotic bone with purulence. Early disease may be managed with careful debridement, meticulous dental hygiene, and antibiotic therapy. For patients with more advanced/established ORN, hyperbaric oxygen (HBO) may be considered with or without surgical resection of necrotic bone. When HBO is used with resection, treatments are usually delivered pre- and postoperatively.

Retrospective series have reported an advantage to the use of HBO for established ORN. However, a prospective trial with HBO alone in the management of ORN was inconclusive [65]. This study considered HBO to be a failure in any patient who subsequently required surgery. Another study reported promising results of HBO and surgery when conservative therapy has been ineffective [64]. It appears that a strict program of smoking cessation may also be important for durable healing. A Cochrane review of studies published between 1975 and 2007 concluded that current information was insufficient in establishing definitive guidelines in the management of ORN [63]. In practice, clinicians appear to utilize HBO in selected cases of advanced injury and in patients with wound healing risk factors (e.g., diabetes).

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Advances in Management of Complications for Head and Neck Cancer Therapy

46

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Abstract

Increased use of the multimodality head and neck cancer (HNC) therapy has led to improvement in the local control, larynx preservation, and overall survival rates, leaving many HNC patients at risk for developing acute and late effects from treatment. The acute and late effects have resulted in substantial symptom burden and functional deficits in HNC population. The symptom control and functional issues associated with HNC and its aggressive treatment are complex, evolve over time, persist long term, and require frequent and ongoing assessment. In recent years, research efforts have focused on better understanding the supportive care needs in HNC patients across the trajectory of the disease treatment and recovery and developing new interventions to improve HNC patients' overall quality of life. The aim of this chapter is to review symptom control issues in HNC, emphasizing areas in which interventions are feasible and have demonstrated improvement in patients' outcome. Due to space limit, this chapter particularly focuses on the following areas: (1) nutrition and swallow function, (2) oral health, (3) acute and late musculoskeletal impairment (MSI), and (4) systemic effects.

Keywords

Head and neck cancer • Complication • Survivorship • Late effects • Symptom • Nutrition • Swallow • Oral health • Musculoskeletal impairment • Systemic effects

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46.1 Introduction

Head and neck cancer (HNC) therapy has evolved over the past several decades to include aggressive multimodality therapy, particularly in those patients with locally advanced disease. Although these aggressive approaches have led to improved local control, larynx preservation, and overall survival, improved disease outcomes have come at the expense of increased acute and late effects from treatment. As a result, attention has been directed to understanding the supportive care needs of patients across the trajectory of the disease process and the development of interventions that impact in a meaningful way on quality of life.

The symptom control and function issues associated with a diagnosis of HNC are complex, change rapidly over time, and are challenging to treat. Symptoms span from physical manifestations of tumor, such as pain secondary to tissue

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infiltration, to treatment-related toxicities such as xerostomia. Symptoms may result in functional decrements and when severe may lead to handicap or disability. Patient management is complicated by a high rate of mood disorders such as depression and anxiety. Furthermore, psychosocial issues may prevent the timely identification and management of supportive care problems. In order to minimize symptom burden, maximize functional outcome, and limit the effect of treatment on quality of life, clinicians must use a comprehensive and holistic approach to care.

HNCs involve structures that are integral to basic functions such as speech, swallowing, hearing, dental, and vision. Side effects of treatment are often categorized based on the impact on these important structures. These are commonly considered to be "head and neck"-specific functional impairment or symptoms. It should be noted that patients also experience more systemic symptoms such as fatigue, cachexia, neurocognitive decline, and depression. The aim of this review is to review symptom control issues in HNC, highlighting areas where interventions are feasible and have demonstrated improvement in outcome. Space precludes an exhaustive review; thus only selected symptoms will be included.

46.2 Nutrition and Swallow Function

It is well established that HNC patients are faced with complex nutritional issues that include weight loss and malnutrition. Malnutrition is a widely accepted risk factor for treatment intolerance, poor local control, and decreased long-term survival [1–3]. A recent study confirmed that a patient's pretreatment BMI and weight maintenance during treatment improves survival outcomes and is associated with better control of distant metastasis [4]. A patient's nutritional status should be assessed soon after diagnosis as well as routinely throughout the course of treatment. Historically it has been recognized that patients experience a rapid decrease in weight during the acute phase of treatment. For patients undergoing surgery, this is usually due to protracted periods without oral intake. For patients receiving radiation therapy, this is usually due to mucositis-associated pain and edema. Recent studies confirm that weight loss during radiation base therapy is high (~10 %); however, what is increasingly understood is that weight loss persists into the early and mid-phase of recovery. Ottosson et al. reported that nadir of weight loss occurs 5–6 months after the termination of radiation treatment [3]. In a randomized trial of 134 patients looking at the role of prophylactic PEG for early enteral feeding versus nutritional care according to clinical practice, neither the study group nor the control group reached their recommended energy intake until 6 months after the start of treatment. In addition, patients experience dietary adaptations for a protracted period of time posttreatment. In a study by Silander et al., real improvements in nutrition and dysphagia were not seen until 12-month follow-up, and oral intake did not return to baseline until 2-year follow-up [5]. A study evaluated the nutritional status, food intake, and dysphagia in long-term HNC survivors with a median posttreatment follow-up of 44 months. Seventy-five percent of patients were found to have dysphagia based on clinical assessment and 57 % had impaired swallowing based on videofluoroscopy [6]. Food modification varying from mild to serious was necessary for all 32 patients, while 19 % still used nutritional supplements or tube feeding. These results underline the importance of nutritional monitoring long after the completion of treatment.

A small number of studies have examined the association of HNC prognosis with specific food groups. Most studies have included small sample sizes and yielded equivocal results. In a landmark trial by Arthur et al. [7], 542 patients with newly diagnosed HNC completed food-frequency questionnaires and health surveys before treatment. Other known prognostic factors such as smoking, drinking, tumor stage, and comorbidities were controlled for. Two major dietary patterns were identified: whole-food pattern and Western pattern. This study demonstrated that a high whole-food pattern before treatment was associated with enhanced survival and a lower risk of recurrence independent of other factors known to influence prognosis. In addition, being overweight or obese at the time of diagnosis was also associated with a better prognosis. The foods that characterize the whole-food pattern were rich in sources of vitamins, polyphenols, and carotenoids, which are known to have anticancer functions. This is the largest study to date examining the association between diet and HNC prognosis and the first to relate specific dietary patterns to cancer outcomes [7].

An additional nutritional concern is the prevalence of vitamin D insufficiency in patients with HNC. In a prospective cohort study by Orell-Kotikangas et al. [8], vitamin D hypovitaminosis and deficiency were seen in 65 % of the study group compared to 21 % of the general population. Vitamin D deficiency was significantly more common in smokers, and smoking seemed to be a stronger risk factor for deficient levels than did low BMI. The clinical meaning of these findings remains unknown, and correlation by no means demonstrates causation. Further studies are needed to determine the role of vitamin D deficiency in tumor development and treatment outcomes [8].

New predictive models are being developed to better identify patients needing nutritional support. Cruz et al. demonstrated that the incidence of dietary restrictions was higher among patients with large tumors (T3/T4), loss of tongue mobility, dental extractions, and the use of radiotherapy [9]. Using the PHQ-9 depression questionnaire, Britton et al. found an independent association between baseline depression and the nutritional status of a patient. Patients

with depression presented with higher rates of malnutrition and developed further malnutrition faster on treatment. Interestingly, depression screening was a more efficient way to predict those patients that will decline nutritionally than other commonly accepted risk factors such as stage, number of radiation fractions, age, gender, and PEG [10].

Finally, there has been an interest in implementing innovative care delivery models. A dietitian-led clinic (DLC) was assessed for acceptability, efficiency, and clinical outcomes of HNC patients [11]. The DLC operated alongside the radiation oncology on treatment review clinics to enable multidisciplinary collaboration. This model was associated with increased efficiency for nasogastric tube insertions, improved transition to oral diets, and a significant decrease in nutrition-related hospitalizations resulting in significant cost savings.

46.2.1 Enteral Nutrition

Feeding tubes are required during active therapy in a high percentage of HNC patients with locally advanced disease. The relative value of gastric (G-tube) versus nasogastric (NG) tube has recently been brought into question. In a retrospective study, patients receiving NG-tubes had a lower risk of complications and higher rate of oral intake at 6 months following radiation therapy compared to G-tubes [12]. Similar data was reported by others. A Cochrane review of randomized clinical trials and studies addressing enteral feeding methods for nutritional management in patients with HNCs concluded that there was insufficient evidence to determine the optimal method of enteral feeding for HNC patients receiving radiation therapy with or without chemotherapy; thus both G-tubes and NG-tubes remain reasonable options for enteral support [13].

Debate also exits regarding the timing of tube placement: some advocate for prophylactic tube placement to ensure optimal caloric intake, while others advocate tube placement in patients unable to take in sufficient calories for weight maintenance. One randomized study of 134 patients with advanced HNC showed that the prophylactic placement of a PEG prior to the initiation of definitive treatment resulted in significantly earlier start and longer use of enteral nutrition and fewer malnourished patients during short-term (2 months) and long-term follow-up (48 months). Additionally prophylactic PEG resulted in higher quality of life, compared to control, 6 months following completion of treatment, including better physical function and cognitive function and significantly less fatigue and feelings of illness. Prophylactic use of a PEG tube had no impact on duration of hospitalization and no adverse effect on dysphagia [5]. Conversely, a retrospective study of 59 patients showed that the prophylactic placement of a PEG tube did not influence long-term weight changes in patients with advanced HNC. However, patients who received prophylactic PEG demonstrated significantly worse diet outcomes than those patients who either had no PEG or those who had a PEG placed therapeutically after the initiation of treatment. An analysis of PEG dependence showed that individuals who were able to maintain 100 % oral intake or at least partial PEG/partial oral intake demonstrated significantly better diets at 3, 6, and 12 months post-RT [14]. Based on the literature, it would be reasonable to take one of two approaches. If a prophylactic feeding tube is utilized, patients must be encouraged to exercise the muscles of dental mutation on a routine basis from the time the feeding tube is placed. If feeding tube placement is delayed, patients must be monitored closely for issues related to dysphasia and decreased caloric intake. As soon as it becomes evident that a patient will be unable to maintain hydration and nutritional status via oral intake, a feeding tube should be placed expeditiously. All patients should be encouraged to advance her diet as quickly as possible.

46.2.2 Dysphagia

Dysphagia results from tumor- or treatment-related effects: tumors may infiltrate or obstruct structures involved in deglutition, surgery may result in extirpation of tissue vital to normal swallow, and radiation may cause soft tissue inflammation, edema, and fibrosis. These effects may be aggravated in the setting of large primary tumors and when multimodality therapy is used. Since persistent dysphagia may lead to decreased oral intake, dietary deficiencies, and long-term feeding tube dependence, there has been strong interest in developing and testing preventive and therapeutic interventions for dysphagia in patients undergoing therapy.

It has been hypothesized that limiting the dose of radiation to structures that are critical for swallow function may prevent long-term dysphagia. Thus, various methods of radiation delivery have been examined to try to spare the base of tongue and the superior, middle, and inferior pharyngeal constrictors and the larynx as a whole from radiation inflammation-induced toxicity. Many studies have been conducted over the past decade focusing on the feasibility and efficacy of dose constraints to these organs of interest. When treating the oropharynx and the cervical neck, IMRT may be used either for the entire field or just the superior portion of the field, with a conventional anteroposterior field for the lower neck. It was traditionally believed that using a conventional low anterior neck field matched to an upper IMRT field would provide better sparing of the pharyngeal constrictors instead of using a whole-IMRT field. Galloway et al. assessed both radiation delivery techniques to determine the relative ability to spare vital structures for swallowing. With appropriate dose constraints on these muscles, it has been demonstrated that IMRT can achieve excellent

larynx protection [15]. Peponi has proposed an IMRT approach of creating a midline avoidance volume, consisting of contoured pharynx, larynx, and esophagus, with exclusion of any portion of this volume that overlaps the disease target. Using a mean dose constraint of <45 Gy to this volume resulted in a rate of only 9 % grade 2 dysphagia at 20 months and 2 % grade 3 dysphagia at 20 months [16].

Swallow therapy has been a cornerstone for the prevention and management of treatment-induced dysphagia. That being said, level 1 evidence to support specific practices for swallowing rehabilitation is scant. Many questions regarding swallow therapy remain unanswered: when should patients see a swallow therapist, when should therapy start, how frequently should patients see the therapist, and what therapies are most effective for a given intervention strategy? To help guide clinicians, Cousins conducted a meta-analysis of clinical studies investigating interventions to enhance swallowing function and jaw mobility posttreatment for HNC patients. The analysis included 27 studies, including RCTs, case-control/cohort studies, and case series [17]. Among the notable findings of these studies are the following: (1) pretreatment exercises may improve long-term swallowing function, (2) electrical stimulation and biofeedback may have a value in the adjuvant setting, (3) mechanical devices effectively increases the intraincisal distance (however, this measurement has not been correlated to swallowing function), and (4) exercises directed at ameliorating swallowing and trismus are most effective if begun before treatment starts. Further study is clearly needed to confirm these findings and to more clearly define the role of specific intervention strategies. For example, Zhen et al. conducted a quasi-experimental parallel cluster study of daily swallowing training in dysphagic cancer patients following tongue resection and rehabilitation. The regimen consisted of 30 min of swallowing training each day, 6 days per week for 2 weeks. The swallow intervention resulted in significantly improved dysphagia and quality of life, compared to patients who did not undergo this training [18]. Larger, randomized, multi-institutional trials utilizing multidimensional interventions such as that described by Zhen et al. are needed to help guide clinicians.

46.2.3 Late Effects: Impact on the Eating Experience

Eating, the function of consuming food and liquid, is necessary to sustain life, and although eating is a daily activity, it is often taken for granted [1]. Late effects including dysphagia, xerostomia, mucosal sensitivity, pain, trismus, and dental disease are common in HNC survivors and impact the ability to eat and drink [2–4, 19]. As a result, eating and the eating experience may remain problematic for months or years, and for some, eating may never return to normal. There is little data on the impact of late effects on the meaning of food, the eating experience, and disruption this causes for patients' lives.

The total eating experience includes physiological, psychological, social, and cultural elements [3]. A person's identity and self-image are based on their daily interactions and life experiences [20, 21]. A portion of this identity involves life experience surrounding food [21–23]. Food and eating also play a significant psychological and social function when it comes to enjoyment of food as well as the socialization that occurs during mealtime [3, 22, 24]. In addition to the physical losses related to an HNC diagnosis and the treatment toxicities, patients may also identify emotional losses due to reduced satisfaction of food and social losses such as not wanting to accept invitations out to dinner or to partake in meals with co-workers in the event that they seem incompetent [3, 24–28]. Although food is fundamentally and physiologically necessary to provide energy and nutrients, the act of eating is both physiological and symbolic [22]. It is through eating that we express prosperity, good health, strength, and love, obtain psychological comfort and hope, and develop new friendships and reconnect with our past [22].

At the present time, there are few qualitative studies specifically exploring the eating experience after treatment for HNC [3, 24, 29]. Systematic reviews of the psychological/lived experience of HNC patients, although not specific to the eating experience, report significant challenges related to eating [19, 30]. Consistent themes that emerged included: disruption to daily life, the diminished self, uncertainty and waiting, sharing the burden/support, psychological well-being, and finding a path/uncertain future [19, 22, 24–27]. Studies specifically explored the eating experience in patients post-HNC treatment and identified themes that included a long journey, a new way of eating, eating without satisfaction, challenging meals outside the family, and the creation and acceptance of a new normal [24, 29]. These studies identified challenges that impacted physical, emotional, and social losses.

46.2.3.1 Disruption to Daily Life

This theme focused on eating problems such as the thickening or lack of saliva, changes to taste, pain, the fear of choking, and the feeling of narrowness in the throat impairing the ability and/or desire to eat [19]. The pleasure of eating was also impacted as the result of the length of time required to eat, the embarrassment of eating in front of others, and the resulting anxiety. Family structure was also impacted as meals were no longer a social occasion [19]. There was also a need to concentrate on food selection, consistency, and the volume of food eaten [24]. Additionally, there was a heightened sense of awareness of what could not be eating.

46.2.3.2 The Diminished Self

HNC survivors may experience temporary or longer-lasting functional, social, and existential losses, which may alter their life expectation [19]. These challenges may impact confidence, self-esteem, self-image, and sense of self. Functional impairments may further erode self-image and self-confidence. The actual physical problems may be a constant reminder of the cancer and the general lack of "normality." Difficulty with speaking and eating and a change in appearance may result in a diminished body image and social withdrawal. Although acute effects (e.g., weight loss, skin changes related to radiation therapy) resolve, changes associated with eating, swallowing, and managing food are often hidden [24].

46.2.3.3 Psychological Well-Being

HNC treatment may have severe psychological consequences including anxiety, depression, distress, feelings of shame and guilt, as well as changes in body image and self-esteem [30]. The ability to eat and drink is associated with the ability to uphold life and general health [22, 27]. Mortensen concluded that patients felt socially marginalized due to their eating impairment and they missed enjoying meals, talking about food, or getting a drink with others [27]. Thus, a social meeting over coffee, a dinner with friends, or a professional lunch had become linked to embarrassment and self-consciousness.

46.2.3.4 A New Way of Eating

Ottosson and McQuestion both found that meals took longer to eat related to dysphagia and the need to chew food more carefully, take smaller bites, and often consume softer foods or moist foods or consuming more fluids with meals [3, 24]. Additionally, McQuestion reported that meals took longer to eat with the need to use trial-and-error strategies to manage the physical act of eating and the need to concentrate on food selection [24].

46.2.3.5 Eating Without Satisfaction

Eating without satisfaction was found to be related to xerostomia, taste loss or change, and pain [3, 24]. Respondents reported that they could eat sufficiently; however, alterations were required that resulted in less variety in food choices and participants struggling to find anything new and/or exciting to eat [3]. Respondents who had diminished taste or taste alterations reported that it felt as though any return in taste was a victory. Taste alterations resulted in a loss of variety in food choices and changed the experience of food and eating which resulted in the feeling that eating was only done to obtain energy and nutrients versus eating for pleasure [3, 24].

46.2.3.6 Creating and Acceptance of a New Normal

Ottosson noted that respondents identified that they were coping with their eating challenges by selectively choosing food [3]. The increased consumption of water or milk with meals was used to facilitate swallowing if xerostomia was present (an adaptive behavior). Avoidance of food was also identified (maladaptation) [3]. Participants indicated that although many aspects related to food, eating, and meals had been altered due to the disease and treatment, they had adapted in order to cope with the new way of living and reasoned that this was "the price to be paid for survival" [3].

46.2.4 Implications for Practice

The recognition and acknowledgment of the significance of eating problems posttreatment is necessary. The eating experience, especially if a patient reports that they are "doing just fine," may not be regularly explored in HNC survivors. Patients may struggle not only with eating but eating for enjoyment. Functional losses may develop so gradually over time that patients may not even recognize the impact of the late effects [31, 32]. Patients may adapt to their current situation and may have learned to cope with their deficits; however, symptom burden and functional problems may have profound long-term physiologic effects [31, 32]. Probing questions will expose patient concerns that may be obscured by patients' downplaying of symptoms. Health-care professionals, including nutrition professionals, should explore potential late effects of HNC treatment in follow-up visits. Providing a holistic interdisciplinary approach that supports patients in regard to the physiological, psychological, and social aspects can maximize nutritional well-being and the eating experience within this population.

46.3 Oral Health

46.3.1 Xerostomia and Hyposalivation

Radiation total doses >50 Gy can cause irreversible damage to the salivary gland [33]. In addition to decrease in salivary flow, radiation may result in altered salivary composition, including decreased secretory immunoglobulins, particularly IgA. Radiation damage to the salivary glands results in xerostomia—the subjective complaint of dry mouth and hypersalivation—and decreased stimulated and unstimulated salivary flow. Xerostomia and hypersalivation are ubiquitous in patients during radiation therapy and in the immediate posttreatment period. A high percentage of patients also experience moderate to severe late-effect xerostomia (grade 2 at 36.6 %, grade 3 at 43.9 %).

Xerostomia and hypersalivation have been purported to be the most debilitating late side effect in HNC patients treated with radiation [33]. First and foremost, hyposalivation results in increased susceptibility to dental caries. Saliva is also critical for food bolus formation (oral preparation) and oral transport. Thus, hyposalivation may affect oral intake and

nutritional status. Vocal fold dryness and increased viscosity of secretions affect vocal function [34]. Hyposalivation results in increased susceptibility to oral infections, particularly those of fungal origin. *Candida* flourishes in the acidic oral environment of xerostomia. Unstimulated and stimulated whole flow rates have been shown to be negatively and significantly related to the *Candida albicans* counts [35]. Finally, xerostomia is one of the major barriers to routine exercise and posttreatment HNC patients.

There are several strategies for prevention of xerostomia. Three-dimensional conformal radiotherapy (CRT) and intensity-modulated RT (IMRT) which allows for sparing of salivary gland tissue result in reduction of the severity and/or frequency of RT-associated xerostomia. As a result, patients have less dysphagia and improved quality of life scores. This benefit remains significantly greater than 3 years postradiation therapy [36]. Amifostine (WR 2721), a free radical scavenger, has been investigated as a pharmacologic measure to prevent salivary gland damage from radiation [37]. Meta-analysis of studies using amifostine shows a modest level of effectiveness; [38] however, the expense, toxicities, and administration challenges have limited its use. Single submandibular gland transfer to the submental space, where it is shielded from radiation, has resulted in improvement in xerostomia and swallow function [39]. Although this is effective, this approach has not been readily adopted. Several reports on the efficacy of submandibular gland transfer (SGT) now exist in the literature. These reports indicate that salivary function can be retained when the gland is transferred into the submental space for shielding during radiation treatment. Rieger et al. studied the outcomes of 69 patients who underwent SGT [40]. Speech and swallowing outcomes were objectively measured by computerized assessment and modified barium swallow. There were no differences in speech outcomes. However, patients who received the SGT procedure had better swallowing outcomes and quality of life scores compared to patients who received pilocarpine. While this procedure may increase the upfront morbidity for nonsurgical patients, it could improve the long-term outcomes for younger patients with oropharyngeal cancers who are expected to have long-term survival. Among the three strategies outlined above, the use of conformal radiation techniques is the most commonly utilized.

Supportive care for patients with xerostomia and hyposalivation may be divided into palliative measures and health maintenance activities. Palliative measures are directed at minimizing pain and discomfort; health maintenance activities are directed at minimizing the adverse overall health impact on patients. Palliative measures begin with avoidance of exposures that can irritate the mucosa including alcohol, smoking, and spicy or citrus foods. Although avoidance of exposures may appear to be simple, it is challenging for patients. Dry air may increase the sensation of xerostomia; thus, humidification may improve patient's comfort particularly during sleep. The liberal use of salivary substitutes, with a pH of greater than 5.1, may ameliorate symptoms for some patients [38]. Salivary flow can be stimulated when sugar-free gum is chewed; xylitol-containing gum is preferred because of the bacteriostatic effect of xylitol [41]. Finally, the use of systemic salivary stimulants (sialogogues) such as nonselective muscarinic receptor agonist may increase stimulated and unstimulated salivary flow [42, 43]. Health maintenance activities are directed at the long-term sequelae of hyposalivation. This includes meticulous dental care, nutritional counseling when needed, and vigilant monitoring for oral infections.

Among non-pharmacological interventions, the most promising is acupuncture. Three randomized studies have reported on the impact of acupuncture on xerostomia and hyposalivation. Acupuncture in a randomized crossover trial comparing 145 patients who received oral care teaching sessions versus acupuncture demonstrated a significant reduction in the symptoms of dry mouth compared to oral care alone. Patients receiving acupuncture reported less severe dry mouth, sticky saliva, waking up at night to drink, or needing to sip liquids to swallow food [44]. In another randomized trial comparing the prevention of radiation-induced xerostomia in nasopharyngeal cancer, patients who received acupuncture 3×/week during radiotherapy had a lower incidence and decreased severity of xerostomia as early as 3 weeks into radiation. These benefits continued to be seen 6 months after the end of treatment. Less than 1/3 of patients in the acupuncture group reported clinically significant symptoms at 6 months versus >2/3 in the control group [45]. The use of IMRT in both of these studies was limited. Despite the promising results, methodological flaws precludes definitive recommendations regarding the use of acupuncture in patients with xerostomia due to head and neck cancer radiation therapy [46, 47].

46.3.2 Dental Health

It is generally recognized that HNC patients planned for radiation therapy require a referral for a dental assessment prior to the start of treatment. Although randomized clinical trials demonstrating the effectiveness of various elements of the standard evaluation and treatment are lacking, there is general consensus regarding the integral component parts of the pre-radiation dental evaluation. These include: (1) identification of preexisting oral and dental disease with treatment if possible prior to the start of radiation, (2) treatment of dental or oral infections, (3) education regarding expected dental complications, and (4) education regarding oral hygiene (to include recommendations regarding the use of fluoride) [48]. One of the problematic dental issues facing clinicians is the decision to delay initiation of radiation therapy pending extraction of diseased dentition.

Delaying curative treatment while waiting for a dental referral can adversely affect symptom management, nutritional status, and tumor progression. To address this question, a recent Cochrane Collaboration looked into evidence from randomized trials on extracting healthy and diseased teeth before radiation and the consequence of leaving teeth in place during radiation treatment. To date, no randomized controlled trials have been reported that either support or refute the contention that extraction of at-risk teeth prior to radiation reduces subsequent dental complications [49]. Thus, clinical judgment should be used in determining whether it is safe and appropriate to wait until completion and healing from dental work before proceeding to radiation therapy. During treatment, patients should maintain meticulous oral hygiene per recommendations by their dental health provider. Upon completion of therapy, patients should continue routine dental follow-up. The optimal follow-up interval has yet to be determined. It should however be frequent enough to identify dental issues at a time when they are early and potentially treatable. Unfortunately, for most patients, posttreatment dental care is suboptimal. In one study, *53.6 % underwent dental professional care prior to treatment with number falling to 34.1 % after treatment* [33].

Posttreatment hyposalivation contributes to long-term adverse dental health outcomes. Hyposalivation favors demineralization due to decreased buffering capacity and decreased availability of calcium and phosphate [50]. Demineralization leads to discoloration of the enamel, cavities, chipping, cracking, and autoamputation of teeth, which can ultimately require whole-mouth extraction. Decreased secretory immunoglobulin A causes microbial shifts toward cariogenic flora including colonization with *Streptococcus mutans* and lactobacillus species [51]. Thus, lifelong diligent preventative care is essential, including brushing, flossing, and daily fluoride therapy. Use of aqueous-based chlorhexidine gluconate can provide protection against bacterial and fungal infections. Patients should be cautioned to avoid formulations with alcohol, caffeine, and tobacco which could exacerbate xerostomia [52]. Consumption of tap water, which contains 1 ppm fluoride, is favored over bottled water [53]. Milk may also be used to lubricate tissues, buffer acids, and help provide calcium and phosphate to aid remineralization [41]. Patients should be encouraged to maintain a diet that avoids known cariogenic food and liquids. *Unfortunately*, patients experience numerous barriers to oral care both during and after treatment. These include: mucosal sensitivity, trismus, and dietary restraints and financial limitations. Finally, patients may have difficulty identifying oral health specialists comfortable with treating the complex dental issues facing head and neck cancer patients who have been treated with radiation therapy [54, 55].

46.3.3 Osteoradionecrosis

Clinically, osteoradionecrosis manifests as an area of exposed bone within the field of radiation which fails to heal within 2–6 months. Several staging systems have been used to describe lesions. They are based on variable parameters including response to treatment, lesion extent, and symptoms [56]. Associated symptoms include pain, halitosis, dysgeusia, and food impaction. Untreated, patients may develop pathologic fractures and oral cutaneous fistulas. Monitoring of the lesion for 2–6 months is necessary in order to rule out mucosal necrosis or delayed healing from trauma. Osteoradionecrosis was originally hypothesized to be secondary to a combination of radiation-induced tissue damage superimposed with trauma and infection. Marks subsequently hypothesized that radiation-induced tissue damage leading to hypocellularity, hypovascularity, and hypoxia results in chronic nonhealing wounds [57]. A more contemporaneous pathophysiologic mechanism postulates that radiation induces an acute inflammatory response with upregulation of fibroblastic activity resulting in replacement of normal bony matrix with fibrous tissue [58]. Concordant with this hypothesis is the observation that osteoradionecrosis is associated with the T-variant allele at -509 within the TGF-beta 1 gene [59].

The incidence of osteoradionecrosis correlates with the dose and volume of bone within the treatment field. At a dose of 70 gray, the incidence of osteoradionecrosis is 9–15 % but decreases significantly as the radiation dose to bone diminishes [60]. The use of intensity-modulated radiation therapy (IMRT) to minimize the dose of radiation to the mandible is associated with marked decrease rates of osteoradionecrosis. In a retrospective study of 83 patients undergoing definitive radiation-based treatment using IMRT or IGRT, the mean mandibular dose was 43.6 gray and 43.8 gray, respectively. At follow-up of 28 months, only one patient had developed osteoradionecrosis [61]. The majority of patients develop osteoradionecrosis within 18 months of completing therapy. That being said, the irradiated bone remains at risk in perpetuity. The mandible is affected more frequently than the maxilla, likely because of a unilateral vascular supply, greater bone density, and thus a tendency to absorb more radiation [51, 60]. Extractions postirradiation portend an increased risk of osteoradionecrosis. Trauma from extraction combined with infection from periodontal disease produces incidence rates of PRON three times higher in dentate as opposed to edentulous patients. The role of hyperbaric oxygen therapy, pentoxifylline, and tocopherol for the prevention and treatment of osteoradionecrosis remains to be determined [62, 63].

46.3.4 Taste Disorders

Taste disorders include total taste loss (ageusia), taste alteration (dysgeusia), heightened sensitivity (hypergeusia), and taste phantoms [64]. These disorders occur due to direct tumor effects, such as blockage of the nostrils or cribriform plate, treatment-related effects, and oral infections, such as candidiasis. Chemotherapy drugs, including cisplatin, commonly result in taste disorders due to direct drug secretion via saliva [65]. Radiation therapy, which is an integral part of treatment for all patients with locally advanced HNC, may result in severe and permanent alteration in taste sensation. The majority of taste buds are located on the tongue, as well as throughout the upper aerodigestive system. Taste buds are composed of 50–100 receptor cells with associated support cells. Receptor cells transmit signals to the trigeminal nerve fibers which carry information to the brain. The exact mechanism of radiation-induced taste alteration remains to be elucidated. Three models have been proposed to explain radiation-triggered taste dysfunction: (1) disruption of the contact between taste cells and nerves via radiation damage leads to taste cell death; (2) radiation directly damages taste cells; and/or (3) radiation targets proliferating immature cells, interrupting the production of new taste cells [66, 67]. Specifically, the volume of radiation delivered to the tongue appears to be a major determinant of taste dysfunction [68]. The impact of hyposalivation on taste loss is controversial, but its presence may interfere with tastant presentation to taste bud receptors, thus altering a patient's perception of taste [64, 69].

Taste disorders in the head and neck population may manifest prior to treatment, worsen and peak during therapy and early recovery, and persist many years as a late toxicity. Taste disorders during treatment are near universal; however the late effects of taste alteration are more prominent than once realized. In a recent study, 82.6 % of patients greater than 6 months posttreatment reported some degree of taste alteration. Thirty-nine percent of patients indicated that taste changes were moderate to severe in nature. Taste alterations resulted in moderate to severe impact on desire to eat, changed food choices, and food in 28.3, 34.8, and 28.3 % of patients, respectively [70]. Thus, loss of taste may have a profound effect on nutritional status and QOL. Patients may describe an inability to take nutrition orally due to severe loss of taste or altered taste sensation. Loss of umami taste appears to have the strongest correlation with QOL due to its role in triggering interest in eating via enjoyment and pleasure pathways [71].

To date, there are no effective therapies for the prevention or treatment of taste disorders in the HNC population. Although small studies have reported that zinc improves taste alterations [72], a randomized trial of zinc in HNC patients failed to demonstrate efficacy for the prevention of radiation-induced taste alterations [73]. Similarly, amifostine [74] and bethanechol [75] failed as preventive therapies. Anecdotal reports of clonazepam reduce olfactory and gustatory complaints. Behavioral modifications appear most beneficial as opposed to pharmacological interventions. Patients should avoid metallic silverware if taste phantoms or metallic taste remains problematic. Patients should be encouraged to "trick" their senses by choosing food with appealing colors, forms, textures, and aromas. In addition, cold food items are preferred given their less offensive odors. Patients may find that the addition of seasoning or marinades may overcome unpleasant taste. Prior to meals, patients should brush their teeth and rinse their mouth with fluids in order to overcome concomitant xerostomia [76].

46.4 Acute and Late Musculoskeletal Impairment

HNC patients may experience functional impairment due to deconditioning and generalized weakness [77, 78] or as a direct effect of musculoskeletal impairment (MSI) involving the jaw, neck, shoulders, and chest [79–84]. MSI associated with the jaw, neck, shoulders, and chest may result in or exacerbate postural abnormalities and cause pain [85]. Unfortunately, little attention has been paid to MSI in HNC survivors. Available data indicate that MSI may result in clinically meaningful symptoms and functional limitations that interfere with daily activities and decrease QOL [79, 81, 86–88]. This results in an increased financial burden for survivors and society due to added health-care expenses and loss of work [85, 89]. Finally, MSI may cause psychological distress (e.g., anxiety, depression, and body image disturbance) [79, 90–92]. There are three main categories of MSI in HNC survivors: (1) neck/shoulder dysfunction including decreased range of motion (ROM) [85, 93–101], (2) trismus [102–104], and (3) postural abnormalities [85, 105].

46.4.1 Neck/Shoulder Dysfunction

Studies reveal that almost 100 % of patients experience shoulder dysfunction after radical neck dissection while less extensive procedures, such as modified radical neck dissections that spare the spinal accessory nerve and/or other structures, result in decreased levels of dysfunction [106–112]. Despite surgical advances, shoulder dysfunction continues to be a problem in HNC survivors [95]. Secondary effects of MSI include adhesive capsulitis and myofascial pain in the upper trapezius, levator scapulae, and rhomboid muscles [113]. In addition, radiation-induced toxicity is another major cause of long-term neck/shoulder disability after HNC treatment [97]. Few studies have used objective measures to specifically assess MSI-associated alterations in

ROM and its associated morbidity [114, 115]. A study of 103 HNC survivors >3 months posttreatment and using the cervical range of motion device (CROM) found that 40 % of survivors had an impairment in at least one direction of neck ROM. This suggests that MSI adversely impacts ROM in a high percentage of survivors [81, 99]. In another longitudinal project, data reveal that in 246 assessments conducted between end of treatment and 12 months posttreatment, the Neck Disability Index identified moderate to severe neck impairment at some point in time in 30 % of participants (data unpublished).

Neck/shoulder dysfunction is often as a chronic, persistent, and progressive condition, which significantly impacts HNC patients' QOL. Identification, monitoring, and treatment of neck/shoulder dysfunction are critically important to decrease associated symptom burden and functional loss. Timely and appropriate physical and occupational therapy is important to improve HNC patients' general conditioning, strengthening, and ROM. Moreover, education about self-management of this condition is of paramount importance to HNC survivors. There are reports describing a number of therapeutic techniques including: progressive resistance exercise training [86], impedance-controlled microcurrent therapy [116], and acupuncture [117]. RCTs, however, are limited in number, small in size [79, 86], and short-term follow-up. Thus, rigorously designed longitudinal research projects are needed to provide level 1 evidence to support specific interventions.

46.4.2 Trismus

Cancer treatment (e.g., surgery and radiation therapy) damages critical structures for normal jaw ROM including the temporal mandibular joint and the muscles of mastication. Tissue damage on these critical structures stimulates abnormal proliferation of fibroblasts and subsequent fibrosis and stricture [82, 84, 118], thus resulting in restricted mouth opening (trismus). Maximum mouth opening through measuring the interincisal distance is commonly used to identify and grade trismus: <35 mm in dentulous patients and <40 mm in edentulous patients [119]. Based on these criteria, trismus is a frequent acute and late toxicity in HNC survivors with a prevalence rate as high as 45 % [119]. Although data are mixed, some studies indicate that intensity-modulated radiation may significantly decrease prevalence and/or severity of trismus compared with conventional radiation (5 % vs. 25.4 %) [119]. Trismus not only affects basic functions such as chewing, speaking, and swallowing but also impacts maintenance of oral health, body image, and overall QOL. Prevention, identification, and early intervention are of incredible importance in trismus, as it can be difficult to treat and improve once trismus has developed (Stubblefield's book). Physical therapy is still the mainstay of treatment of trismus. Other treatment options are critical for HNC patients for maintaining the effect of physical therapy or decreasing symptom burden, such as a structured jaw exercise program, use of a jaw rehabilitation device (e.g., TheraBite, Dynasplint), and botulinum toxin injections (for management of pain and spasm of the masticatory muscles). For individuals with trismus refractory to physical therapy or with severe trismus, a surgery intervention (e.g., coronoidectomy) may be needed to improve oral function.

46.4.3 Postural Abnormalities

Clinical experience indicates that HNC survivors are highly likely to develop postural abnormalities [85] including: central collapse of the anterior chest, kyphosis, loss of normal lordosis in the low back, protrusion of the head in a forward direction, and internal rotation of the humerus. Currently, no published data are available on incidence or severity of postural abnormalities in HNC survivors. A number of tumor and/or treatment-related factors may contribute to postural abnormalities. First, surgery and radiation therapy damage neck/shoulder soft tissue with resultant fibrosis and contracture [85]. Second, neurologic damage and atrophy related to surgery and/or radiation may lead to denervation and neuromuscular-associated complications, which are most commonly manifested after prolonged activity [85]. Finally, survivors who were treated with combined modality therapy develop severe deconditioning and muscle weakness resulting in an inability to maintain proper spinal alignment. A study assessed the changes in body mass and physical function pre- and post-chemoradiation in 17 HNC patients. The study found a loss of lean muscle of 5.6 kg (mean) during the 7 weeks of chemoradiation therapy and associated decreased functional status as measured by self-report [120]. Potential adverse effects of postural abnormalities include: musculoskeletal pain, increased risk of aspiration, and decreased pulmonary function due to restriction of chest wall movement and decreased inspiratory effort. Currently, measurement and long-term management of postural abnormalities are challenging. A multidisciplinary team effort needs to be initiated to better the management of this chronic condition.

46.5 Systemic Effects

46.5.1 Cancer-Related Fatigue

Cancer-related fatigue is defined as "a distressing persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with

usual functioning" [121]. Data on CRF is scant in the head and neck population; available information indicates high prevalence rates. Up to 50–75 % of HNC patients report fatigue at baseline even prior to intensive chemoradiation therapy [122]. Fatigue in HNC patients is nearly universal, gradually increasing throughout radiation with a peak during the 6th week of radiation therapy [123, 124]. Unfortunately, for many patients, CRF persists above baseline even several years following completion of chemoradiation.

The impact from fatigue on HNC patients' quality of life is profound. The majority of patients demonstrate major shifts in their daily routine with increasing difficulty performing activities of daily living and increasing reliance on their caregivers. An inverse correlation between self-reported fatigue and physical functioning exists [125]. Fatigue has profound emotional outcomes for HNC patients, including social isolation, loss of motivation, and mental exhaustion [126]. A substantial impact on work productivity of cancer patients and their caregivers occurs, with significant economic and financial consequences. On average, caregivers miss 4.5 work days in order to provide assistance for fatigued patients [126].

Treatment of CRF remains a challenge due to the pervasiveness of the symptom. In a study by Vogelzang et al., 50–70 % of patients and their caregivers report discussing treatment of fatigue with their oncologist; however only 27 % of patients reported receiving a treatment for this distressing symptom [127]. In addition, there are discrepancies in fatigue ratings between patients and their physicians, possibly accounting for undertreatment of this condition. General non-pharmacological interventions, such as adapting activities of daily living and employing energy conservation and distraction maneuvers, aid patients and caregivers in coping with their fatigue [128]. HNC patients often experience pain and difficulty with clearing oral secretions, thus interrupting their sleep patterns. Adapting sleep habits with elevation of the head of the bed or sleeping upright in a recliner may alleviate this sleep disruption, lessening their fatigue [129]. HNC patients are at increased risk for obstructive sleep apnea; thus, referral for sleep studies is indicated for any patient with concerning clinical complaints that indicate this as a possible contributing factor to fatigue. Patients, even with limited life expectancy, may benefit by engaging in exercise or receiving physical and occupational therapy [130]. Modifiable comorbidities should be addressed to alleviate their contribution to CRF. As an example, periodic TSH monitoring should occur in HNC patients, intervening with thyroid replacement therapy when posttreatment hypothyroidism is detected [131]. Psychostimulant agents, such as methylphenidate [132] or modafinil, may be considered in cancer patients with severe CRF [133]. Although depression is associated with fatigue, there is mixed data regarding antidepressants for treatment of CRF in patients with comorbid depression or anxiety [134, 135].

46.5.2 Neurocognitive Impairment

Postoperative delirium, particularly in patients with a history of alcohol abuse, has been well recognized. Neurocognitive impairment related to chemotherapy and/or radiation therapy is an underappreciated and understudied complication of head and neck cancer and its treatment [136]. During therapy, neurocognitive impairment may limit a patient's ability to understand, recall, and implement supportive care measures including medication management. In survivors, neurocognitive impairment may impact on the patient's ability to return to previous life activities and to be independent in their day-to-day functioning. Finally, long-term neurocognitive impairment results in decreased quality of life and increased psychological distress [137]. Thus, the early identification and effective management of neurocognitive impairment are critical.

Most studies report neurocognitive functioning in survivors who received radiation, as the single treatment modality for skull base tumors, including nasopharyngeal carcinoma (NPC) and paranasal sinus cancer. These populations were studied because treatment entails incidental radiation to normal brain tissues. Early studies demonstrated that HNC survivors are at risk for late neurocognitive deficits. Lee et al. found that patients ($n = 16$) treated with radiation a median of 5.5 years earlier exhibited lower overall IQ, impaired nonverbal memory recall, and increased self-reports of memory complaints compared to control subjects [138]. In another study, Woo et al. described the development of combined neurocognitive impairment and endocrine dysfunction in 11 patients following radiation therapy for NPC [139]. More recent studies have demonstrated problems in neurocognitive functioning following radiation for HNC despite improvements in treatment techniques (e.g., intensity-modulated radiation therapy [IMRT]). Meyers et al. identified problems with learning and memory in 19 patients who received paranasal sinus radiation; 50 % had difficulty learning new information and 80 % forgot the information over time [140]. Additionally, a third of the patients had difficulty with visual motor speed, executive functioning, and fine motor coordination. Similarly, results were reported by Hsiao et al. [141]. Cheung et al. observed that posttreatment NPC patients without temporal lobe necrosis performed similar to controls, but patients with postradiation necrosis had significant impairments in multiple domains including verbal and visual memory, language, motor ability, planning, overall cognitive ability, and abstract thinking [142]. In contrast, Lam et al. found that NPC patients treated with radiation more than 2 years before exhibited greater memory impairment when compared to controls regardless of evidence of radiation-induced temporal lobe injury [143].

Data on patients treated for non-skull base tumors is scant. A prospective study of 69 HNC patients demonstrated that

47 % of patients had baseline neurocognitive deficits [144]. In addition, a subset of patients developed perceived neurocognitive deficits during CCR [145] and 8.9 % of patients developed syndromal delirium. In addition, 31 % of patients and 43.5 % of caregivers reported at least one episode of subsyndromal delirium during the active and immediate post-treatment period [146]. The impact of neurocognitive and neuropsychiatric symptoms on caregivers was profound.

Multiple factors, including radiation-induced vascular injury and inflammation, radionecrosis, radiation injury to the subcortical white matter, pituitary and hypothalamic dysfunction, cerebral atrophy, and comorbid conditions such as hypertension, diabetes, hyperlipidemia, obesity, and smoking, contribute to the pathogenesis of neurocognitive impairment following radiation-based therapy for HNC [147]. In studies of patients with NPC, neurocognitive impairment was associated with the extent of radiation necrosis [148], the total RT dose [140], RT dose to the temporal lobes [141], volume of temporal lobes receiving >60 Gy [141], and time since treatment [140]. In the study by Cheung et al., patients who were older at the time of radiation therapy had more extensive radiation necrosis. The location of radionecrosis lesions also affected the pattern of neurocognitive impairment [148]. For example, left hemisphere lesions were associated with language deficits and impaired verbal memory, whereas right hemisphere lesions were strongly associated with visual memory impairments.

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Rehabilitation of Heavily Treated Head and Neck Cancer Patients

47

Katherine A. Hutcheson

Abstract

Optimizing functional outcomes of heavily treated head and neck cancer patients requires proactive, multidisciplinary efforts. Multimodality therapy can adversely affect multiple facets of head and neck functioning. Speech and swallowing problems are among the most challenging functional problems to rehabilitate. In this chapter, we provide a comprehensive approach to swallowing rehabilitation for patients treated with chemoradiation for locoregionally advanced stage head and neck cancers. Speech and swallowing rehabilitation models are also illustrated for surgically treated groups including major oral cavity resections and total laryngectomy.

Keywords

Swallowing • Speech • Voice • Chemoradiation • Glossectomy • Laryngectomy

47.1 Introduction

Multimodality therapy provides optimal control of locoregionally advanced head and neck cancers. Yet, survival advantages of aggressive therapies come at a high cost in loss of normal head and neck functions and quality of life. This chapter will focus on rehabilitation of *speech and swallowing function* in heavily treated patients focusing particularly on patients treated with (1) *nonsurgical organ preservation using chemoradiation* and (2) *surgery with adjuvant chemoradiation*. General principles of multidisciplinary rehabilitation in these populations will be presented.

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47.2 Principles of Rehabilitation

47.2.1 Multidisciplinary Team

Multidisciplinary care directed jointly by a head and neck surgeon, radiation oncologist, and medical oncologist is recognized as best practice for oncologic treatment for advanced stage head and neck cancer. This same multidisciplinary approach is required for appropriate rehabilitation. Rehabilitation of heavily treated head and neck cancer patients is a team sport. Heavily treated patients present with coexisting functional problems including among others:

Dysphagia (difficulty swallowing)
Stricture (pharyngeal or cervical esophageal narrowing)
Communication impairment (dysphonia, dysarthria, or resonance disturbance)
Head and neck lymphedema (head and neck swelling)
Trismus (restricted mouth opening)
Neck and shoulder dysfunction (weakness, stiffness, or impaired range of motion)
Salivary dysfunction (xerostomia or thick mucus)
Ototoxicity (hearing loss)

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These multilayered and diverse functional problems require assessment and management by multiple specialists including:

Speech-language pathologists
Physical therapists
Dental oncologists and maxillofacial prosthodontists
Dietitians
Gastroenterologists
Audiologists

This chapter will focus on rehabilitation of *speech and swallowing function*, but it is imperative to screen for and address all affected functional domains to achieve the best quality of life outcomes. Beyond functional limitations, treatment-related symptoms such as pain and fatigue further limit survivors' capacity to perform or enjoy routine daily activities. While beyond the scope of this chapter, proactive symptom management and supportive care, particularly pain management, are critical components of multidisciplinary care necessary to achieve optimal rehabilitation outcomes. For example, prophylactic neuropathic pain management during chemoradiation for oropharyngeal cancer patients has been shown to significantly correlate with better posttreatment functioning [1].

47.2.2 Defining Speech and Swallowing Rehabilitation Targets through Comprehensive Evaluation

Effective rehabilitation begins with a clear therapeutic target (i.e., goal-directed therapy). Multidimensional functional assessment is critical to define what areas of impairment will be targeted in therapy. At a minimum, *physiologic function*, *functional performance* status of the patient (i.e., how an individual routinely eats and communicates in daily life), and *patients' perceived function* should be examined. Components of multidimensional evaluation are illustrated in Fig. 47.1a, and to illustrate this concept, Fig. 47.1b applies this approach to swallow evaluation.

Functional status of the patient pertains to their level of oral intake, their preferred method of verbal or nonverbal communication, and the tracheostomy and gastrostomy status of the patient. During the functional evaluation, each of these factors should be included in the patient history interview. The Performance Status Scale for Head and Neck (PSS-HN) is widely adopted to standardize the rating of the functional status of the patient. This brief, semi-structured interview rates three domains: (1) normalcy of diet, (2) public eating, and (3) understandability of speech. The PSS-HN can be incorporated into the patient's history interview during routine assessment to quantify functional status. Additionally, the tracheostomy and gastrostomy status of the patient should be ascertained.

Measuring the patient's perception of their functioning and quality of life is a critical aspect of patient-centered care. Significant progress has been made in the last 2 decades to develop, validate, and translate patient-reported outcome (PRO) questionnaires for this purpose. Domain-specific measures are available to quantify perceived swallowing function [2–4], speech and voice [5–7], neck/shoulder, dry mouth [8], and symptom burden [9, 10]. Incorporating these questionnaire instruments into routine clinical practice is extremely valuable when establishing patient-centered therapy goals. PRO questionnaires are a standardized way to help clinicians identify the primary concerns of patients.

The pathophysiology of speech and swallowing dysfunction is best detailed on instrumental examinations or imaging studies. Head and neck functions are exquisitely complex

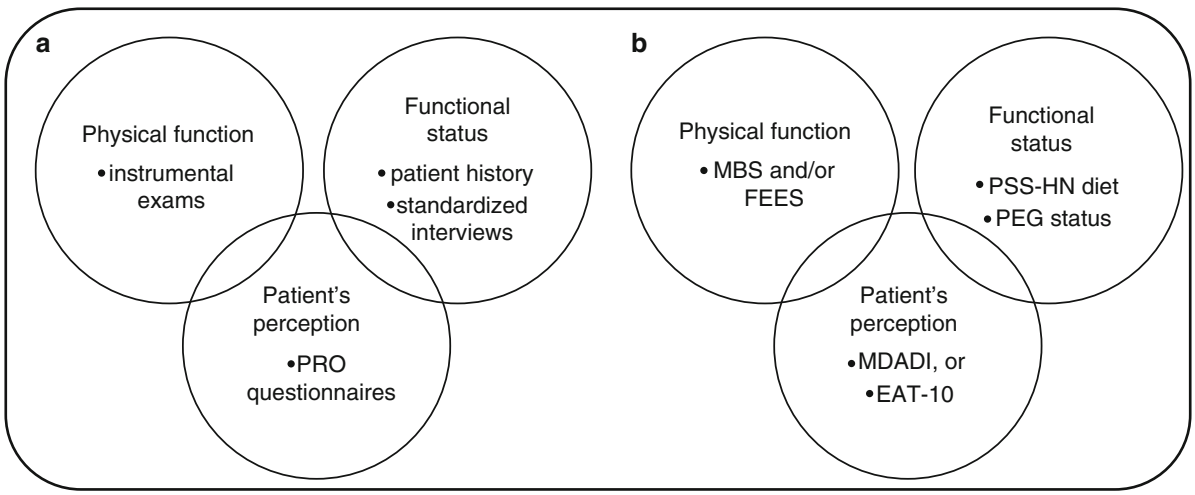

Fig. 47.1 (**a**) Multidimensional assessment panel for speech and swallowing outcomes. (**b**) Multidimensional assessment panel for dysphagia

Table 47.1 Validated measures to quantify results of instrumental functional examinations

Method	Functional domain	Selected Metrics
Videofluoroscopy (aka, MBS)	Oropharyngeal swallow	Dynamic Imaging Grade of Swallowing Toxicity (DIGEST): CTCAE-compatible ordinal grade of pharyngeal swallow safety and efficiency *Oropharyngeal swallow efficiency* (OPSE) [80]: % swallowed/transit time *Penetration–aspiration scale* (PAS) [81]: Ordinal grade of airway entry *MBS impairment profile* (MBSImP) [82]: 17-item summary grade of oral and pharyngeal swallow physiology *Pharyngeal constriction ratio* [83–85]: Area measure of pharynx maximally constricted over maximum pharyngeal space at rest
Fiberoptic endoscopic evaluation of swallowing	Pharyngeal swallow	*Penetration–aspiration scale* [86]: Ordinal grade of airway entry *Patterson edema scale* [87]: Summary grade of edema of laryngopharyngeal structures on endoscopy
Videostroboscopy	Laryngeal function	No validated metric in HNC

Table 47.2 Principles of rehabilitation in heavily treated head and neck cancer patients

- Multidisciplinary care
- Multidimensional evaluation
- Goal directed therapy targets defined by instrumental examination
- Mobilize, early and often
- Task-specific exercise
- Mass practice of functional activity

involving internal structures best visualized using instrumentation. Instrumental examinations, particularly videofluoroscopy (radiographic assessment of swallowing also known as the *modified barium swallow* study) and endoscopy (for dynamic examination of velopharyngeal, pharyngeal, and laryngeal functions), are cornerstones of functional workup before swallow and speech rehabilitation. Validated metrics should be applied to quantify results of instrumental examinations. Selected metrics used to quantify results of instrumental exams are detailed in Table 47.1.

47.2.3 Principles of Rehabilitation of Speech and Swallowing

Principles of rehabilitation are outlined in Table 47.2. Two principal components of effective speech and swallowing rehabilitation of heavily treated head and neck cancer patients are:

1. Mobilization, early and often
2. Mass practice of functional activities

Principles of exercise therapy have been established in the fields of physical rehabilitation, sports medicine, and exercise science. Intensity and specificity are among the most critical features of effective exercise training. Exercises must be specific to the target, for instance, following the clinical adage that "swallowing is the best therapy for swallowing," but must also force the neuromuscular system beyond its usual level of activity. Acknowledging that speech and swallowing are submaximal tasks (i.e., muscular force generated during speech and swallowing is well below the maximum capacity of the system), therapy must push the functional activity beyond conventional intensity. Intensifying the task can be accomplished by (1) more frequent or longer repetitions and/or (2) resistive loading [11].

Resistive loading of speech and swallowing musculature is obviously not as simple as adding another weight to the barbell. The most popular methods used to increase the resistive load of during oropharyngeal muscle exercises are (1) *device-driven* methods and/or (2) *bolus-driven* paradigms.

With *device-driven therapy*, biofeedback or neuromuscular electrical stimulation is applied to augment the intensity of task-specific speech and swallowing exercise. Biofeedback devices like tongue resistance bulbs or surface electromyography take a reading of muscle activity during a functional task. Patients watch their performance in real time and try to meet a specified level of intensity during task-specific exercise. Goals are set based on a percentage of their peak force and increased as strength improves. Exercise principles guide the pace of resistive loading using biofeedback devices. Biofeedback-driven exercise typically starts at roughly 60 % intensity (i.e., 60 % of the patient's maximum ability) and peaks at 80 % intensity [11]. Efficacy of device-driven biofeedback therapies is suggested in a number of case series in patients with dysphagia related to head and neck cancers and other pathologies [12–14].

Neuromuscular electrical stimulation is another device that can be added to conventional exercise therapy with the goal of enhancing neuromuscular recruitment. Conflicting data have been reported with regard to the potential benefit of electrical stimulation as a component of swallowing rehabilitation. Furthermore, a multi-site, randomized, sham-controlled clinical trial found no added therapeutic benefit of NMES over traditional swallowing exercise after chemoradiation [15].

A *bolus-driven* model of progressive resistance dysphagia therapy has been developed and published (the McNeil Dysphagia Therapy Program), whereby clinicians systematically navigate patients up a food hierarchy to increase the workload of swallowing exercise [16]. In bolus-driven

swallowing therapy, patients must master and maintain an ideal swallowing form while increasing the volume and viscosity of what they are eating. Promising results of bolus-driven, daily therapy (over 3 weeks) have been reported in small case series. Bolus-driven methods were found superior to device-driven therapy (using sEMG) in a matched case–control comparison [17].

Regardless of the method or techniques applied, mass practice of functional tasks under conditions that require progressive work over time is the hallmark of successful swallowing rehabilitation programs in heavily treated head and neck cancer patients. Device-driven and bolus-driven therapies are often delivered in a "boot camp" type of schedule in which patients participate in a short, intense series of daily therapy sessions over a 2–3-week period of time. For dysphagia, bolus-driven boot camp models (i.e., MDTP) outperformed device-driven therapy in a matched case–control study. Patients treated with bolus-driven therapy were significantly more likely to have reduced aspiration, less gastrostomy dependence, and better diet levels after therapy compared to those who participated in device-driven therapy with sEMG biofeedback [17]. On the basis of these results and relevance of functionally driven therapy, bolus-driven therapy should be preferred or incorporated into other paradigms whenever possible. Various methods of progressive resistance exercise therapy for dysphagia are depicted in Fig. 47.2.

Speech and swallowing critical muscles of the tongue, larynx, and pharynx are often immobilized for varying degrees of time over the course of multimodality therapy for head and neck cancers. Immobilization of speech and swallowing structures can occur when postsurgical restrictions mandate that patients remain nothing per oral (NPO) or observe vocal rest to allow time for healing after surgery. Immobilization of the head and neck structures also occurs when patients stop eating for prolonged periods of time owing to acute toxicities of chemoradiation that make eating unpleasant (e.g., mucositis and related odynophagia). Regardless the source, immobilization prompts disuse atrophy that encourages adverse remodeling of aerodigestive tract muscles, likely exacerbating edema and fibrosis that result from surgery and/or chemoradiation [17, 18]. Skeletal muscles can begin to show evidence of disuse atrophy just hours after immobilization. Myoarchitecture changes rapidly with disuse showing a decrease in muscle mass, infiltration of adipose tissue, and redistribution of fibers within the muscle. Over time, disuse atrophy manifests as a reduction in muscle strength, increased fatigability, and aberrant motor control. The extent of injury is dependent on the severity of restriction. Thus, early and more frequent mobilization of speech and swallowing muscles (in functional tasks—i.e., starting talking and eating as early as possible) should equate to more normal muscle composition and function after treatment [17, 18]. This premise is supported by prior work in which patients randomized to proactive swallowing exercise during chemoradiation had significantly less deterioration in muscle mass and composition per T2-weighted MRI analysis of the genioglossus, hyoglossus, and mylohyoid after chemoradiation [12].

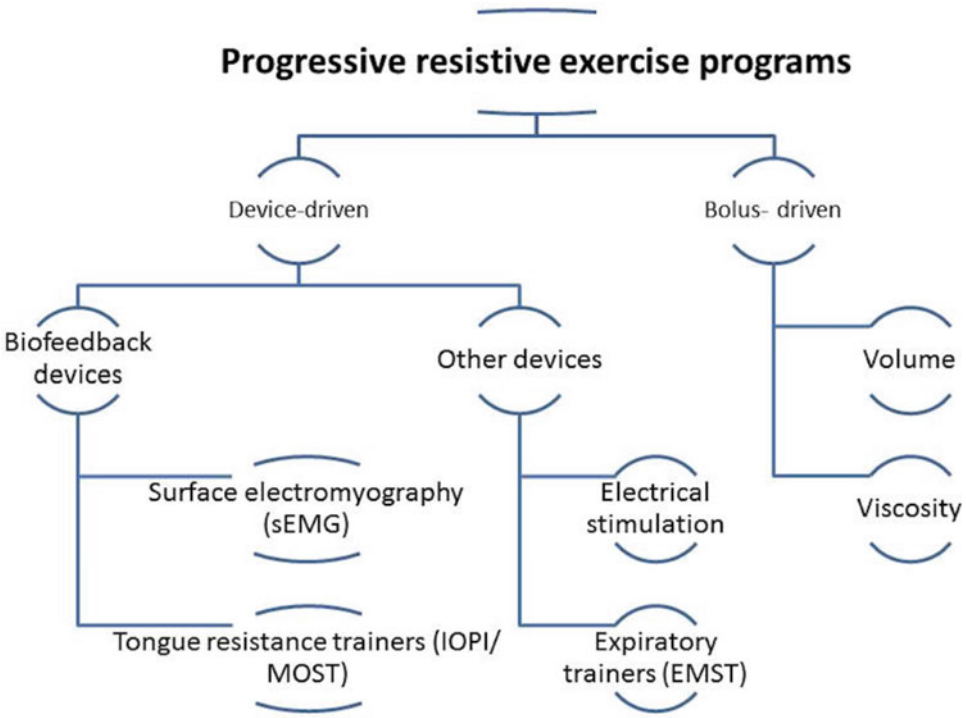

Fig. 47.2 Progressive resistive exercise programs for dysphagia sEMG, surface electromyography IOPI, Iowa Oral Pressure Instrument MOST, Madison Oral Strength Trainer EMST, expiratory muscle strength trainer

47.3 Chemoradiation

Dysphagia is a dose-limiting toxicity of chemoradiation for head and neck cancers. Dysphagia is also the primary functional concern of patients treated with nonsurgical therapy [18], drives perception of QOL after chemoradiation [19], and significantly predicts for pneumonia in long-term survivorship [20]. In addition, objective measures of dysphagia per videofluoroscopy are stronger predictor of long-term quality of life after chemoradiation than xerostomia [19]. Thus, swallowing rehabilitation is the focus of this section pertaining to the chemoradiated head and neck cancer patient.

Great strides have been made in delivery of chemoradiation. Highly conformal methods of radiotherapy have been developed (e.g., dysphagia-optimized IMRT and proton therapy) to minimize dose to nontarget swallowing critical structures, and targeted agents show promise to lessen mucosal toxicities when compared to conventional cytotoxic agents [21–24]. Yet even in modern practice, at least half of patients require a feeding tube during chemoradiation [25, 26]. More alarmingly, still up to 30 % of survivors develop chronic aspiration, even after dysphagia-optimized IMRT incorporating dose constraints to the pharyngeal constrictors and larynx [24, 25].

Classically, *radiation-associated dysphagia (RAD)* develops during chemoradiation as an acute toxicity of treatment. The majority of patients who develop acute RAD will experience partial recovery of swallowing function. That is, most regain an acceptable but not normal level of swallowing function (i.e., "the new normal"), while a smaller minority suffer clinically significant levels of chronic dysphagia as consequential late effect of acute toxicities of aggressive therapy. The degree of recovery is highly dependent upon tumor burden and baseline functionality, treatment intensity (radiation particle, dose-volume distribution, systemic therapy), and supportive care. Among patients with primary tumors of the oropharynx, it is estimated that 7–31 % develop chronic aspiration [24, 27], 11 % develop aspiration pneumonia [20], and 4 % are chronically feeding tube dependent after chemoradiation [28]. Among patients with cancers of the larynx or hypopharynx, it is estimated that 22–30 % develop chronic aspiration/pneumonia [29, 30], and 5 % are chronically feeding tube dependent [29].

47.3.1 Pathophysiology of RAD

Normal tissue effects that drive RAD occur along a continuum, but features predominate in each phase of survivorship (Fig. 47.3). In the early months after chemoradiation, the dysphagia–aspiration-related structures (DARS), i.e., the constrictors and larynx, in the field of radiotherapy become edematous but then stiffen over time as fibrosis sets in as chronic sequela of treatment. Acute and persistent RAD in the first year or so of survivorship has traditionally been thought to reflect varying degrees of muscle edema, subcutaneous fibrosis, and disuse atrophy [31]. Neuropathic injury is also noteworthy when considering the source of RAD. Delayed mono- or polyneuropathies of the lower cranial nerves, while rare, appear to be a major contributor to late-onset radiation-associated dysphagia [32, 33]. Regardless of the pathology, the end result of edema, fibrosis, or neuropathy is reduced mobility of critical laryngeal and oropharyngeal structures (i.e., the DARS). In videofluoroscopic studies, it is estimated that tongue base retraction, hyoid excursion, laryngeal lift, and pharyngeal contraction are abnormal in between 50 and 75 % of patients who have been previously treated with chemoradiation [34, 35]. Collectively, these normal tissue changes ultimately impair supraglottic closure and pharyngeal propulsion in most survivors who experience RAD.

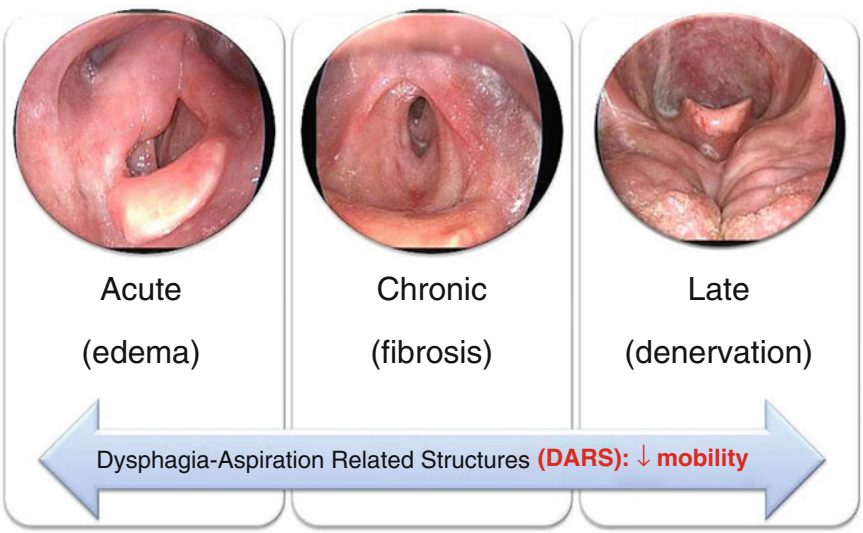

Fig. 47.3 Pathophysiology of radiation-associated dysphagia

47.3.2 Stricture After Chemoradiation

It is a common misconception that stricture is the primary driver of dysphagia after chemoradiation. A recent meta-analysis reported a 7 % summary risk estimate of stricture after head and neck radiotherapy, suggesting that stricture is the source of dysphagia in a small minority of patients [36]. Notably, stricture was more common in the IMRT era (17 %) and in studies that prospectively ascertained outcomes (19 %). Common symptoms of stricture include solid foods sticking in the distal pharynx or sternal region, inability to swallow pills, and difficulty belching or vomiting. Suspicion for stricture should be heightened in patients with a history of hypopharyngeal cancer requiring high target doses of radiotherapy to the esophageal inlet as well as patients who had prolonged intervals (3+ months) with high-grade mucositis or nothing by mouth [37, 38]. Stricture should be confirmed on fluoroscopic examination and/or by endoscopy.

Stricture is treated with esophageal dilation. Only mild, focal strictures respond sufficiently to a single dilation procedure. Serial dilation is required for more complex or severe strictures. Stricture almost always presents with coexisting physiologic impairments in the propulsive phase of swallowing. As such, dilation alone rarely fully rehabilitates the swallow. Persistent aspiration and pharyngeal weakness often necessitate behavioral dysphagia therapy with a speech pathologist even after successful dilation. It is often advocated to "optimize structure" before beginning conventional dysphagia therapy with swallowing exercise and compensatory techniques. Under this therapeutic philosophy, it is customary to dilate first before starting aggressive behavioral therapy. That said, it is prudent still to avoid prolonged immobilization of the pharynx while waiting for the dilation procedure. Thus, a good compromise is to train a home program of swallow exercises and encourage any safe oral intake while the patient is waiting to be dilated. Then, schedule the patient for instrumental swallow examination shortly after dilation (ideally within a week) to reassess and establish a plan for more intense oropharyngeal swallowing therapy and particularly to resume oral intake as quickly as possible after dilation in a patient who has been NPO.

47.3.3 Preventive Swallowing Therapy: Eat and Exercise

Preventive swallowing therapy is considered best practice for patients treated with curative chemoradiation for head and neck cancer. Acute toxicities of chemoradiation including mucositis, salivary dysfunction, and dysgeusia make eating unpleasant. For this reason, at least half of patients require feeding tube placement to get through treatment, and the vast majority stop eating solid foods. It is suggested that loss of the normal resistive load on the pharyngeal musculature that occurs when patients stop eating heavy foods prompts varying degrees of disuse atrophy. Thus, the central premise of proactive swallowing therapy is "use it or lose it" to mitigate muscular wasting and remodeling that occurs after even brief intervals of disuse. Preventive or proactive swallowing therapy encourages maximal use of the swallowing musculature during treatment by (1) avoiding NPO intervals and (2) adhering to swallowing exercise. The benefits of these swallowing activities (*eat* and *exercise*) are reported by numerous investigators, in randomized trials and observational studies.

Three randomized trials have shown a benefit of *preventive swallowing exercise* during chemoradiation. A sham-controlled trial found a 36 % absolute risk reduction for loss of functional swallow ability in patients randomized to active swallow exercise during chemoradiation. Other favorable outcomes reported in association with preventive exercise include superior swallowing-related quality of life [39, 40]; better tongue base and epiglottic inversion [41]; larger post-chemoradiation muscle mass and T2 signal intensity on MRI of the genioglossus, mylohyoid, and hyoglossus muscles [42]; shorter duration of gastrostomy [43]; and greater return to normal oral diet levels [43].

Observational studies also suggest the benefit of maintaining any oral intake during chemoradiation (i.e., avoidance of NPO intervals). Even brief NPO intervals of just 2 weeks have been shown to significantly and independently predict lower swallowing-related quality of life scores in long-term survivorship after chemoradiation (median, 4.7 years) [44]. Multidisciplinary management of acute chemoradiation toxicities including pain, mucositis, odynophagia, dysgeusia, weight loss, and dysphagia is necessary to help patients safely maintain oral intake. Prophylactic neuropathic pain management has also been associated with lower pain scores, decreased PEG utilization, and decreased aspiration after chemoradiation [1]. Authors of this study posited that optimization of pain management allowed patients to keep eating and adhere to exercises and ultimately conferred a physiologic advantage in preserved swallowing function.

Many patients ask if they can just eat *or* exercise. That is, if they are eating throughout chemoradiation, they (reasonably) want to know if there is any added benefit to doing swallowing exercises—or conversely, if they are doing their swallowing exercise, is there any reason to keep up with PO intake? Multivariate models suggest that eat and exercise independently and significantly predict for better short- and long-term functional outcomes. That is, patients who both *eat and exercise* during chemoradiation do better than those who do either—and those who *eat or exercise* do better than those who do neither [43].

A practical, evidence-based approach to implement preventive swallowing therapy includes:

1. Pretreatment referral to speech pathologist: For baseline evaluation (preferably via instrumental examination) and training on swallow exercise
2. On-treatment swallowing therapy with speech pathologist: At minimum, mid-RT and end-RT sessions to monitor swallowing function and adjust swallow exercise program as needed as toxicities increase
3. Speech pathology evaluation (preferably via instrumental examination) posttreatment

47.3.4 Reactive Therapy

Persistent RAD after chemoradiation is a challenging clinical problem. While to some degree RAD is irreversible, intensive swallowing therapy has been shown to optimize functional status and quality of life of the patient with persistent posttreatment RAD [12, 17, 45]. That is, most patients with persistent posttreatment RAD will have longstanding physiologic dysphagia but can learn in therapy how to better compensate the problem. This includes learning techniques (commonly referred to as compensatory strategies) to help minimize or clear aspiration and/or to improve swallowing efficiency (i.e., how much and how fast one can eat). Because aspiration is extremely common in patients with moderate to severe persistent RAD, a major therapeutic goal is to maximize quality of life while simultaneously minimizing the risk of life-threatening aspiration pneumonia.

Patients experiencing persistent posttreatment RAD need a thorough multidimensional functional evaluation (including instrumental examination) once the acute toxicities of chemoradiation have started to reasonably abate. As previously described, therapeutic targets must be clearly delineated and driven by understanding the pathophysiology of RAD from the instrumental testing. While many disorders may be evident on videofluoroscopy or endoscopy, clinicians must strive to seek out targets using these primary questions:

- What's the primary source of RAD?
- What's changeable about the swallow?
- What's trainable?

In addition, patients' goals and priorities must be incorporated into the treatment plan. Data from the standardized interview and PRO inventories are helpful to understand the patient's perception of the problem and high-burden or high-concern areas.

Posttreatment swallowing therapy may incorporate:

1. Swallowing exercise (without bolus)
2. Bolus-driven or device-driven exercise (i.e., a progressive resistance paradigm)
3. Training on compensatory strategies to minimize aspiration or improve bolus clearance (i.e., improve safety and efficiency of transport)
4. Esophageal dilation

Published literature shows no single best approach to dysphagia therapy for persistent posttreatment RAD. In current practice, dysphagia therapy remains highly individualized, and in the absence of many comparative dysphagia rehabilitation trials, best practice dictates beginning with a comprehensive evaluation and adhering to established exercise principles previously outlined in this chapter.

47.3.5 Late-RAD

Acute toxicities are now characterized extremely well with prospective data [46]. The same is not true for late effects of chemoradiation. Prospective late-effect data are rare and are certainly not available among patients treated with highly conformal radiotherapy or targeted therapies. Most data are derived from single-institution cross-sectional samples or small case series. Commonly referenced on this topic is Machtay's pooled analysis of three RTOG chemoradiation trials finding that 43 % of patients who had adequate baseline function suffered grade 3–4 (severe) late laryngopharyngeal toxicity attributable to treatment, most commonly manifesting in chronic gastrostomy dependence [47]. Dysphagia was also a substantial issue encountered in a prospective late-effect clinic of 5-year survivors of accelerated radiotherapy with concurrent cisplatin; 23 % had silent aspiration and 85 % had restricted diets [48]. Notably, both of these studies report findings of 2D and 3D conformal methods that have largely been replaced by IMRT and now in some centers proton therapy. These data also do not distinguish chronic/persistent late dysphagia from late-onset dysphagia, and there appear to be striking, clinically significant distinctions in these conditions.

Late-onset radiation-associated dysphagia (late-RAD) is a particularly challenging form of dysphagia in long-term survivors. Late-RAD has a different time course than classic RAD. With late-RAD, patients enjoy adequate functioning for many years after chemoradiation before presenting back with clinically significant delayed onset or progressing dysphagia. In the initial case series reporting late-RAD [33], median latency was 9 years, and late-RAD was commonly precipitated by delayed onset of lower cranial neuropathies in long-term oropharyngeal cancer survivors

Table 47.3 Radiation-associated dysphagia (RAD)

	Classic RAD	Late-RAD
Onset	Acute or persistent consequential late effect	Delayed (typically 5+ years)
Pathophysiology	Edema, fibrosis	Fibrosis, delayed lower cranial neuropathy
Stricture	Site dependent risk	Rare

(likely related to a survival bias from HPV attributable disease). Late-RAD is presumably rare with an estimated prevalence <10 % in the first 10 years of survivorship, but it is associated with significant dysfunction that is refractory to conventional nonsurgical therapies. Silent aspiration and pharyngeal paresis are the norm in patients with late-RAD. Bleak outcomes of late-RAD (66 % prevalence of pneumonia in late-RAD series) and limited functional gains observed to date with conventional therapy motivate investigations into novel therapies. In the meantime, a major focus of therapy for late-RAD is helping patients make informed decisions about balancing quality of life while managing risk of life-threatening pneumonia from chronic (often severe) aspiration. Table 47.3 overviews various forms of RAD.

47.4 Primary Surgery

Major surgery for resection of primary head and neck tumors clearly adds a layer of complexity to the rehabilitation needs of patients treated with multimodality therapy for locally advanced head and neck cancers. Primary surgery followed by chemoradiation is routine for patients with advanced oral cavity cancers, as well as those with laryngeal or hypopharyngeal cancers not amenable to nonsurgical therapy, thus mandating total laryngectomy or laryngopharyngectomy. Rehabilitation considerations for these two populations will be reviewed in the following sections: (1) oral cavity resection with laryngeal preservation followed by adjuvant (chemo)radiation and (2) total laryngectomy or laryngopharyngectomy after (chemo) radiotherapy failure or with adjuvant (chemo)radiation.

Functional outcomes after head and neck surgery vary widely. Primary factors that affect postsurgical functional outcomes are (1) location/size of resection, (2) surgical approach, (3) closure technique, and (4) management of the neck.

- *Location*: It is natural that the size and location of the primary tumor will dictate the type and extent of functional change postsurgically. Functional loss after surgery can be predicted by asking: (1) What is the functional role of the structure to be resected? How much will be resected (per T stage)? Does the surgical bed extend to relevant adjacent structures? Extension of the surgical bed to adjacent, functionally relevant structures will also increase the likelihood or degree of functional problems.
- *Approach*: Open surgical procedures via a transmandibular or transoral approach damage functionally relevant structures adjacent to the primary tumor. Among these, suprahyoid elevators in the floor of mouth region are commonly disrupted in conventional open resections with downstream effects on airway closure and esophageal opening. Functional advantages of transoral resections have been demonstrated in many comparative observational studies. One of the most common themes to emerge is earlier functional recovery after transoral surgery compared to conventional surgery. Long-term comparisons are sparse, but superior long-term outcomes of transoral versus open surgery are suggested in published studies.
- *Closure*: Closure techniques that do not tether or restrict mobility of remnant structures create the best functional outcome. When reconstruction is required to cover vessels or fill a large defect, the ideal balance is to reconstitute the missing bulk while retaining as much mobility as possible in the remaining structures.
- *Neck*: It is generally accepted that an adjuvant neck dissection imparts added morbidity, particularly in the areas of neck fibrosis, lymphedema, range of motion, and ultimately quality of life. Downstream functional implications on speech and swallowing function are less clear.

47.5 Oral Cavity Resections with Postoperative (Chemo)Radiation

Surgical resection remains the primary treatment for most primary oral cavity cancers, and adjuvant (chemo)radiation is standard for advanced stage disease. The most commonly expected functional problems after oral resection with adjuvant therapy are related to speech production and swallowing (both oral and pharyngeal phases).

47.5.1 Speech Rehabilitation After Oral Resection

Speech production is dependent on four processes: respiration, phonation, resonation, and articulation. Each process involves precise biomechanical coordination of multiple structures in the oral cavity and aerodigestive tract. Speech production is most adversely affected when oral cavity resections involve the mobile tongue or extend posteriorly to include the soft palate. Oral cavity cancers involving the tongue most commonly impair articulation. A published systematic review of the literature suggested that speech is

largely understandable (92–98 % intelligible at the sentence level per blinded ratings) for the majority of surgically treated patients with advanced stage oral cancer (tumor stage ≥2), including those with tumors involving the tongue. Data suggest that most patients will ultimately acquire acceptable intelligibility after partial or hemiglossectomy procedures that preserve 50 % or more of the native tongue, but outcomes are highly variable after subtotal and total glossectomy [49]. When intelligible, speech is still not normal. Most patients had long-standing, deviant speech characteristics that correlated with the extent of resection.

Treatment of oral cavity cancers can also disrupt speech resonance. Resection of maxillary cancers causes significant rhinolalia until the oronasal defect is adequately sealed. Acceptable speech quality is achieved in most patients after successful prosthetic obturation or surgical reconstruction of the oronasal defect [50, 51], but surveys find that self-reported speech function is still significantly lower in maxillary cancer patients relative to controls [52]. It must be expected that obturation (whether prosthetic or surgical) will be less successful when the defect extends to involve the soft palate because of the dynamic role of the soft palate in velopharyngeal closure [53]. For this reason, while counterintuitive, obturation (and velopharyngeal reconstruction) can be more successful with complete resection/obturation of the soft palate in lieu of attempting to spare a small remnant of native soft palate.

Speech rehabilitation for patients with postoperative dysarthria teaches compensatory mechanisms of articulation that rely on exaggeration of the uninvolved labial, mandibular, pharyngeal, and laryngeal structures. Glossectomy-specific compensatory phonetic strategies pioneered by the work of Skelly et al. in the 1970s remain useful in contemporary practice [54, 55]. Articulation targets are selected on the basis of standardized articulation batteries such as the Fisher–Logemann Test of Articulation. After glossectomy, findings of articulation testing are also useful to plan or adjust the shape and design of palatal augmentation prostheses. Palatal augmentation prostheses are made by maxillofacial prosthodontists to improve the accuracy of consonant production and can normalize vowel production by reshaping the contour of the hard palate for better contact by the surgically altered tongue [56]. A systematic review that evaluated studies over more than 35 years found that palatal prostheses improve objective ratings of both speech and swallowing functions in roughly 85% of patients. Published data also suggested an inverse relationship between the efficacy of a palatal prosthesis and mobility of the residual tongue. That is, the likelihood of improving speech with a palatal prosthesis is less favorable as the mobility of the residual tongue increases [57]. It is a general rule of thumb that most patients with more than 50 % of the native, mobile tongue preserved do not benefit from a palatal augmentation prosthesis.

47.5.2 Swallowing Rehabilitation After Oral Resection

Oropharyngeal swallowing function can be impaired by the direct effects of oral resection on oral preparatory functions (i.e., mastication, collecting a bolus in the mouth) and oral transit functions (i.e., posterior propulsion from the mouth to the pharynx). Oral cavity resection can also indirectly affect pharyngeal bolus transit by way of premature spillage that accompanies the loss of oral control, decreased lingual driving pressure on a bolus through the pharynx, or loss of stabilization of the hyolaryngeal complex required for airway closure and upper esophageal opening. Swallowing, particularly pharyngeal stage function, is further disrupted by adjuvant radiotherapy or chemoradiation, as has been previously detailed in this chapter. Data from a systematic review suggest that swallowing efficiency is commonly impaired after surgical management of advanced stage oral cancers (i.e., prolonged bolus transit times and incomplete bolus clearance), but chronic aspiration is a less common consequence of surgical management (12–25 % prevalence) [49]. Therefore, it is not surprising that patients surgically treated for oral cavity cancer perceive the greatest degree of trouble swallowing dry or hard foods when polled about specific dysphagia symptoms [58].

Because most patients with locally advanced disease necessitating multimodality therapy require larger resections and associated reconstruction of the surgical defect, they are NPO for a period of at least several weeks after surgery while the flap heals. In this scenario (where a patient is NPO for several weeks after oral resection and postoperative radiotherapy is anticipated), swallowing rehabilitation then follows these logical steps:

1. *Saliva management*: Saliva swallows are functional swallows. Patients should be encouraged to start swallowing their saliva (rather than exclusively suctioning) within a few days of surgery, often long before they are cleared for oral intake. Those with limited tongue mobility can benefit from training in a "slurp–swallow" combination.
2. *Reintroduce oral intake*: A patient is ready to eat when (1) the surgical anastomosis has healed and (2) the oropharyngeal swallow is safe (for at least some textures). Videofluoroscopy is ideal to test both of these factors (i.e., to simultaneously rule out leak and rule out aspiration) and thereby to determine a patient's readiness for oral intake after major oral resection. In addition to imaging the postsurgical bed with contrast to rule out leak (as indicated by abnormal extravasation of contrast into oral soft tissues), MBS allows the clinician to test in real time the efficacy of swallow therapies (such as head rotations, supraglottic swallow strategies, adaptive equipment, or thickener) to identify any means by which oral intake can be safely delivered when aspiration is detected

(as is expected in patients with subtotal/total glossectomy or large field composite resections). Most patients are ready for their first MBS by 10–20 days postsurgically, with studies delayed 4–6 weeks for extremely complex cases or in patients with prior radiotherapy to the head and neck. While some patients may have oropharyngeal dysphagia sufficient to require ongoing feeding tube support, the goal of the first MBS is to find something that they can safely begin swallowing for practice.

3. *Increase volume then complexity of oral intake*: Surgically treated patients with advanced stage oral cavity cancers often initially resume oral intake of a quite limited range of textures (e.g., only liquids or very runny pureed foods) and often in quite limited amounts. The end goal is to normalize their diet as much as possible. Normalizing the diet is not simply getting back to solid foods but also normalizing how much ("volume") and how fast one can eat. After reintroducing oral intake, the focus becomes increasing the volume of oral intake of those consistencies that were safely swallowed on MBS, followed by increasing the complexity of intake; this may include advancing patient to chewable foods or (if once restricted from liquids) moving back to thin liquids (if previously aspirated). The length of this stage of rehabilitation varies, but one should strive to advance oral intake, both volume *and* complexity, as much as possible before the patient begins adjuvant radiation. Mass practice of functional swallows is the hallmark of this phase.
4. *Preventive swallow therapy during adjuvant radiotherapy*: Two goals take focus during adjuvant therapy—eat and exercise. The approach to preventive swallowing therapy during adjuvant radiotherapy is no different than the approach previously described for patients receiving definitive chemoradiotherapy. Two goals are outlined: (1) eat (maintain oral intake throughout radiotherapy) and (2) exercise (adhere to swallowing-specific exercises). The obvious caveat is that these goals are carried out in the context of any preexisting postsurgical dysphagia.
5. *Posttreatment swallowing therapy*: Persistent dysphagia after surgery and adjuvant radiotherapy can vary significantly in its severity and presentation. Rehabilitation needs are driven by the functional profile of the patient and findings of the posttreatment MBS study. Methods and principles of swallowing therapy in this interval of care follow those previously outlined in the section entitled "Reactive Swallowing Therapy."

47.5.3 Surgical Considerations to Optimize Functional Outcomes After Glossectomy

Reconstructive factors associated with functional outcomes include sensory repair and the contour and volume of the flap. Intraoral sensation has been shown to correlate with functional outcomes including pharyngeal swallowing competency [59, 60]. While sensory reinnervation is highly feasible during microvascular reconstruction, published studies report conflicting results regarding the functional advantage of this technique. For instance, objective swallowing ratings (per MBS studies) did not differ after sensory reinnervation in a prospective functional analysis of 44 surgically treated oral cancer patients [61]. In contrast, Yu et al. [62] found significantly higher diet levels in patients with reinnervated ALT flaps compared with those with noninnervated flaps after near-total or total glossectomy. Regardless, authors have advocated that a relatively simple reinnervation procedure improves intraoral sensation and should be attempted when possible [63]. The shape and volume of the reconstructed tongue have also been shown to affect postglossectomy functional outcomes. Reconstructed flaps that are protuberant or semi-protuberant and those with greater volume are associated with significantly better speech intelligibility and dietary outcomes [64]. On the basis of these findings, some advocate for overcorrection of the defect to account for the expected volume loss associated with postradiation atrophy and fibrosis. Finally, the utility of laryngeal suspension in patients requiring total or subtotal glossectomy has been demonstrated both to help protect the airway from aspiration and to prevent prolapse of the flap [64, 65].

47.6 Total Laryngectomy with Prior or Adjuvant (Chemo)radiation

Total laryngectomy results in a number of lifelong functional changes. Chief among these are:

- Creation of a permanent tracheostoma through which the patient breathes
- Loss of the laryngeal speaking voice
- Separation of the upper airway and digestive tract from the lower airway

Comprehensive rehabilitation addresses at a minimum these primary functional issues. Secondary issues that may also require attention include anosmia (loss of smell), dysgeusia (change in taste), lymphedema, and body image concerns.

47.6.1 Airway

Overwhelming evidence suggests that early fitting of a heat–moisture exchanger (also known as a "humidifilter" or "HME filter") is best practiced in postlaryngectomy rehabilitation. Positive effects of HME use include significantly less cough and bronchorrhea [66]. A variety of HME systems are commercially available. Components of the HME system

include a tracheostoma attachment (tube, button, or adhesive) and a disposable HME cassette (generally exchanged every 24 h). HME systems are compatible with tracheoesophageal voice prostheses and hands-free valves.

47.6.2 Swallowing

Postlaryngectomy dysphagia is often overlooked because surgical separation of the airway and digestive tract prevents aspiration in its conventional form. Numerous studies, however, suggest that roughly half of patients experience clinically detectable levels of dysphagia after total laryngectomy [67–69]. Removal of the hyoid and larynx alters normal upper esophageal opening. Without the anterior hyoid traction, the UES is no longer actively pulled open. Instead, the UES opens only by relaxation of the cricopharyngeus (if no myotomy) and by bolus pressure. So, there is more resistance on the bolus when it is leaving the pharynx and entering the esophagus (i.e., "outlet obstruction"). Disruption of the pharyngeal constrictors also results in less propulsive force on the bolus. Postlaryngectomy manometry depicts these changes quantitatively as less "push" (i.e., lower pharyngeal propulsive pressures) and more "resistance" (i.e., greater UES intrabolus pressures) when comparing to normal controls [70]. The aberrant pressure patterns depicted in postlaryngectomy manometry translate to impaired swallowing efficiency. Propulsive issues may be responsive to tongue resistance and base of tongue exercises. Postlaryngectomy stricture is estimated to occur in 19 % of patients but is significantly more common in certain high-risk groups. Almost half of patients requiring tubed pharyngeal reconstruction after salvage laryngopharyngectomy for radiation failure were found to develop stricture in a single-institution series [71]. Postlaryngectomy stricture is managed well in most patients by esophageal dilation. Refractory strictures may require surgical resection and pharyngoesophageal reconstruction. Postlaryngectomy stricture significantly complicates voice restoration since swallowing and voice rely on a common tube after laryngectomy.

47.6.3 Alaryngeal Voice

After laryngectomy, verbal communication is restored using three major approaches: (1) the artificial larynx or electrolarynx, (2) esophageal speech production, and (3) tracheoesophageal (TE) puncture. Mobile applications on modern tablets and smart phones can provide sophisticated nonverbal means of communication; however, the state of the field is such that with rare exceptions no patient who desires it should be without some means of verbal communication in current practice.

- *Electrolarynx*: The electrolarynx, or artificial larynx, as shown in Fig. 47.4, produces vibratory sound using an

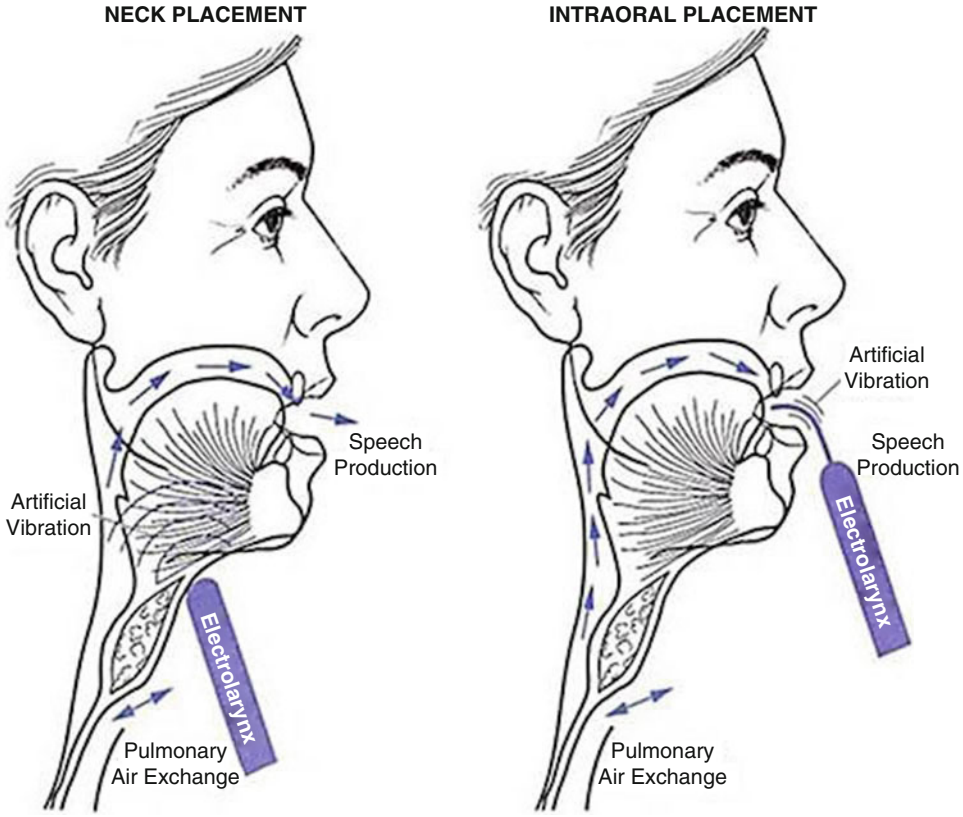

Fig. 47.4 Electrolarynx or artificial larynx

external, mechanical sound source placed intraorally or against the neck. Regardless of the ultimate method of voice restoration, all laryngectomized individuals should be encouraged to learn to use an artificial larynx because it provides a simple means of immediate verbal communication and requires little maintenance. The use of the electrolarynx does not interfere with subsequent development of esophageal or TE speech. Despite the advances in alaryngeal voice restoration, particularly TE voice restoration, the electrolarynx remains the most commonly used method of alaryngeal communication worldwide [72].

- *Esophageal speech*: For most of the twentieth century, esophageal speech production was a primary method of alaryngeal speech rehabilitation. The esophageal speaker learns to transfer ambient air from the oral cavity into the esophagus for vibration of the pharyngoesophageal walls to provide a sound source for speech production. Although esophageal speech production provides the advantage of oral communication without any secondary device (i.e., no electrolarynx or prosthesis), it is rarely the primary method of voice restoration in current practice in North America and Europe. Esophageal speech fell out of fashion as the primary method of voicing with the rising popularity of TEP because it is comparatively slower to learn and yields lower capacity speech. Conservative estimates suggest that it takes 4–12 months of consistent therapy and daily practice to learn esophageal speech, and less than 30 % of patients eventually acquire functional esophageal speech production, and comparisons show esophageal speakers have less volume and durability of voice compared to TE speakers [73–75]. Esophageal speech may still be the best option for select subgroups of patients such as those who are not surgical candidates for TEP but have viable sound production of the pharyngoesophagus. Figure 47.5 illustrates the method of esophageal speech production.
- *Tracheoesophageal puncture (TEP)*: TEP has been widely adopted in North America and Europe since its first report by Singer and Blom in 1979 [76]. TEP is now considered by many to be the gold standard method of postlaryngectomy voice restoration. Its popularity is based on several key advantages over other methods. TEP is associated with (relatively) fast voice restoration, provides a nonmechanical sound, and has vocal parameters most comparable to natural laryngeal speech (in quality, fluency, and intensity). TE voice restoration, however, comes at a cost because it relies on surgical creation of a controlled TE fistula (referred to as the TEP). A unidirectional valved prosthesis is required to maintain the TEP. The valve of the prosthesis remains closed to protect the airway aginst aspiration during swallowing and opens to divert pulmonary air across the pharyngoesophageal mucosa for phonation when the tracheostoma is occluded. The resulting sound is shaped into words by articulatory movements of the structures of the oral cavity. The tracheostoma can be manually occluded by the patient or automatically occluded by means of a hands-free valve to shunt air into the pharyngoesophagus for sound production. TE voice restoration and methods of stomal occlusion are shown in Fig. 47.6. Thus, TE voice restoration necessitates a secondary surgical procedure, periodic replacement and daily care of a voice prosthesis lifelong, and reconnection of the airway and digestive tract (thus, reintroducing the risk of postsurgical aspiration). Feasibility of TEP in heavily treated patients such as those with a history of (prior or postoperative) chemoradiation and those requiring laryngopharyngectomy has been demonstrated empirically and in published series [77]. It is generally accepted that these treatments affecting the vibratory parameters and health of the pharyngeal soft tissues will adversely impact the functionality (swallowing and TE voice quality) and elevate the risk of TEP-related complications (such as widening or enlargement of the fistula) [78]. Thus, appropriate counseling and patient selection are critical to optimize TEP success in the heavily treated patient. Procedural and practical guidelines on TEP management are beyond the scope of this chapter, and the reader is referred to extensive work in this area [77, 79].

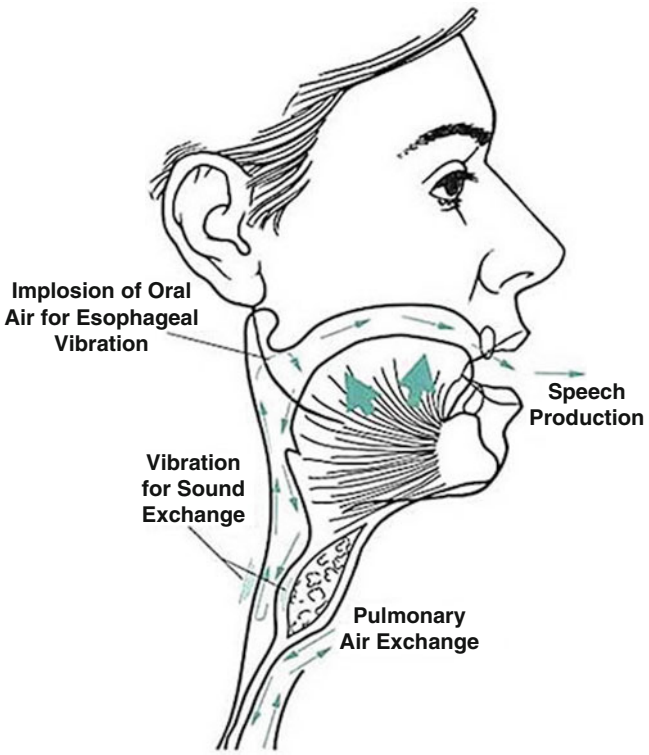

Fig. 47.5 Esophageal speech

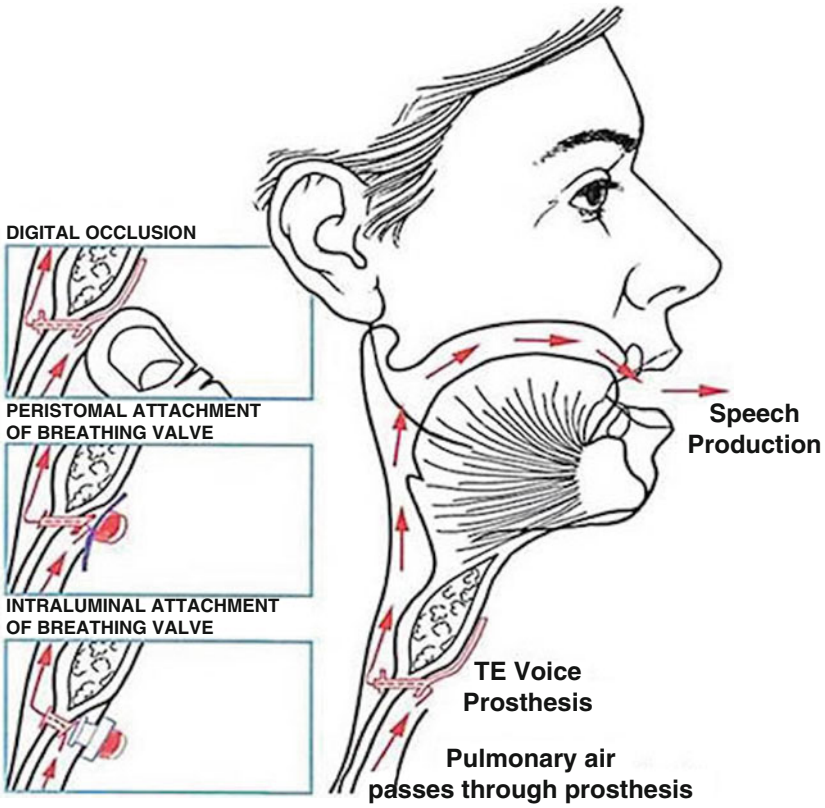

Fig. 47.6 Tracheoesophageal puncture (TEP)

47.7 Conclusions

Speech and swallowing function drives quality of life in heavily treated head and neck cancer patients. Effective speech and swallowing rehabilitation is required to optimize the quality of head and neck cancer survivorship. Proactive, multidisciplinary rehabilitation should begin early in the trajectory of care. Goal-directed therapies should target abnormalities detected on multidimensional evaluation panels combining complementary data from patient-reported outcome questionnaires and instrumental examinations. While rehabilitation paradigms are highly personalized based on the specific treatment history and priorities of the individual patient, evidence-based principles of exercise therapy should be applied to guide best practice in rehabilitation sciences.

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Salvage Therapy in Head and Neck Cancer Patients

48

John Heaphy, Rod Rezaee, and Pierre Lavertu

Abstract

This chapter discusses the unique challenges in the diagnosis, workup, treatment, and follow-up of patients who may have, or have failed, chemoradiation protocols. The role of various imaging modalities, particularly PET scanning, is reviewed. Surgical salvage in this population is emphasized, addressing the extent of resection both at the primary site and the neck and the surgical complications encountered in this population. Options for surgical reconstruction are discussed, including free tissue transfer.

While surgical salvage is the main focus of this chapter, other salvage modalities available to patients who have been previously chemoirradiated are examined. These include re-irradiation with or without chemotherapy, brachytherapy, and photodynamic therapy. Finally, the treatment outcomes with respect to morbidity and mortality in this population are reviewed.

Keywords

Salvage surgery • Chemoradiation • Head and neck reconstruction • Neck dissection • PET scanning • Re-irradiation

Key Points

- Most tumor recurrence occurs in the first 2 years after treatment. Any suspicion of a tumor should prompt further evaluation. This involves endoscopy, biopsy, and/or imaging.
- Due to the very high negative predictive value of PET scanning, many centers now defer planned neck dissection after chemoradiation in favor of careful observation if the 12-week posttreatment PET scan is negative.
- Biopsy of recurrent disease can yield false-negative results.
- Recurrent head and neck carcinomas often display different growth patterns compared with primary carcinomas—they tend to be multifocal and submucosal.
- The use of free flap reconstruction has expanded the realm of salvage surgery, allowing more aggressive extirpative procedures with decreased morbidity.

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48.1 Introduction

The pattern of care for head and neck cancer patients has changed considerably since the landmark paper by the Department of Veterans Affairs Laryngeal Cancer Study Group in 1991. Organ preservation protocols involving chemotherapy and radiation have become standard at many institutions for not only the treatment of advanced laryngeal carcinomas but also for advanced lesions of other head and neck sites. As more patients are treated with chemoradiation as a primary modality, the role of surgery is evolving. The head and neck cancer surgeon must now be familiar with the unique diagnostic and therapeutic challenges presented by the patient who may have, or has failed, radiation or chemoradiotherapy.

This chapter will discuss the challenges in diagnosis, workup, treatment, and follow-up of patients with head and neck squamous cell carcinoma who present after chemoradiation protocols. The role of surgical salvage will be emphasized. In addition, the treatment of patients who present with

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persistent disease (an incomplete response to chemoradiation) versus those with *recurrent* disease (complete initial clinical response to chemoradiation, with the presence of tumor found >6 months after completion of treatment), will be highlighted. This chapter will focus mainly on tumors involving the oral cavity, oropharynx, hypopharynx, and larynx. Carcinoma of the nasopharynx generally behaves differently than squamous cell carcinomas of the remainder of the head and neck and therefore will not be discussed here.

48.2 Diagnosis

The clinical diagnosis of persistent or recurrent squamous cell carcinoma after chemoradiation is often challenging. Radiation and chemotherapy-induced changes in mucosa and soft tissue can mimic many of the worrisome signs and symptoms of local recurrence. For example, treatment-induced mucositis, pain, edema, dysphagia, and hoarseness can be significant and prolonged. Tumor necrosis can leave residual ulceration that is difficult to distinguish from malignancy. Radionecrosis of the mandible and the larynx can occur late after treatment, and present with ulceration, pain, and edema. This is often difficult to distinguish from tumor recurrence. Palpation of lymphadenopathy is often problematic because of postradiation neck fibrosis.

The best hope of a successful surgical salvage is if recurrent disease is found early. Most tumor recurrence occurs in the first 2 years after therapy. It is for this reason that clinical guidelines suggest frequent follow-up visits in the head and neck cancer population. Carefully elicited histories and physical examinations can sometimes detect subtle changes in signs and symptoms, which are often the only clue to the presence of a tumor persistence or recurrence. Any suspicion of a tumor should prompt further evaluation. This involves endoscopy, biopsy, and/or imaging, which will be discussed in detail in the following sections.

48.2.1 Imaging

Obtaining imaging studies is often the first step in evaluating the patient with suspected tumor persistence or recurrence. Comparison of these images with prior imaging is essential, so it is beneficial to ensure that these examinations are available both to the surgeon and the interpreting radiologist.

48.2.1.1 CT and MRI

Many patients undergo CT and/or MRI imaging with contrast to evaluate extent of tumor, bony involvement, and the presence or absence of lymphadenopathy. However, it is difficult to suspect recurrence on the basis of imaging studies alone. Interpretation of CT and MRI is challenging in the presence of postradiation changes. Edema, tumor necrosis, and inflammation can lead to MRI signal characteristics that are similar to tumor. A prospective study by Lell et al. followed patients with serial MRI scanning before and after undergoing concurrent chemoradiation, correlating suspicious MRI findings with biopsy. MRI led to false-positive results in 46 % of patients in the first 3 months after completion of therapy and 58 % in the interval 3–6 months after therapy. In a similar analysis of CT scanning to detect recurrences, these authors also found that the presence of osteonecrosis, abscess, and inflammation led to false-positive results [1].

In the case of biopsy-proven disease, CT and/or MRI can be helpful to provide spatial detail in planning for salvage surgery. As will be discussed later, the surgeon must be cautioned, however, that the true extent of tumor is often difficult to assess and is often beyond what can be appreciated clinically and radiologically. However, there are some recent data which show that advances in MRI technology enable whole-body imaging without spatial resolution compromise and may provide superior visualization of metastatic disease as compared to PET [2]. Furthermore, this does not expose the patient to ionizing radiation.

48.2.1.2 PET Scanning

18 F-FDG-PET and ^{18}F-FDG-PET-CT scanning are emerging as very useful tools to evaluate suspected persistent or recurrent head and neck cancer. Their utility as a screening tool is also being investigated. In a study by Salaun et al., PET scanning was performed on 30 patients considered free of their disease by routine negative physical exam, flexible endoscopy, and lack of worrisome symptoms. A single scan was performed at an interval ranging from 6 to 35 months posttreatment. They were able to detect tumor recurrence in eight patients, with a sensitivity of 100 %, specificity of 95 %, and overall accuracy of 97 % [3]. A similar study by Abgral et al. prospectively followed 91 patients considered free of their disease by conventional surveillance with PET scanning done 7–15 months after the completion of therapy. The PET scan was positive in 39 patients, and 30 of those patients had proven recurrence, leading to a sensitivity of 100 %, specificity of 85 %, and overall accuracy of 90 % [4]. Neither of these studies addressed whether surveillance PET scanning had any impact on survival. For the assessment of tumor response and detection of residual tumor, multiple studies have shown that PET-CT is superior to conventional anatomic imaging [5, 6, 1]. From a cost analysis standpoint, Pryor et al. showed that considerable cost savings were generated with the incorporation of PET-CT into nodal response assessment. This was secondary to the reduction in number of unnecessary neck dissections [7].

The benefit of PET scanning to detect persistent disease after chemoradiation has been better studied. If performed 10–12 weeks after the completion of chemoradiotherapy,

PET scanning has been shown to be beneficial in evaluating for the presence of persistent disease both at the primary site and in the neck. A recent meta-analysis of 27 studies by Isles et al. showed the pooled mean positive and negative predictive values for the detection of residual/recurrent disease at the primary site were 75 and 95 %. For the neck these numbers were 49 and 96 %, respectively. The overall pooled sensitivity was 94 % for the detection of disease at the primary site. The same analysis revealed that the sensitivity of PET scanning improves if done 10 or more weeks after completion of treatment [8]. A meta-analysis by Wong showed similar promising results for the use of PET scan in detecting recurrent disease. The analysis of eight studies showed the sensitivity of PET scanning for detecting recurrent carcinoma as 84–100 %, with specificities of 61–93 %. The negative predictive value of PET scanning was 96 %, similar to the high value in the analysis by Isles et al. [9].

The results of these meta-analyses, among other studies in the literature, have laid the foundation for the changing standard of care regarding post-chemoradiation protocols. Previously it was standard of care that any patient with N2 or N3 disease should undergo routine planned neck dissection approximately 6 weeks after treatment, regardless of the clinical response to therapy. This was due to the high incidence of treatment failures with bulky adenopathy, the difficulty of following these patients for recurrence, and the devastating consequences of uncontrolled neck disease. PET scanning has now greatly improved our ability to detect persistent disease in this population. Due to the very high negative predictive value of PET scanning as quoted in the above studies, many centers now defer planned neck dissection after chemoradiation in favor of careful observation if the posttreatment PET scan is negative.

48.3 Imaging for Evaluation of Distant Disease

If clinical suspicion dictates, imaging should also be performed to evaluate for distant metastases when a patient presents with recurrent head and neck carcinoma. Patients with more advanced carcinomas are more likely to present with distant metastases, and the main site of metastasis is the lung. Currently there is no consensus regarding the best imaging modalities for detection of distant metastases. In fact according to the National Comprehensive Cancer Network (NCCN) guidelines for head and neck cancer version 2.2014, there are no definitive imaging modalities recommended for the work up of any primary or recurrent head and neck cancers in any subsite. Chest imaging should be ordered as clinically indicated and PET-CT should be considered in advanced disease states. In addition to this, the guidelines point out that PET-CT for stage III and IV oral cavity cancer may alter management by upstaging patients [10]. Many practitioners will order a routine chest xray (CXR) to look for pulmonary nodules, followed by a chest CT if the CXR is suspicious. Measurement of serum aminotransferases and radionuclide bone scintigraphy can be used to screen for liver or bone metastases, respectively, as clinical suspicion dictates.

The use of ^{18}F-FDG-PET scanning for evaluation of distant metastases has been investigated. In a review by Wong, data from five studies with a total of 233 subjects was pooled. The overall true positive rate of PET scan to detect second primary or distant metastases was 73 %, while the false-positive rate was 27 %. The analyzed studies rarely reported the incidence of false-negative PET scans. Overall, he found no large clinical trials that showed the benefit of PET over other cross-sectional imaging to detect distant metastases [11].

More recent work may suggest otherwise. A prospective study by Senft et al. suggests that PET scanning is superior to conventional chest CT to detect pulmonary metastases, with the best results obtained by combination PET-CT. The negative predictive value and accuracy of PET-CT to detect distant metastases was 84 % versus 75 % for chest CT alone [12]. Gourin et al. showed that PET-CT is superior to conventional screening modalities (defined as CXR and liver function tests in this study) to detect distant metastases in previously untreated patients with head and neck cancer [13]. In the largest and most recent meta-analysis on the use of PET-CT for the diagnosis of lung malignancy in patients with head and neck carcinomas, Xi et al. analyzed 12 papers from 2006 through 2013 comprising 1431 patients [14]. They showed that the overall sensitivity and specificity of PET-CT to detect lung malignancy in head and neck cancer patients was 85 % and 98 %, respectively. However they also point out that when looked at separately, the sensitivity for detection of lung metastasis in a primary workup was higher (96 %) than for restaging purposes (83 %). No clear reason could be found to explain this difference.

Gourin et al. have also investigated the utility of PET-CT scanning to detect distant metastases in patients with suspected head and neck cancer recurrence. They retrospectively analyzed data of 64 consecutive patients with suspected recurrence. All patients had CXR and liver function tests in addition to whole-body PET-CT imaging. Ten patients had biopsy-proven pulmonary malignancy, of which only two were suspected by CXR alone, and seven were detected by a positive PET-CT scan. Five patients had extrathoracic metastases or second primary tumors detected by PET-CT scanning, and all of these patients were previously unsuspected to have metastases by both clinical suspicion and negative liver function testing. Overall, 23 % of patients had distant metastases, and only 3 % had distant disease suspected by conventional methods prior to PET-CT imaging [15]. This study highlights two important points with respect to patients with recurrent head and neck cancer. First, the absolute rate of

Table 48.1 Summary of the main considerations in imaging a suspected head and neck cancer recurrence or persistence

	Advantages	Disadvantages	Main indications
Key points: imaging			
CT	Excellent delineation of bony anatomy	Posttreatment changes difficult to distinguish from tumor	Good spatial detail of tumor and/or lymphadenopathy Surgical planning
MRI	Excellent delineation of soft tissue anatomy	Posttreatment changes difficult to distinguish from tumor	Good spatial detail of tumor and/or lymphadenopathy Surgical planning *Not used as frequently as CT scanning*
PET	High negative predictive value to detect persistent local or regional disease	False positives if done too early or in the presence of infection or inflammation	Monitor disease at primary site Screening for regional or distant metastases Screening for second primary tumor Helps determine the need for posttreatment neck dissection

distant metastases in this population is high, illustrating the importance of a thorough evaluation for distant disease prior to initiating any salvage therapy. Second, it appears combination PET-CT imaging may offer superior detection of this distant disease versus other modalities (Table 48.1).

48.3.1 Biopsies

The use of ^{18}F-FDG-PET scanning approximately 10 weeks after the completion of chemoradiotherapy has decreased the need for planned posttreatment surveillance endoscopies with biopsies of suspicious areas due to its high negative predictive value in detecting recurrent or persistent carcinoma. In the face of clinical suspicion or a positive PET scan, biopsies of suspicious areas should be performed. It is important to remember that biopsies performed less than 10 weeks after the completion of treatment can be erroneously positive because tumor regression continues even after the completion of radiotherapy.

It is also important to remember that biopsy of recurrent disease can yield false-negative results. Recurrent head and neck carcinomas often display different growth patterns compared with primary carcinomas—they tend to be multifocal and submucosal [16]. Sampling tissue that is too superficial or is in between foci of tumor can lead to erroneous results. If the clinician maintains a high index of suspicion despite a negative biopsy, it is prudent to continue a very close follow-up with repeat biopsies of suspicious areas.

The use of fine-needle aspiration cytology for the evaluation of suspicious neck nodes has been shown to be efficacious in the setting of previously untreated neck disease. However, its use in the setting of a previously chemoirradiated neck has not been well studied. One of the few papers to address this question showed disappointing results, with an overall accuracy of FNA in detecting persistent or recurrent neck disease as only 57 % [17]. More recently Yom et al. evaluated ultrasound-guided FNAs in postradiated oropharyngeal cancer patients. They found that from 87 US-guided FNAs, 71 % yielded a nonequivocal tissue diagnosis. The PPV and NPV of US-guided FNA were 33 % and 95 %, and the sensitivity and specificity were 75 % and 74 % [18]. Although these results are an improvement from past investigations, it still shows that an FNA in this population is nondiagnostic 29 % of this time. This poor yield likely results from the difficulty in obtaining good FNA samples in the postradiated neck due to fibrosis as well as the increased difficulty in interpreting the samples from nodes exposed to radiation.

48.4 Surgical Treatment

48.4.1 Management of the Primary Site

The extent of resection required to extirpate a tumor in the case of persistent or recurrent head and neck carcinoma following chemoradiation is unclear. Some authors would advocate tailoring the extent of resection to pretreatment tumor size with appropriate margins, even if the posttreatment tumor is significantly smaller in size. Others would argue that the chemoradiation reduces tumor load, and thus, resection margins should encompass only presently active disease, thereby reducing morbidity and the need for extensive reconstruction. This follows the concept that unresectable tumors can be "downstaged" with chemoradiation to make them operable.

To date, no prospective, randomized trials have been conducted to answer this question. In fact, a recent survey of members of the American Head and Neck Society showed that current surgical practice varies widely. Seventy percent of respondents stated they used pretreatment margins to tailor surgical resection, and 26 % stated they used the margins of the recurrence only [19].

The argument against restaging the tumor after chemoradiation therapy is that even though the tumor may appear clinically, endoscopically, and radiologically smaller in size, it may not be by histologic analysis. A recurrent tumor is often submucosal and difficult to detect on clinical examination, especially among surrounding radiation-induced edema, fibrosis, and inflammation. A histologic analysis of whole organ slices in recurrent laryngeal carcinoma versus primary laryngeal carcinoma showed that recurrent tumor is

much more likely to have perineural spread, contralateral spread, and cricoid cartilage invasion. The same authors showed that recurrent tumors tend to be multifocal rather than follow a concentric growth pattern. There is also a much greater incidence of dissociated, isolated tumor cells separate to tumor foci in the laryngectomy specimens of recurrent tumors [17].

As outlined earlier, radiologic studies in previously irradiated or chemoirradiated patients are difficult to interpret, and thus, preoperative imaging is less reliable in planning the extent of dissection. Zbären et al. compared preoperative imaging and endoscopy results of patients with recurrent laryngeal cancer with their postoperative histopathologic specimens. Endoscopy was able to accurately evaluate tumor extension in only 52 %. Radiologic examination of tumor extension was correct in only 24 %, with the majority of incorrect interpretations underestimating tumor extension [20].

Thus, in discussing the concept of "restaging" tumors after chemoradiation to plan extent of resection, it is important to remember that preoperative endoscopy and imaging is not always reliable. Tumors do not always follow the concentric growth pattern, and resecting only visible disease (vs. tailoring to pretreatment tumor size) may leave behind microscopic nests of tumor cells. This emphasizes the need for strict frozen section control, even with wide margins of resection. In addition, it has implications in preoperative counseling for patients. Given the uncertainties involved, the accurate planning of surgery is difficult. The extirpative surgeon, reconstructive surgeon, and the patient should always be prepared for a larger than anticipated resection.

48.4.2 Management of the Neck

48.4.2.1 N0 Neck

Traditionally, a neck dissection for recurrent head and neck carcinoma in the clinically N0 neck is advocated if there is a >20 % likelihood of occult neck disease, based on site and size of the recurrent primary tumor. This follows similar principles to the need for elective neck dissection in any primary head and neck carcinoma. Some authors continue to follow this principle, arguing that the neck should be managed aggressively due to the devastating consequences of regional failure in this population and the difficulty in clinically following these patients [21]. The disadvantage of this is the additional morbidity incurred in an already compromised population. There are other reports to suggest a more conservative approach should be taken. A retrospective review by Farrag et al. of patients treated with salvage laryngeal surgery after primary radiation therapy suggested that the management of the neck should be based on the presurgical CT scan of the neck, as opposed to the risk of occult metastasis. Even though 85 % of their patients had T3 or T4 disease, which would normally have a high likelihood of occult metastasis, the majority of their patients had a pathologically N0 neck after neck dissection. Their analysis revealed that 97 % of patients with a negative CT scan also had a pathologically negative neck dissection, concluding that a presurgical CT scan of the neck had a high negative predictive value [22]. This suggests that previous (chemo) radiotherapy renders patients unlikely to harbor the same degree of occult metastases. More recently Basheeth et al. concluded in their retrospective analysis of 45 patients that the incidence of occult neck metastasis was low and that elective neck dissection in this population did not have an impact on regional control [23]. However Amit et al. found in their review of 42 patients with recurrence after either radiation to the central neck (14 patients) or central and lateral neck (28 patients) that the overall rate of occult neck metastasis was 19 % and that the risk was similar between the two different groups. They concluded that elective neck dissection in this population was appropriate [24]. Hilly et al. show in their review that elective neck dissection in advanced recurrent laryngeal disease improves survival. But this benefit was not shown in the patients who had limited disease on their recurrence [25]. And in their review of 18 patients with head and neck mucosal squamous cell carcinoma with N+ necks treated with primary radiation who developed primary site recurrence with radiologically resolved neck lymphadenopathy who underwent elective neck dissection, Prendes et al. found that their rate of occult neck metastasis was 22.2 %. They conclude that lymphadenectomy should especially be considered in patients with persistent tumors, with advanced recurrent T-stage, and in those undergoing free flap reconstruction [26]. In patients with an N0 neck who require neck exploration, whether for access to the primary site or for free flap reconstruction, a selective neck dissection should be considered as it adds little morbidity or operative time.

48.4.2.2 N+ Neck

In patients with persistent neck disease, there is no doubt that the neck needs to be addressed surgically. The extent of neck dissection, however, is still under debate. A radical or modified radical neck dissection is certainly efficacious to eradicate persistent neck disease. Recent reports in the literature purport the feasibility of a more conservative approach. In this population, patients often have significant preexisting problems with soft tissue fibrosis, dysphagia, and poor neck range of motion secondary to the effects of chemoradiation. A selective neck dissection may afford smaller incisions, less tissue dissection, as well as a shorter hospitalization [27]. It can decrease the significant morbidity of more radical procedures that may lead to chronic neck and shoulder pain, decreased range of motion, and chronic numbness. Stenson et al. report in their series of 58 patients who underwent

selective (unilateral or bilateral) neck dissection after chemoradiation that only one patient developed disease recurrence in the neck [28]. Robbins et al. performed a prospective study to compare radical or modified radical neck dissection against more selective neck dissections in patients with persistent disease after chemoradiation. After a median follow-up of 58 months, the rates of regional failure were low in the selective neck dissection group, and there was no difference in overall survival and distant metastases [29]. This study was not randomized and thus confounded by selection bias, but the results do suggest that selective neck dissections are a safe and feasible option in selected patients. Interestingly, in this paper, and in other published works, Robbins has suggested that a "superselective" neck dissection may also be a feasible option. Robbins et al. suggest that patients with residual post-chemoradiation adenopathy confined to one single neck level can be salvaged with a neck dissection limited to only two contiguous neck levels. They analyzed a series of 54 patients undergoing complete neck dissection. Pathologic analysis of neck dissection specimens revealed that only one patient had disease outside of the two contiguous neck levels, and thus in this population, it would have been safe to do a superselective neck dissection only [27].

The studies advocating the use of more selective neck dissections emphasize that this approach should be tailored to those with persistent disease who have nodal disease addressed as part of a "planned" neck dissection or an early salvage neck dissection when chemoradiation has failed to fully eradicate neck disease. The data for more limited neck dissections is lacking when patients present with late recurrences in the neck. It is thus recommended that in this population with late recurrence, radical or modified radical neck dissections should be performed.

In patients with isolated neck recurrence, resection of the disease in toto is often easier compared to recurrence at a local site. In their analysis of 377 patients, Wong et al. showed that in the 188 patients who had regional recurrence only, this group was more likely to have successful disease clearance at the time of surgery (42 % vs. 29 %). But the 5-year disease-free survival (DFS) was lower in this group (26 % vs. 42 %). It was also noted that the DFS was lower if the neck had been previously dissected (18 %) as compared to those patients who had not previously undergone neck dissection (32 %) [9].

48.5 Surgical Reconstruction

Reconstruction of salvage surgical defects in general follows the same principles as for primary surgical defects. Options span the "reconstructive ladder," from primary closure to the use of free tissue transfer. In the previously chemoirradiated population, the use of regional or free flaps is especially important, as it allows the transfer of abundant, healthy, non-irradiated tissue with good vascular supply. Regional flap reconstruction, particularly the pectoralis major myocutaneous flap, has been used successfully in salvage surgical reconstruction, especially for large defects involving the oral cavity and oropharynx [30, 31]. Myocutaneous flaps are useful to protect the carotid artery, which is at an increased risk of exposure in previously radiated patients. They are also used in combination with free flap reconstruction for larger defects to provide soft tissue bulk [32]. Regional flap reconstruction is an especially useful option in elderly or medically compromised patients who may not tolerate lengthy free flap reconstructions.

Free flaps have been shown to be safe in patients previously treated with radiotherapy and/or chemotherapy, with complication rates similar to previously untreated patients [33]. The use of free flap reconstruction has expanded the realm of salvage surgery, allowing more aggressive extirpative procedures with decreased morbidity. Patients that were previously considered "unresectable" are now offered a chance of cure with acceptable outcomes with respect to speech, swallowing, and cosmesis. Hanasono et al. analyzed 117 patients undergoing one or more sequential head and neck free flap reconstructions between 2000 and 2012. Their success rate of subsequent free flaps was 98.7 % compared to 99.1 % for initial free flaps in the same patient. There was no significant difference in the complication rates. In the patients receiving free flap reconstruction for oral or pharyngeal sequential reconstruction, 90.1 % demonstrated at least either normal or mostly intelligible speech and 81.6 % remained feeding tube independent. This study demonstrates that in appropriately selected patients, multiple sequential free flaps are both feasible and reliable [34].

As part of the multidisciplinary approach to managing these patients, the reconstructive surgeon should be involved early in the process. As mentioned earlier in this chapter, surgical defects can become much larger than anticipated intraoperatively, and careful planning and anticipation of this by the primary and reconstructive surgeon is imperative.

48.6 Surgical Complications

Salvage surgery has classically been associated with an increased rate of surgical complications. In particular, wound complications such as breakdown and fistula, pharyngoesophageal stenosis, and carotid rupture have been reported with increased frequency. Ganly et al. showed a significant increase in postoperative wound complications (45 % vs. 25 %) and pharyngocutaneous fistulas (32 % vs. 12 %) in their 38 patients who underwent salvage total laryngectomy after chemoradiation compared to their primary total laryngectomy patients. They showed that the overall complication

rate and local complication rate was higher in the chemoradiation group compared to the primary group as well as to those patients previously treated with radiation only [35]. Other authors have also shown that prior chemoradiation leads to increased surgical complications versus radiation alone or primary surgery [36, 37], but other reports do not demonstrate an increased surgical complication rate after chemoradiation versus radiation therapy alone [36, 38]. Nonetheless, it is clear that prior therapy does predispose patients to an overall higher risk of surgical complications.

With the increased use of free flap reconstruction, however, the incidence of surgical complications in salvage surgical procedures may be decreasing. In fact, some studies have shown that the wound complication rate with the use of free flap reconstruction equals that of nonirradiated patients. Fung et al. showed that the use of free tissue transfer in the salvage total laryngectomy population did not reduce the overall incidence of pharyngocutaneous fistula, but did reduce the rate of major complications, defined as rehospitalization, re-exploration, or death [39]. In a meta-analysis of studies showing the use of vascularized tissue to reduce the risk of pharyngocutaneous fistulae (PCF) after salvage total laryngectomy, the outcomes of 591 patients from seven identified articles were analyzed. The pooled relative risk was 0.63 (95 % CI: 0.47–0.85), indicating that patients who have flap reconstruction reduced the risk of PCF by one-third. In addition to showing a clear reduction in PCF rates, some of the papers suggest that fistulae that occur are smaller and rarely need repair [40]. Supplementing pharyngeal mucosa in the closure of a post-laryngectomy defect can also decrease the pharyngeal constriction and stenosis that previously chemoirradiated patients are prone to develop. By utilizing vascularized free flap reconstruction after salvage total laryngectomy, Withrow et al. reduced the rate of esophageal strictures to 18 % (vs. 25 % for primary closure) and dependence on tube feeding to 23 % (vs. 45 %) [41].

In summary, salvage surgery after chemoradiation can lead to an increased risk of local wound complications, but many of these risks can be decreased with the use of free flap reconstruction of defects.

48.7 Adjuvant Therapy

Traditionally, head and neck radiation oncologists have been reluctant to offer re-irradiation as adjuvant therapy for fear of unacceptable toxicity and morbidity. Modern treatment planning protocols, in particular IMRT, have allowed repeat courses of radiation to be delivered while minimizing lifetime doses to critical structures such as the spinal cord and brainstem [42]. This has led to a substantial reduction in complications in the salvage population [43, 44]. However, the advantages gained from IMRT are counteracted by the radioresistant and multifocal nature of recurrence which necessitates larger dosage delivery and wider radiation fields [45, 46]. Recent trials have shown adjuvant re-irradiation (with or without chemotherapy) to be both feasible and effective. Machtay et al. showed that adjuvant chemotherapy and re-irradiation in patients with stage III or IV recurrent carcinoma had promising results, offering 3-year locoregional control of 81 % and overall survival of 63 %. These outcomes are better than would be expected with surgical salvage treatment alone. However, the rate of severe and long-term toxicities was also higher in this group [47]. A randomized trial by Janot et al. comparing salvage surgery alone versus salvage surgery with postoperative re-irradiation and chemotherapy showed a significant improved disease-free survival in the adjuvant therapy arm, but no improvement in overall survival. As in the previous study, the improved locoregional control in this group came at the expense of higher toxicities [48].

Although surgery remains the preferred primary treatment option for previously chemoirradiated patients, there are certain patients who are considered unresectable based on size and location of tumor recurrence or who cannot tolerate surgery due to other comorbidities. The use of re-irradiation with or without adjuvant chemotherapy is currently being studied as the sole treatment modality for this population and, in some scenarios, may even be curative. A review of this topic by Mendenhall et al. shows that external beam re-irradiation with or without chemotherapy for recurrent head and neck cancer results in 2-year overall survival rates of 16–35 %, with a small fraction of patients achieving long-term survival [44]. Similar to postoperative re-irradiation therapy, primary re-irradiation protocols are associated with higher toxicities. A review by Salama et al. showed that chemotherapy and re-irradiation protocols do not carry an increased risk of acute toxicities such as mucositis or hematologic abnormalities compared to primary chemoradiation protocols, but treatment-related mortality and late toxicities appear to be higher [49].

Some patients are not good candidates for external beam re-irradiation, and for this population, other adjuvant treatment modalities can be considered. Brachytherapy and photodynamic therapy are currently under investigation as potential treatment options. Their use as a single treatment modality at this time is generally limited to palliation, although small numbers of patients have been cured of their disease. In a phase I–II study of patients referred for "last hope" treatment for recurrent head and neck cancer, interstitial photodynamic therapy offered significant palliation; long-term disease-free survival was observed in a small number of patients [50]. A recent retrospective review of the efficacy and safety of photodynamic therapy with temoporfin for recurrent carcinoma of the oral cavity and oral pharynx was performed. Overall survival at 1 year was 72 % and

Table 48.2 Summary of the main treatment considerations in a patient with persistent or recurrent squamous cell carcinoma after chemoradiation therapy

	Advantages	Disadvantages	Main indications
Key points: treatment of persistent or recurrent carcinoma after chemoradiation			
Surgery	Best chance for cure	High morbidity, especially with advanced stage disease Increased wound complications (decreased with regional or free flap reconstruction)	Persistent or recurrent resectable disease Absence of metastatic disease
Re-irradiation (+/– chemotherapy)	Can offer cure in some number of patients with unresectable disease, good locoregional control	Higher incidence of late toxicities	Adjuvant therapy postoperatively [advanced stage disease, positive margins, multiple positive nodes, extranodal spread] Nonsurgical candidates [unresectable, medical comorbidities, patient preference]
Chemotherapy alone	Relatively less morbid than XRT/surgery	Rarely curative Variable morbidity	Palliation, local control Nonsurgical, nonreirradiation candidates
Adjuvant therapies (brachytherapy, PDT)	Minimal morbidity	Rarely curative	Palliation, local control Nonsurgical candidates

PDT photodynamic therapy, *XRT* radiation therapy

36 % at 5 years. The 1- and 5-year disease-specific survival were 82 % and 45 %, respectively. Recurrence-resurvival at 1 year was 52 % and at 5 years was 34 % [51]. Both low-dose and high-dose interstitial brachytherapy can also be effective tools in providing durable palliation and local control of disease with acceptable toxicities. In certain cases, patients receiving these therapies have shown prolonged disease-free survival [52, 53] (Table 48.2). In a recent analysis of re-irradiation with interstitial pulsed-dose-rate (PDR) brachytherapy for unresectable recurrent head and neck carcinoma, 51 patients were treated [54]. Local control rates after 2 and 5 years were 71 % and 57 %, respectively. Comparing results of salvage PDR brachytherapy with or without concurrent chemotherapy, the 5-year local recurrence-free survival rates were 78.9 % versus 38.5 % ($p=0.01$), respectively. PDR interstitial brachytherapy with simultaneous chemotherapy is an effective and safe option for curative therapy in patients not suitable for salvage therapy.

48.8 Outcomes

The prognosis of patients requiring surgical salvage for chemoradiation failure has not been well studied in long-term prospective studies. Nonetheless, some generalities can be made based on current data and extrapolating data from patients with radiation or other primary treatment failures. A meta-analysis by Goodwin of 1080 patients undergoing salvage surgical therapy showed the 5-year survival to be 39 % [55]. Certain characteristics of persistent or recurrent tumor correlate with prognosis. For example, patients with greater initial tumor burden in the neck (N3 disease), positive surgical margins, and extranodal extension of disease have poorer survival [56]. Stage of recurrent disease is important and correlates strongly with disease-free survival. A prospective study by Goodwin illustrated median disease-free survival after surgical salvage was greater than the 22-month study for stage I recurrence and only 5.5 months in stage IV recurrence [55].

Patients with recurrence in certain subsites of the head and neck fare better. In particular, the survival rates for patients with recurrent carcinoma of the larynx after chemoradiation failure are better than those with recurrent oropharyngeal or hypopharyngeal tumors. The cause for this is likely multifactorial. Patients treated with organ preservation protocols for the hypopharynx or oropharynx were more likely to have advanced disease at the outset, and these subsites tend to have greater propensity for regional metastases. In addition, tumors of the oropharynx and hypopharynx can spread to involve unresectable areas such as the pterygoid plates and prevertebral muscles, whereas recurrent disease of the larynx tends to be more confined to resectable areas [57].

When one describes surgical success after salvage procedures, the morbidity of such interventions must also be considered. The ability to improve a patient's quality of life is an inherent part of defining surgical success. Patients who present with stage I or II recurrence have a better quality of life after surgical salvage compared with those with recurrent stage III or IV disease. In Goodwin's study, only 41 and 39 % of patients with stage III and IV recurrence, respectively, reported an improved quality of life postsurgical salvage [55]. The poor quality of life and survival outcomes in advanced stage recurrence, coupled with the prolonged recovery time after free tissue transfer or other major extirpative procedures, have prompted some authors to advocate a careful, individualized risk/benefit analysis of the role of surgical salvage for therapeutic or palliative purposes in this group of patients [58].

48.9 Conclusion

Salvage surgical therapy is one of the most difficult challenges facing the head and neck cancer surgeon. It remains the best option for treatment in patients with persistent or recurrent disease after failed chemoradiotherapy. Advances in imaging techniques, surgical reconstruction, and adjuvant therapies have improved our ability to diagnose and manage patients with this difficult problem. Surgical salvage can be a very successful operation in select groups of patients, offering long-term survival with minimal morbidity. Nonetheless, the overall survival in this population remains poor, and thorough discussions must be held with the family and caregivers prior to treatment to establish reasonable expectations. The multidisciplinary management of these patients is essential, and all members of the head and neck cancer team must be involved early in the process.

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Quality of Life in Head and Neck Cancer Patients

49

Jolie Ringash

Abstract

Quality of life (QOL) is a measure of an individual's overall well-being. It is a patient-reported outcome that can only be accurately assessed by the individual. It is measured using standardized instruments with known validity and reliability. These include multidimensional questionnaires or single-item indices. Specialized QOL instruments are available for certain diseases, symptoms, or treatments. A related concept is health utility, which quantifies not only health but its value to the individual under conditions of uncertainty. Results for both QOL and utility instruments are most useful when reported in the context of their significance—both statistical (probability of error) and clinical (whether magnitude is meaningful to patients).

Each individual conceptualizes QOL in a personal way. When QOL is an outcome of a clinical trial, prospective measurement at multiple time points is preferred. However, "baseline QOL" is measured after cancer diagnosis and does not reflect "healthy" QOL. Additionally, individuals may reconceptualize QOL over time, so concurrent comparative cohorts are needed to interpret QOL changes over time. Missing data is especially important in QOL research, because healthier patients are more likely to comply with assessments.

Specific concerns such as xerostomia, pain, dysphagia, and speech disruption often dominate the posttreatment QOL experience of head and neck cancer (HNC) patients. Instruments designed specifically for HNC will best discriminate between patients and respond to change over time. Among a number of HNC-specific QOL instruments, the most commonly used are the EORTC QLQ-C30/HN35, FACT-H&N, and UW-QOL. Few phase III randomized controlled trials in HNC have yet reported QOL results. The use of intensity-modulated radiation therapy to reduce parotid dose lessens xerostomia and improves QOL; certain supportive care initiatives improve QOL during HNC treatment. Additionally, baseline QOL is among the strongest prognostic factors in HNC and is an obvious candidate for stratification in future clinical trials.

Keywords

Quality of life • Head and neck neoplasms • Patient-reported outcomes • Survivorship • Questionnaires • Health utility

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49.1 Introduction: What Is QOL?

Traditionally, the outcome of cancer care was assessed in terms of survival and/or tumor response. As early as 1948, Karnofsky recognized that other outcomes were important to patients. In his study, he used a performance status scale, showing that "subjective improvement was indicated by the patient's feeling of well-being, his increased appetite and strength, and the relief of specific complaints…" [1]. In the intervening 65 years, his initial concept of patient well-being has evolved into our modern, patient-reported concept of quality of life (QOL). QOL is now recognized as an important outcome of cancer care.

49.1.1 Definition

Broadly speaking, QOL is a measure of an individual's overall personal well-being. Three aspects critical to the concept are subjectivity (only the individual truly knows his or her own internal state), multidimensionality, and sociocultural context.

49.1.2 QOL and "Health-Related" QOL

Overall QOL is impacted by issues such as income and adequacy of housing, which cannot typically be influenced by the health-care system. In the context of health care, QOL measures are often used to measure the effect of disease, illness, and treatment on the patient and family. For this purpose, issues which are not expected to change based on these effects become measurement "noise" and reduce the ability of questionnaires to detect actual changes. For this reason, the more limited concept of "health-related" QOL is usually applied. The World Health Organization (WHO) has defined it as: "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychosocial state, level of independence, social relationships, and their relationships to salient features of their environment." [2] When the term "quality of life" is used in the context of health care (and in the remainder of this chapter), it is usually health-related QOL which is meant.

49.1.3 Domains and Multidimensionality

Human beings are complex: the overall human experience reflects many underlying functions and roles. Under the stress of illness, that experience is influenced as well by specific symptoms. Such complexity may be addressed by two very different methods. The first method attempts to explicitly address the many dimensions of experience by constructing specific "domains" within a questionnaire, including cognitive, emotional, social, spiritual, role and physical functioning, and specific symptoms. This approach results in long questionnaires with multiple items organized into separate subscales relating to each domain. The alternative method is to rely upon the respondent's ability to internally integrate his or her experience and to report overall QOL as a single-item index. One example would be the use of visual analogue scales, such as the "feeling thermometer," originally developed in 1964 by the US National Election Services to allow voters to rate their feelings toward political candidates but more recently adapted as a health utility instrument [3, 4]. Some instruments use a mixture of both methods; for example, "overall QOL" may be included as a single item, along with more specific domains. Typically, multi-item instruments are more reliable and more sensitive to change over time than single items; however, they require more time to complete.

49.1.4 Patient-Reported Outcomes

In 2006, the US Food and Drug Administration issued a draft guidance document, subsequently finalized in 2009, addressing the use of patient-reported outcomes (PROs) in support of drug-labeling claims [5]. This document was received as both a strong recognition of the importance of QOL research and as a controversial perspective, especially due to several methodological recommendations. Nevertheless, although QOL research is conducted for many reasons beyond the development of new drugs, it has been influential around the world. The term PRO, which has become increasingly popular as a result of the guidance, covers both QOL and other outcomes which may be solicited directly from the patient, such as adherence to therapy, satisfaction with treatment, and direct symptom ratings.

49.1.5 Health Utilities

Utility measures are intended to quantify not only health but also its value to the individual. They are derived from utility theory to address preference under conditions of uncertainty [6]. Direct utility assessment uses one of two methods: the standard gamble, in which the respondent must accept a risk of immediate death to gain QOL, or the time trade-off, in which he or she gives up time in order to gain QOL. Both methods use the concept of "perfect health," defined by the WHO as "a state of complete physical, mental and social well-being, not merely the absence of disease and infirmity" [7].

Utilities have the advantage that they may be used directly as quality weights to determine "quality adjusted life years" (QALYs) for use in decision analyses, thus allowing integration of quality and quantity of life. Direct utility measurement requires abstract thinking and an understanding of probabilities, so it can be cognitively challenging for some patients and cumbersome to use in busy clinical settings [8]. More feasible alternatives include ratings scales, such as the feeling thermometer, or multi-attribute utility scales (questionnaires for which response options have known utility weights).

49.2 Dominant QOL Issues in Head and Neck Cancer Patients

Specific concerns such as xerostomia, pain, dysphagia, and speech disruption often dominate the posttreatment QOL experience of head and neck cancer (HNC) patients. Only a brief review can be provided below. More detail is available in a recent review article [9]. Additionally, under the auspices of the National Cancer Institute (NCI) of the USA, a "Toolbox" was recently published, suggesting commonly used and acceptable measures for assessing these issues [10].

49.2.1 Pain

Pain in HNC patients arises as a result of many factors: tumor-related ulceration, pressure effect, or nerve infiltration; acute treatment-related pain due to radiation and/or chemotherapy mucositis and postoperative wounds; and late treatment-related effects such as shoulder dysfunction, trismus, chronic edema, or osteoradionecrosis (bone necrosis due to radiotherapy). The quality and timing of pain can differ for each responsible mechanism so that a full characterization of pain may require detailed questioning. QOL instruments for HNC will typically include 2–3 pain-related questions: one on general pain, one specific to pain in the mouth or throat, and perhaps one related to shoulder discomfort [11]. A PRO specifically focused on pain, such as the Brief Pain Inventory (BPI), may complement QOL instruments when pain relief is a focus of treatment, such as in the palliative care setting [12]. International efforts to harmonize the classification of pain are ongoing [13].

49.2.2 Xerostomia

Xerostomia, or dry mouth, is a complex problem. Acute and late phases of xerostomia differ in both their pathophysiology and their response to preventive strategies [14]. Salivary fraction from the parotid glands, submandibular/submental glands, and minor salivary glands may play different roles in baseline dryness and in eating-related difficulties. Similarly, swallowing and speech performance have been shown to be impaired in xerostomic patients [15, 16]. Evidence to link xerostomia prevention strategies to reduction in late complications such as dental caries, osteoradionecrosis, and chronic malnutrition is lacking.

The relationship between reduced salivary flow, patient-reported dry mouth, and overall QOL is complex. Reduction in salivary flow to ≤ 25 % of baseline has been arbitrarily classified as xerostomia [17]. Physician-rated outcomes include the Radiation Therapy Oncology Group (RTOG)/EORTC grading scale; the Late Effects in Normal Tissue—Subjective, Objective, Management, and Analytic (LENT-SOMA); and the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4) systems [18, 19, 20, 21]. These measures have rarely been validated against salivary flow or PRO data. All common HNC-specific QOL instruments include at least one item related to xerostomia; however, non-QOL PROs specific to xerostomia have also been developed. Two popular instruments have been a six-item linear analogue scale (LAS) [22] and the eight-item University of Michigan XQ [23]. Though less rigorously developed and validated than most HNC QOL questionnaires, these instruments have performed well in research use.

Clinical strategies to reduce the risk of xerostomia for patients treated with radiotherapy (RT) have included the use of the drugs pilocarpine [24] and amifostine [25], intensity-modulated RT (IMRT) [26, 27], and surgical salivary gland transfer [28–30]. A recent review discusses the literature supporting each strategy, with the latter two approaches having the best evidence of effectiveness [9].

49.2.3 Speech

Of HNC patients who undergo surgical treatment, speech will be affected in most patients immediately after surgery [31] and continues to be affected in over a third (37 %) of patients at 3 months post-surgery [32]. Measures that target speech include the Swedish Self-Evaluation of Communication Experiences after Laryngeal Cancer (S-SECEL) [33] and the voice handicap index (VHI) [34]. A linear analogue self-assessment (LASA) tool has also been developed [35].

49.2.4 Swallowing

Swallowing relies on complex coordination of function and is frequently disrupted by both surgical treatment and RT. After head and neck surgery, short-term dysphagia is common, with about half of the patients experiencing dysphagia at 3 years [36]. Post-RT dysphagia may be worsened

with concurrent chemotherapy [31] and may increase in severity over the years [37]. There is good evidence that impairment of both swallowing and speech significantly reduce overall QOL [38]. Fortunately, more than 75 % of selected patients with dysphagia may return to oral intake with swallowing rehabilitation [39].

The gold standard for assessment of dysphagia is the videofluoroscopic (VFS) assessment. A popular clinician-rated performance status measure, the Performance Status Scale for Head and Neck Cancer (PSS-HN) [40], focuses on the impact of dysphagia. Patient-reported QOL measures targeting dysphagia include the MD Anderson Dysphagia Inventory (MDADI) [41], the swallowing quality of life (SWAL-QOL) [42–44], and the swallowing quality of care (SWAL-CARE) [42–44]. Patients' perceptions of their swallowing problems are not always consistent with their physiological swallowing ability. Some patients with normal VFS may perceive swallowing difficulties, whereas silent aspiration leading to pneumonia can occur in others [45].

49.3 Measurement of QOL: Basic Methodology

QOL instruments measure a subjective concept, but their measurement properties are based on sound scientific principles. Psychometrics, the science of indirect measurement through questionnaires and other related instruments, evolved in educational and psychology research over the course of the twentieth century. It has been applied to health-related questionnaires and PROs for over 20 years [46]. Instruments chosen for use in clinical research should adhere to the principles outlined below.

Item generation should incorporate information about the issues of importance to patients from literature review, health professional expertise, and direct input from patients similar to the instrument's target population. Questions should be written at an appropriate educational level; grade 6 is often recommended [47]. Items should be formatted in a standard way, including both positively and negatively worded items, and avoid jargon, skip formats, and double-barreled questions. Utilization in other languages and cultural groups requires a formal process of cultural adaptation, including forward and back translation and pilot and field testing in the new language/culture [48].

Item reduction is often required to produce a questionnaire of practical length that remains sufficiently sensitive to change over time for *evaluative* (longitudinal) use. Direct testing in patients is typically carried out to identify the items most frequently endorsed by patients and ranked as being of the greatest importance. Statistical methods may also be used to identify items which are most informative [49].

Questionnaire design includes principles of readability and clarity. Questionnaires should include a large proportion of white space, with font size and type which is easy to read. Special requirements for the target group need to be considered (e.g., the visually impaired, young children, low-literacy populations, etc.) [47].

49.3.1 Indices and Profiles

Controversy exists regarding the relative preferability of *indices* or *profiles* for QOL measurement. Different individuals may apply personal weights to aspects of their quality of life, so summation of scores over multiple domains, as is done for indices, may impose the developer's values inappropriately on the patient. Exploration of individual, patient-assigned weighting has proven cumbersome and is rarely used. Other instruments present scores separately for each domain (profiles), without summation. Popular questionnaires of both types are currently in use.

Reliability refers to the reproducibility of scores. It may be assessed by repeated administration of the instrument to a population with stable QOL (test-retest reliability) or by correlation of items within a questionnaire (internal consistency). Higher levels of reliability coefficients are conventionally required for *evaluative* use (to measure change in individuals over time) than in *discriminative* use (to measure difference between groups of patients), typically 0.8 and 0.7, respectively, for internal consistency [50, 51].

Validity refers to the ability of a questionnaire score to reflect the actual concept of interest. It is important that a "QOL questionnaire" is actually related to the patient's overall well-being during a defined period (e.g., one week) and not his or her momentary comfort or passing mood. Questionnaire validation lacks a gold standard, so validity is defined by hypothesis testing with respect to convergence or divergence from other findings (concurrent validity). For example, QOL scores might be expected to be better in patients with better performance status and to improve over time in patients who were gaining weight posttreatment. An HNC-specific QOL questionnaire would also be expected to show a moderate correlation with other, more general, QOL or utility instruments. It is important that validation studies included patients similar to those for whom the instrument will be used; a questionnaire validated exclusively in surgically treated patients may not exhibit the same measurement properties in chemoradiation patients.

Responsiveness is the sensitivity of the instrument to changes over time in an individual patient. Responsiveness is correlated with instrument length and the specificity of items. A very detailed, HNC-specific QOL instrument would be highly responsive, whereas a short, general QOL instrument would be less responsive, to change in a HNC patient. Prospective evaluation is required to determine instrument responsiveness.

Table 49.1 Selected characteristics of HNC-specific QOL questionnaires

Instrument	Administration	Questions	Language(s)	Summary score	Focus[b]
EORTC QLQ-C30/HN35	Self	65	Many	No	All HNC
FACT-H&N	Self	37[a]	Many	Yes	All HNC
UW-QOL	Self	13	English	Yes	Surgical
HNQOLQ	Interview	21	English	No	All HNC
HNCI	Self	30	English	Yes	Surgical
QOL-RTI/H&N	Self	39	English	Yes	Radiation
HNRQ	Interview	22	English	Yes	RT/chemoRT

[a]Two additional items are not scored
[b]Derived from initial development of the instrument and does not necessarily imply lack of validity for other patient types

Minimal clinically important difference (MID) is defined as the smallest change in value on a measurement instrument, which, from the point of view of the patient, represents an important rather than trivial change. In practice, it has been estimated for groups by the use of the minimal detectable difference, that is, the smallest difference which is detectable by the average patient [52]. It is important to differentiate this clinical concept from statistically significant differences, which reflect only the likelihood of observing a given difference, not what it may or may not mean to a patient. Ideally, MID should be determined for every new instrument; however, several studies suggest that a change of 5–10 % of instrument range may represent the MID for many instruments [53, 54].

49.4 Types of QOL Questionnaires

General QOL instruments can be applied to the general population, as well as to those suffering from various types of illness. Popular examples include the SF-36 [55, 56] and the EQ-5D [57].

Disease-specific QOL instruments have been developed in patients with specific types of illness, such as cardiac or respiratory disease, or of course cancer. Two of the most popular cancer-specific QOL instruments are the EORTC QLQ-C30 [58] and the FACT-G [59]. Their questions are better suited to the difficulties of cancer patients, resulting in better validity and responsiveness as compared to general instruments; however, the trade-off is increased difficulty in comparing results with those from healthy people.

Symptom-specific QOL instruments have been developed for several symptoms of importance to HNC patients, such as dysphagia (e.g., MD Anderson Dysphagia Index or MDADI) [41].

Treatment-specific QOL instruments exist for many cancer treatments which are not specific to HNC (e.g., FACT-Taxane) [60]. The author has recently developed an instrument for HNC patients with prophylactic feeding tubes, originally called the QOL-EF and now FACT-EF [61].

Oncology and disease site-specific QOL instruments are a subset of cancer-specific instruments designed for a specific cancer site, such as HNC. Two structured literature reviews have evaluated such instruments for HNC [11, 62]. Several of these instruments are modular, incorporating a cancer-specific instrument and a disease site-specific module (e.g., EORTC, FACT, and QOL-RTI instruments). A selection of the more popular, well-validated questionnaires is mentioned below, with a summary of their characteristics in Table 49.1. Other PROs which are designed for HNC but which focus on performance status, symptoms, specific treatments, or functional issues (e.g., dysphagia, voice, disfigurement, xerostomia) may be complimentary to these HNC QOL instruments.

49.5 Popular H&N Cancer-Specific QOL Instruments

EORTC QLQ-C30/HN35 [63, 64] is the most commonly used instrument [65], as well as the longest. It has been translated and cross-culturally validated in many languages. *FACT-H&N* [40, 59] is another modular instrument which has been translated into many languages; it has been popular in North America. Several English-language instruments have been developed at American universities: the popular, surgically oriented *UW-QOL* [66, 67] at the University of Washington; the *HNQOLQ* [68] at the University of Michigan; the *HNCI* [69] at the University of Iowa; and a modular instrument designed for RT patients, the *QOL-RTI* [70], at the University of South Florida. Finally, the *HNRQ* [71] was developed with a specific focus on acute QOL in patients with advanced HNC receiving RT or chemoRT but has been used infrequently.

49.6 Interpretation of QOL Results

Each individual conceptualizes QOL in a personal way. Life experience, optimism or pessimism, and psychological state all contribute to the perception of QOL. Consequently,

cross-sectional comparisons among individuals are subject to measurement "noise" which should be less problematic when patient scores are self-controlled, by calculating one individual's change in QOL over time in a longitudinal study. For this reason, if QOL is to be used as an outcome of a treatment in a clinical trial, prospective measurement at multiple time points is preferred. However, it is important to realize that the baseline administration usually occurs soon after a patient has received a cancer diagnosis or has been found to have disease recurrence or progression. Thus, the "baseline QOL" does not reflect that person's QOL when healthy. QOL scores that return to baseline over a period of time cannot be interpreted as indicating a resolution of tumor- and treatment-related effects; in many cases, the patient may, in fact, have exchanged tumor-related impairments for different problems induced by treatment.

49.6.1 Response Shift

An additional important consideration in the interpretation of longitudinal QOL data relates to response shift or changing internal standards [72]. Over time, an individual confronted with critical illness may modify his or her values, or standards of measurement, and may also reconceptualize QOL entirely. Response shift may play a role in some initially unexpected findings, such as the fact that patients with serious illness will routinely rate their own QOL as better than the ratings applied to them by surrogates (e.g., family members or health-care professionals). Response shift may be viewed as a beneficial adaptive process; however, it also introduces an additional source of measurement error. Methods of quantifying response shift exist but are labor intensive. One approach in descriptive studies is to compare QOL results with population norms drawn from healthy individuals [73]. Once again, the randomized trial design is favored for studies with QOL outcomes, since it is hoped that unmeasured covariates such as response shift should be balanced between the arms by chance.

49.6.2 Compliance and Missing Data

Results of any study must be assessed for two types of validity: internal validity (does the study measure what it says it does?) and external validity (generalizability). In QOL studies, compliance with planned questionnaires and missing data can threaten both types of validity. Patients self-select study participation, which influences external validity (i.e., study results are applicable only to the type of patients who agreed to participate). Once enrolled in the study, participants determine whether or not they complete requested evaluations. Certain questions or even pages of a given questionnaire may not be completed, or the entire questionnaire may have been missed, either because the patient did not attend a scheduled appointment or because he or she attended but did not complete the QOL instrument. Missed questionnaires threaten both types of validity, since reported results do not really reflect the experience of *all* patients in the study. Specifically, it has been shown that healthier patients are more likely to comply with QOL assessments [74]. While statistical methods exist to attempt to correct for missing data, they require the assumption that data is missing at random, which is known to be unlikely in QOL studies. Consequently, every effort should be made to maximize compliance. Strategies to do so include adequate resources, education and feedback for those administering the questionnaires, real-time monitoring of compliance, and backup methods of administering questionnaires if an error is detected within an acceptable time window [75].

49.6.3 Mean Changes Versus Response Analyses

Longitudinal studies may report mean change in an overall group; however, this can overestimate longer-term QOL due to "survivor effect": data from all patients will be included at baseline, but only patients who survive and continue to comply with assessments are included in the follow-up. In comparative two-arm trials, it is even possible that the QOL may appear to be better in the arm with fewer survivors, since a more toxic treatment may selectively eliminate those with poorer QOL. One alternative is to prespecify the QOL hypothesis and MID and analyze QOL response. Each participant is categorized according to "improved," "stable," or "worsened" QOL, and arms are compared for proportion of patients with a QOL benefit [76]. This approach also allows calculation of a number needed to treat (NNT) statistic [77].

49.6.4 Knowledge Translation

The concept of knowledge translation refers to the gap between evidence and practice [78]. Awareness, agreement, adoption, and adherence have been proposed as the necessary steps required before clinicians will use new knowledge. A prerequisite of both awareness and agreement is that information must be presented in a manner which is interpretable and usable. This has been a challenge for QOL data [79]. Two user's guides have been published to assist the clinician with evaluating and interpreting QOL results [80, 81]. The International Society for Quality of Life Research (ISOQOL) has recently published guidelines on methodologic details which should be included in publications of

QOL results [82]. However, a review showed that in recent publications of oncology clinical trials, recommended information items were included in only 10–70 % of cases; a trend to improvement of most data points was seen over time [83]. In a survey of academic oncologists in Canada, the UK, and Australia, 73 % reported that published QOL data were useful; however, only 45 % integrated such data in consultations with most of their patients; there was a call for consistent, improved reporting standards, and discussion of clinical implications in reports of QOL results [84]. Additional research is needed to help bridge the current gap between QOL researchers and oncologists in the clinical setting.

49.7 Research and Clinical Applications

49.7.1 Clinical Trials

The concept of levels of evidence for medical decision-making applies to QOL research just as it does to studies with survival outcomes. However, the field of QOL research is newer, and few phase III randomized controlled trials (RCTs) in HNC have yet reported QOL results. Two recent systematic reviews searched for high-quality studies of QOL for HNC patients receiving definitive (chemo)radiotherapy [85] and primary surgical treatment with or without adjuvant treatment [86]. The first found 18 papers, 8 of them prospective, while the second found 26 and 9, respectively; no phase III randomized controlled trial (RCT) results were identified among papers that met quality criteria. However, RCTs using valid instruments have begun to appear [87], and most current ongoing phase III trials include a QOL component. Publication of QOL results from several large RCTs led from Australia/New Zealand (TROG 02.02 HeadSTART), Canada (NCIC-CTG HN.6), and the USA (NRG/RTOG 1016 and 0129) is expected in 2016.

A few useful results have been reported for definitive therapy. QOL after RT for nasopharynx cancer (NPC) was found to be superior after parotid sparing with IMRT than with conventional RT [27], and HNC patients had better experience with selected domains of QOL (especially dry mouth and mouth opening) with IMRT versus 3D conformal RT [88]. QOL was found to return to baseline 12 months after treatment of locoregionally advanced HNC, regardless of whether patients received RT or RT plus cetuximab [87], and sequential versus alternating chemotherapy and radiation [89]. A comparison of intravenous versus intra-arterial cisplatin given with concurrent RT showed only a transient worsening of nausea and vomiting reported in the intravenous group, with no differences in QOL at 1 or 5 years [90]. Induction TPF chemotherapy before RT, relative to PF, did not worsen and may have improved global QOL, while showing better survival and toxicity [91].

In the adjuvant setting, the addition of subcutaneous mistletoe extract to surgery +/− postoperative RT had no effect on QOL as compared to no further therapy [92].

In the palliative setting, injection of a cisplatin/epinephrine gel into HNC tumors, as compared to placebo, did not appear to alter QOL, although QOL compliance was poor [93]. No differences in QOL change from baseline were seen between methotrexate and gefitinib for recurrent/metastatic HNC [94].

Other RCTs have focused on supportive care for HNC patients. A 12-month nurse-led psychosocial intervention, relative to usual care, improved multiple QOL domains with persistent benefits out to 24 months for emotional functioning and fatigue [95]. Low-level laser application during radiotherapy showed short-term QOL improvements, likely related to reduced mucositis [96–98]. Placement of a prophylactic enteral feeding tube prior to (chemo)RT improved 6-month QOL scores on multiple domains, relative to usual care [99]. Two RCTs of pilocarpine showed no QOL benefit over placebo in patients with post-RT xerostomia [24, 100], and three others showed no QOL benefit from a lozenge intended to reduce mucositis [101], from a cream intended to reduce dermatitis [102], or from subcutaneous GM-CSF during radiotherapy [103]. More such studies are needed and, indeed, anticipated.

Cancer rehabilitation is attracting increasing interest and attention. Three small randomized trials have assessed the QOL effects of exercise interventions in HNC patients. In two studies of exercise during (chemo)RT, QOL declined less in patients randomized to resistance exercise versus usual care [104] and improved with a personalized exercise program (versus a decline with usual care) [105]. HNC patient groups randomized to 12 weeks of progressive resistance training either 2 or 5 months post-RT both had physical benefit, but QOL improved more with the earlier intervention [106]. Larger studies are needed to demonstrate the feasibility and acceptability of such programs to HNC patients in general.

49.7.2 Prognostic Applications

In cancer generally, baseline QOL is among the strongest available prognostic factors. A *confounding variable* is defined as a covariate which is associated with both the predictor and the outcome; for baseline QOL and survival, there are many potential confounders. Less baseline comorbidity, lack of ongoing tobacco and alcohol use, higher socioeconomic status and education levels, better social supports, a more optimistic outlook, and less extensive disease have all been associated with both higher QOL and improved survival. Nonetheless, several studies have shown the independent value of baseline QOL in multivariable analyses.

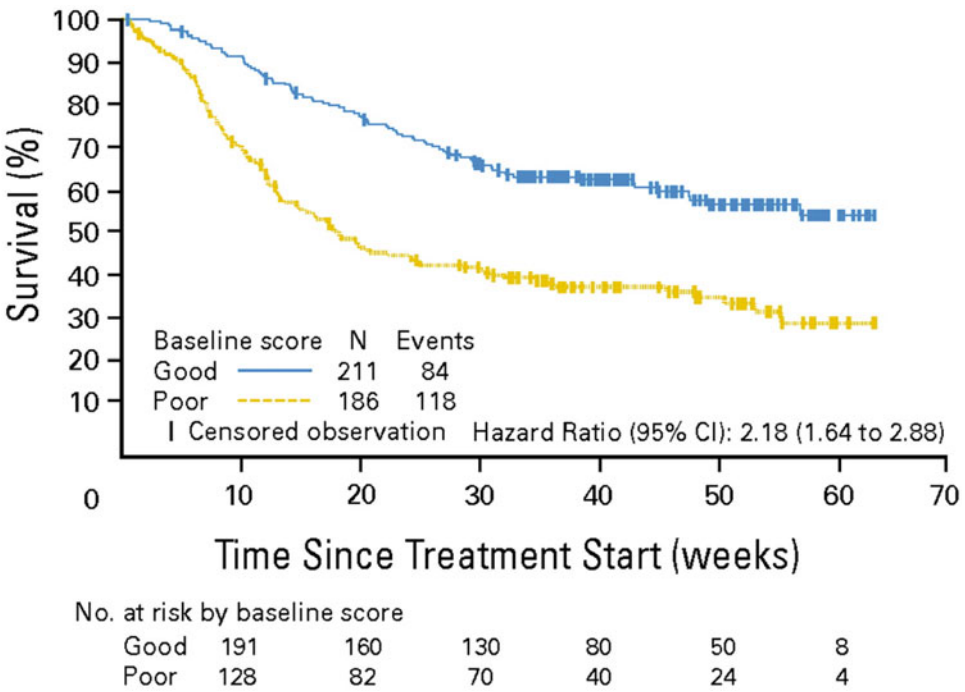

Fig. 49.1 Kaplan-Meier survival curves stratified by baseline EORTC QLQ-C30 global health status/quality of life scores [Reprinted from Curran D, Giralt J, Harari P, et al. Quality of life in head and neck cancer patients after treatment with high-dose radiotherapy alone or in combination with cetuximab. J Clin Oncol. 2007;25(16):2191–2197. © 2008 American Society of Clinical Oncology. All rights reserved]

Figure 49.1 shows the overall survival by baseline global QOL on the EORTC QLQ-C30 in a study of RT versus RT and cetuximab; only Karnofsky performance status was a stronger predictor of survival [87].

A retrospective analysis of prospectively collected QOL data categorized HNC patients as short- (<1 year), intermediate- (1–3 years), or long- (>3 years) term survivors and found significant differences in QOL at all time points, including baseline [107]. The RTOG has published a combined analysis of two HNC randomized trials using FACT-H&N, which showed baseline QOL to be predictive of locoregional control but not overall survival [108]. Finally, a recently completed study of concurrent chemoRT with or without the hypoxic cell sensitizer tirapazamine has shown QOL to be a strong predictor of overall survival, even independently of p16 status in oropharyngeal cancer patients [109]. These results suggest that baseline QOL may be useful as a future tool to assist in selecting patients for differing treatment intensities or for additional supportive care measures, but such a strategy has not yet been explored.

49.7.3 Routine Clinical Application

The use of QOL instruments in clinical trial protocols has become widely accepted; however, their use in general clinical practice is just beginning. An overview of RCTs allocating patients or physicians to use versus not to use QOL data in routine practice showed mixed results, with some studies showing benefits in patient satisfaction or process of care but others failing to show such benefits [110]. Two oncology RCTs have suggested positive effects: Velikova et al. found more frequent discussion of symptoms and improved emotional well-being in patients for whom QOL data was provided to the physician before a visit compared to those for whom it was not [111]. Detmar et al. found more frequent discussion of QOL issues by physicians who had been provided QOL data for patients receiving palliative chemotherapy [112]. Although neither of these studies demonstrated a change in patient management, a recent focus on patient-centered care in many jurisdictions has led to some early initiatives. For example, the province of Ontario (Canada) has incorporated patient-reported outcomes (the Edmonton Symptom Assessment System) throughout all cancer centers, while its largest center (the Princess Margaret) has added patient-reported screening for depression, anxiety, and social difficulties, as well as a head and neck cancer-specific instrument (MDASI-HN), at every HNC patient visit [113]. A recent review identified 33 systems in use to track such data [114]. No published studies evaluating the impact of routine QOL measurement for HNC patients have yet been identified.

49.7.4 Special Challenges (Compliance, Education, and Communication)

The incident population of HNC patients is undergoing a period of rapid change. The traditional risk factors of smoking and alcohol use translated into a patient population with lower than average socioeconomic status and educational levels [115]. For QOL measurement, this led to special

considerations, including the need for instruments that were short, easy to read, and not excessively intellectually complex. In many studies, compliance with questionnaire completion was low; moreover, lack of social support, alcohol abuse, and lower levels of education have all been shown to correlate with lower QOL [116]. More recently, however, 66 % of oropharynx cancer patients in Toronto, Canada, were shown to have HPV/p16-associated cancers; such patients often lack the risk factors of smoking or alcohol use and tend to be younger with higher socioeconomic status and education levels [117]. HPV-associated cancer has an improved prognosis and a unique QOL trajectory [109]. Results from clinical trials designed to test less toxic treatment approaches (such as the use of EGFR inhibitors or trans-oral resection) in such patients, employing QOL and specific symptoms such as dysphagia as central outcomes, are anticipated.

49.8 A Glimpse into the Future

Computer-adaptive tests (CATs) use technology to deliver questionnaires in a logical manner and can significantly reduce respondent burden by producing high reliability and validity with far fewer questions. The approach combines the capability of computers to adapt using if/then algorithms, with the application of item response theory (IRT) to individual questions. IRT is a statistical method which uses mathematical modeling to characterize the ability of each individual item to discriminate differences depending on the level of a patient's problem. Together, this type of system allows the computer to present questions which are most likely to produce a reliable and valid characterization of the underlying trait of interest. For example, a CAT test might begin with an item such as "do you have pain?", which does not make any assumptions about pain level. However, a respondent who answers "yes" would receive follow-up questions regarding pain severity, whereas one who answers "no" might have confirmatory question such as, "does discomfort interfere with your ability to participate in sports?".

49.8.1 PROMIS and CaPS

The Patient-Reported Outcomes Measurement Information System (PROMIS) is a large-scale project sponsored by the National Institute of Health (NIH) in the USA [118]. The goal of PROMIS is to develop a comprehensive bank of items with known IRT characteristics, drawn from existing PRO instruments. These items may then be used for CAT or combined in new ways to create fixed-length PROs for specific purposes [49]. Significant progress has been made for the general health bank, and a prototype online CAT administration tool now exists [119]. Validation of the PROMIS instruments is ongoing. The Cancer PROMIS Supplement (CaPS) has been funded to insure that PROMIS adequately meets the needs for PRO measurement in cancer patients; currently available PROMIS-Cancer instruments exist to measure fatigue, pain interference, and physical function.

49.9 Summary

Improving the survival outcomes of HNC patients remains the primary goal of most advances in therapy. However, the importance of QOL to patients cannot be overemphasized. Both tumor characteristics and treatment strategy influence QOL in the short and long term. The measurement science of QOL and other PRO tools is well developed, and these instruments have been increasingly incorporated into clinical trials. Evidence from prospective, phase III trials is emerging. Future questions include the potential value of using QOL questionnaires in routine clinical care, the best strategies for translating QOL knowledge to clinicians, and the role of CAT administration of PROs.

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Psycho-oncologic Aspects of Head and Neck Cancer Patients

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Michel Reich

Abstract

Head and neck cancer, especially squamous cell carcinoma, represents a worldwide health-care problem. Behavioral and lifestyle risk factors associated to deleterious social environment, treatment-related physical aftermaths, and psychosocial stressors such as disfigurement, stigma, illness intrusiveness, marital impact, and impaired quality of life are commonly associated with head and neck cancer. This can generate psychosocial problems, sexuality concerns, psychological distress, and psychiatric disorders. All these psychopathological complications can interfere with optimal outcomes in terms of patients' compliance to their care and survival. Therefore, all these several psychosocial problematics open some tremendous challenges for multidisciplinary health-care teams in terms of emotional distress screening, referral to mental health or psycho-oncologic team, and psychological and pharmacological intervention proposal.

Keywords

Head and neck cancer • Psycho-oncology • Quality of life • Depressive disorders • Body image impairment • Psychosocial interventions

50.1 Introduction

Head and neck cancer is a life-threatening illness requiring aversive and traumatic treatments. Therefore organ preservation strategy is a real challenge for health professionals in charge of these patients. Nevertheless, due to physical impairment such as facial disfigurement and dysfunction, head and neck cancer patients are considered to be at high risk of developing emotional distress [1], psychiatric morbidity [2], and post-traumatic stress disorder [3, 4]. Life habits, fragile sociodemographic conditions, and physical side effects secondary to the illness and /or treatments can enhance the psycho-oncologic morbidity [5]. Moreover disfigurement, illness intrusiveness, stigma, speech and swallowing impaired function can impact the quality of life of both patients [6, 7] and their partners or spouses [8]. Paradoxically, these categories of patients are not seeking spontaneously for psycho-oncologic support. Moreover, health professionals are lacking in screening mental health disorders or even basic psychological distress in oncologic routine consultation [9]. Therefore, not surprisingly, unmet supportive care needs, especially psychosocial needs, remain predominant, even among head and neck cancer survivors [10, 11], and will affect quality of life and compliance to their care and survival [12].

In this chapter, we would like to focus on behavioral and lifestyle-related factors, on psychosocial stressors, on emotional distress screening, on psychiatric morbidity related to head and neck cancer treatment, on sexuality impact, and on psychosocial and pharmacological interventions.

50.2 Behavioral and Lifestyle-Related Factors

Head and neck cancer without being stigmatizing can usually present a typical profile and background. Epidemiological studies all around the world have now well demonstrated the

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negative and paramount role of tobacco and alcohol use in head and neck cancer occurrence [13, 14]. From a psychosocial point of view, these addictions can contribute to the vulnerability of the patient with socioeconomic impact (unemployment, rehabilitation difficulties, and social isolation) and marital disruption. Some studies in occidental countries like Canada have found a significant link between socioeconomic status with lower income and the incidence of oropharyngeal cancer [15, 16]. It has been demonstrated that in head and neck cancer patients, psychological factors (e.g., less active coping, less health hardiness, less optimism) in excessive drinkers can affect health-care-seeking behavior with an average 3 months' delay before seeking medical care [17].

Other studies have found a significant correlation between delayed consultation by patients with head and neck cancer and psychological factors such as anxiety and lack of social support (absence of spouse or partner) [18]. Denial and difficulties in recognizing potential cancer symptoms and lack of knowledge about its issues can also explain delay in seeking medical consultation [19].

Patients' individual interpretation of oral cancer symptoms and personal beliefs (e.g., not being concerned by their symptoms), patients' social responsibilities, and difficulties with access to health-care professionals can adversely affect subsequent help-seeking behavior [20].

Besides these classical risk factors, human papillomavirus (HPV) infection due to special sexual activity is emerging as a strong carcinogen involved in some head and neck squamous cell carcinomas (HNSCC) [21, 22]. Psychosocial consequences and needs in terms of information, emotional reactions, and education of this new risk population remain to be investigated [12, 23]. Patients with HPV-associated squamous cell carcinomas arising in the oropharynx tend to be generally much younger and are in good general health due to minimal or absent tobacco and alcohol addiction but might have increased number of lifetime sexual partners with specific sexual habits (oral and genital sex) [24].

50.3 Psychosocial Stressors

As mentioned previously, many studies highlight the overwhelming presence of unmet psychological needs in head and neck cancer patients and underline the importance of implementing interventions to address these areas perceived by patients as important and neglected by the health professionals [10, 12, 25]. Many patients express dissatisfaction with care received about body image issues and the lack of additional resources to help them cope with body image changes [26]. Confronted to uncertainty about recurrence and prognosis, disruption of lifestyles and familial and professional lives, head and neck cancer patients must implement ongoing adaptive mechanisms which they cannot always challenge. They have to face incremental psychosocial stressors related to functional difficulties such as swallowing or chewing, speech, and disfigurement concerns with individual's sense of self and body integrity impaired which will maintain them in stigma with a feeling of exclusion and rejection [7].

50.4 Screening

Implementation of routine screening programs for detecting and managing psychosocial distress among cancer patients is promoted by the National Comprehensive Cancer Network [27].

Screening for psychological distress in head and neck cancer patient is important for early referral for psychosocial care. One of the major challenges is to propose to oncologists some brief screening tools that may help clinicians in busy settings in detecting patients who are experiencing severe psychological distress [28]. The most common tools used in the oncologic setting and recommended by studies found in the literature are the Hospital Anxiety and Depression Scale (HADS) and the Distress Thermometer (DT) [29]. HADS questionnaire can easily and quickly assess symptoms of anxiety and depression [30] and be used for the follow-up in head and neck cancer patients [31]. Among several screening instruments, HADS has been associated with the best level of sensitivity and specificity for detecting mental disorders in laryngeal cancer patients [32] and especially depression in head and neck cancer [33].

DT is a well-validated screening tool, sensitive and specific to assess the level of distress in cancer patients [34]. The DT is a simple, self-report, pencil and paper measure consisting of a line with a 0–10 scale anchored at the zero point with "no distress" and at scale point ten with "extreme distress." Patients are given the instruction, "How distressed have you been during the past week on a scale of 0–10?" The cutoff score is usually 5. So patients scoring 5 or above would need a psychological intervention. Distress Thermometer has been recommended in head and neck cancer patients to assess psychological distress [35].

50.5 Psychological Side Effects of Treatment

Patients with head and neck cancer experience profound functional and visible changes as a result of the disease and treatment. Psychosocial problems include anxiety, depression, loss of self-esteem, and uncertainty about the future [36].

These patients can have a specific psychological experience to live with head and neck cancer which is mainly characterized by uncertainty and waiting, disruption to daily life, diminished self, and difficulties to making sense of this experience, sharing the burden, and finding a path [37].

Loss of speech due to laryngectomy can result in functional disability and physical disfigurement due to the presence of the stoma. Paradoxically, a majority of patients do not consider the permanent stoma and voice loss to be the most important determinant of quality of life [38]. Interestingly, some studies show that there are no differences in terms of psychosocial adjustment [38] or psychiatric disorders occurrence regarding the type of surgery (total laryngectomy versus horizontal supraglottic laryngectomy or partial vertical surgery) [39].

The impact of mutilating head and neck treatment is enhanced by gender and social support. In that way, women with head and neck cancer who experience low social support and face disfiguring treatment are at greatest risk for psychosocial dysfunction such as low emotional well-being and altered social interaction [40].

Incidence and prevalence of mood disorders in head and neck cancer patients are estimated, respectively, between 15 and 50 % [41] and 6 and 15 % [42]. It can persist to 8 % at 18-month follow-up after radiotherapy regimen has been completed [43].

This population is at risk for depression because of the life-threatening nature of the illness and treatment-induced oral morbidity [33].

Depression in head and neck cancer patients increases following cancer treatment such as radiotherapy and is related to tumor-/treatment-related physical symptoms [43].

Depressive disorders are risk factors of continued smoking after head and neck cancer diagnosis and even problem drinking which will negatively affect outcomes and will impair severely treatment benefits [44]. Moreover, psychological factors, including distress and fears of recurrence, may be implicated in explaining the persistence of a smoking behavior among head and neck oncology patients in their first 15 months of recovery following initial treatment [45].

Some studies have focused on the relation between the presence of depressive symptoms before the initiation of cancer treatment and the significant negative and deleterious impact on health-related quality of life at follow-up over time in head and neck cancer survivors [46].

50.6 Impact on Sexuality

Head and neck cancer treatment can affect intimacy, sexuality, and marital satisfaction, but this subject is underestimated, underreported, and not so often discuss with patients and their partners in routine follow-up clinics [47]. Nevertheless, in studies involved in the impact of sexuality on quality of life, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Head and Neck 35 (EORTC H&N35) regarding sexuality and intimacy has found that approximately one-third of patients treated by laryngectomy reported substantial problems with sexual interest and enjoyment, and one-quarter reported problems with intimacy [48]. Nevertheless, a recent study done in 42 patients after treatment for head and neck cancer found that a majority of them (57 %) show sexual satisfaction during recovery [49].

Key Messages

1. Socioeconomic status, addictions, and lifestyle behaviors can contribute to enhance head and neck cancer patient's vulnerability and delay in seeking diagnosis and treatment initiation.
2. Health professionals must be aware of psychosocial stressors and unmet psychological needs in head and neck cancer patients.
3. HADS and DT can be used as screening tools by oncologists for detecting psychological distress in head and neck cancer patients. Early screening is linked with a better referral for psycho-oncologic care.
4. Psychological side effects of treatment include anxiety and depressive disorders and body image impairment and can impact sexuality and quality of life.

50.7 Psychosocial Treatment

A European group from the European Head and Neck Cancer Society Make Sense campaign has recently published some guidelines in order to define and deliver emotional support for head and neck cancer patients at each stage of their care [5].

If psychological morbidity in head and neck cancer patients is a clinical reality, in daily practice, it is still complicated to be able to convince these patients to subscribe to psycho-oncologic care. Still, psychoeducational and cognitive and behavioral interventions can improve the psychological outcomes of these patients [50, 51]. Moreover, the impact of psychological treatment at least when a psychological interview is performed with head and neck cancer patients can improve their quality of life if this interview does meet the needs of the patients [52]. The psycho-oncologic approach is integrated in a coordinated multidisciplinary management [53] and rehabilitative approach [9]. It will focus on physical and functional problems encountered during the disease evolution and its treatment. From a practical point of view, delivery and coordination of care among health professionals should be implemented before the patient starts physical treatment such as surgery and radiotherapy. Preparation of the patient with provision of gradual information about treatment strategies, side effects expected, functional limitations that may occur, and rehabilitation techniques is one of the very important steps in patient psychoeducation and management. This will help him in developing coping strategies to overcome, facilitate recovery, and if not prevent at least limit psychological distress. Collaborating with the

supportive department will be helpful regarding nutritional, communication, pain and social concerns. It will facilitate adequately management of the complex needs of these patients and their families.

Nevertheless, the effectiveness of these psychosocial interventions in improving quality of life and psychological well-being for patients with head and neck cancer has been questioned in a recent meta-analysis, and furthered studies must be implemented [54].

50.8 Psychotherapeutic Treatment

Cognitive-behavior therapy and supportive expressive therapy and specific treatment for anxiety such as relaxation techniques are the most often provided treatments in head and neck cancer patients [51, 55]. Some recent studies tend to demonstrate that early provision of psychotherapy has utilized in reducing post-traumatic stress disorder and anxiety and depressive symptoms and preventing chronic psychopathology in distressed head and neck cancer patients [4].

Some psychosocial parameters can influence the success of voice rehabilitation after laryngectomy: motivation is correlated with the use of an esophageal voice whereas speech intelligibility is associated with active communication behavior [56].

50.9 Pharmacological Treatment

Antidepressants can be useful for treating depressive disorders that might occur during the illness and treatment course. Some authors have hypothesized the benefit to use an antidepressant (citalopram [57] or escitalopram [58]) in prophylaxis during physical treatment, in order to prevent the occurrence of depressive disorders. Tricyclic antidepressants which are known to have an analgesic effect have been used for radiation-induced mucositis pain in head and neck cancer [59].

Nevertheless, clinical trials of antidepressant remain rare in this population.

Besides all these therapies, referral to support group and associations, provision of smoking, and alcohol cessation programs can be provided.

As depression is often associated with smoking and alcohol abuse, a tailored intervention for treating these three comorbidities would be more useful than treating these disorders separately [60].

Key Messages

1. Psychosocial interventions are part of the multidisciplinary approach of head and neck cancer patient management.
2. Combined psychotherapeutic and pharmacological treatments are necessary in order to get efficient results in treating psychological distress and psychiatric complications.

50.10 Conclusion

Head and neck cancer patients have many reasons to develop either psychological distress or psychiatric disorders. Coping needs and adaptive challenges are often questioned regarding tremendous disturbances with disfigurement, speech, and swallowing; functional limitations, and impaired quality of life. Symptom burden, illness intrusiveness, and stigmatization can contribute to an ongoing psychosocial strain for these patients. A better screening and the active support of a multidisciplinary team in which a psycho-oncologic team is involved could be the cornerstone to their rehabilitation and recovery.

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Advances in Nanomedicine for Head and Neck Cancer

51

Sajanlal R. Panikkanvalappil, Mostafa A. El-Sayed, and Ivan H. El-Sayed

Abstract

Nanomedicine represents an emerging and innovative field, which can potentially improve the way we diagnose, treat, and prevent cancer. At the nanoscale, some elements demonstrate unique properties that are not observed in their bulk entity, such as paramagnetism and surface plasmon resonance. Engineering nanostructures with precise control of size, shape, and surface functionalities at a size range well matched to work at the cellular level, which have large surface to volume ratio (for drug loading), apparent biocompatibility, possible in vivo targetability, combined with their physical properties, is paving the way for novel treatments and diagnostic procedures in the field of nanomedicine and oncology. Innovative nanotechnology-based diagnostic imaging procedures, drug delivery techniques, and novel treatment modalities are under development. In this chapter we introduce key concepts of nanotechnology-based cancer research along with recent innovations with potential to address head and neck cancer.

Keywords

Nanomedicine • Head and neck cancer • Diagnosis • Targeting • Therapy

51.1 Introduction

Head and neck cancer (HNC) is the sixth most common cancer worldwide (around 6 %) of all cancer cases [1]. HNC can arise from the epithelium of the upper aerodigestive tract such as the oral cavity, pharynx, larynx, paranasal sinuses, and nasal cavity, as well as the deeper tissues of the bone, salivary glands, and various cell types (Fig. 51.1a). Among the HNC, oral squamous cell carcinoma represents more than 90 % of the cancer incidents [2, 3].

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While there is a recent epidemic of human papilloma virus (HPV) oropharyngeal carcinoma, with relative high survival rates, mortality rates for non-HPV-related HNC remain relatively unchanged for the past 50 years. HNC is difficult to treat due to the aggressive biology of the tumor with highly locally invasive character and tendency for regional and distant metastases. Treatment of HNC typically requires either surgical resection or radiation therapy with or without chemotherapy. Chemotherapy as a sole therapy is fairly ineffective for HNC. Recently, immunotherapies, which use antibody to epidermal growth factor receptor (EGFR), have shown some promise as adjuvant treatment with radiation.

HNC occurs in close proximity to several cosmetically and functionally critical structures, such as the carotid artery and the organs necessary for speech, swallowing, olfaction, hearing and balance, and vision, as well as the spine, brain stem, and brain. Treating HNC without causing significant morbidity as a result is challenging. Since conventional chemotherapy agents lack tumor specificity, surgery requires access and margins of normal tissue and radiation adjacent areas or oropharyngeal carcinoma; high

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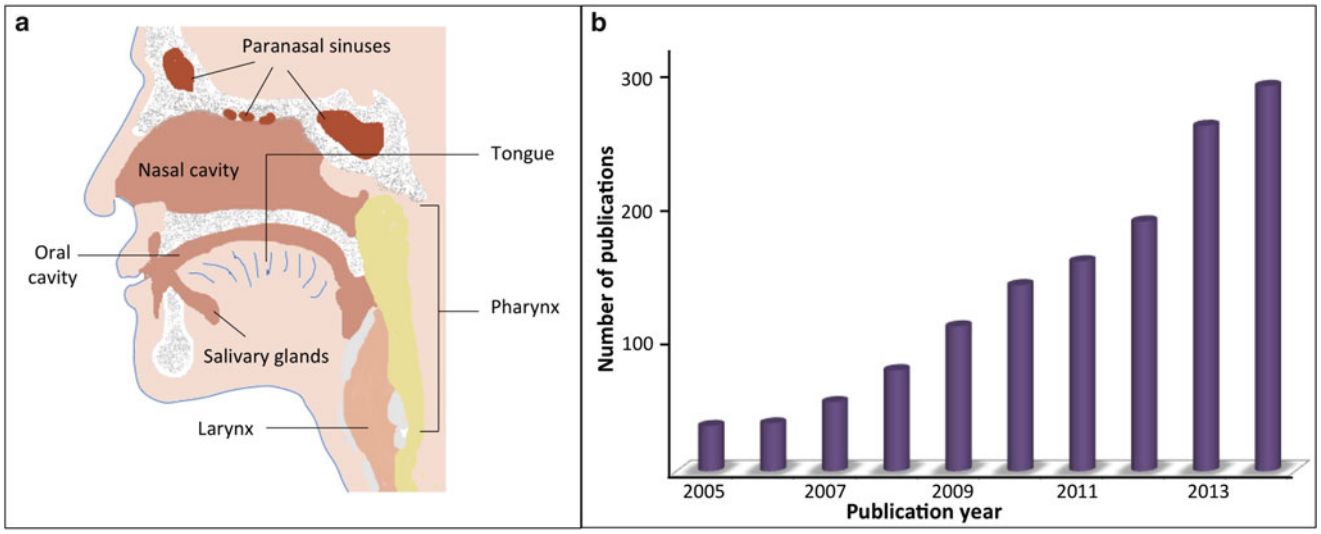

Fig. 51.1 (**a**) Anatomic subsites of some common primary sites of origin of HNC [20]. (**b**) Number of papers published on nanomaterial-based oral cancer management during the last decade (2005–2014), which was collected from ISI Web of Science using a keyword search of "oral cancer nano*"(source: ISI Web of Science). When expanded with further directed terms such as nanoparticle, nanotechnology, oral carcinoma, etc., the number of publications increases. (**b**) Based on data from ISI Web of Science

rates of gastrostomy tube dependence after successful radiation and chemotherapy reported up to 20 % using current regimens [4–6]. Despite recent advances in the diagnosis and treatments for HNC patients, the overall treatment-associated toxicities make the eradication of this cancer challenging.

Emerging nanotechnologies resulting from interdisciplinary research from physics, chemistry, biology, engineering, and medicine offer new avenues of biomedical applications for cancer diagnosis and treatment [7–10]. In medicine, nanotechnology offers a vast array of opportunities to identify and address challenges in cancer management. Advancements in nanomaterial research are providing new pathways to engineer nanostructures with precise control of size, shape, and surface functionalization. At the nanoscale, elements exhibit novel physical properties not witnessed at the bulk scale. For example, gold nanoparticles (GNPs) become optically active; other nanoparticles made of magnetic material such as iron oxide exhibit super-magnetisms and show magneto-thermal effects. A myriad of nanoparticles are reported by 2015; the continued discoveries of new properties suggest unforeseen possibilities of nanotechnology. Exploiting their physical and biofunctional properties may allow creation of highly specific therapies and diagnostic tools to manage cancer. The appropriate size match of nanoparticles and biological molecules allows the functionalization of inorganic nano-particles to be used at the molecular scale. Toward this direction, multifunctional nanostructures are being developed, which can simultaneously be used for cancer diagnosis and targeted drug delivery or therapies. Understanding how to manipulate nanostructures in vivo in biologic environments is required to advance nanomedicine research.

Taking advantage of the unique properties of organic and inorganic nanomaterials at the nanoscale, such as large surface area to volume ratio, novel optical and magnetic properties, and interesting structural properties, combined with possibilities of functionalizing the nanoparticles to make them biocompatible, can be exploited to overcome biological barriers important to targeting cancer. Improved tumor uptake can be achieved through standard methods by designing nanoparticles and small molecules to prolong circulation times to enhance uptake in the tumor bed, adding ligands to increase endocytosis, or by developing unprecedented techniques such as attracting metallic nanoparticles to a tumor with external magnets [11, 12]. In the area of HNC research, the novel physiochemical properties of plasmonic nanoparticles such as localized surface plasmon resonance (LSPR), enhanced light scattering, and photothermal and photoacoustic properties [13, 14] have generated widespread international attention to develop diagnostic tests and effective treatments in HNCs [9, 15–19]. Figure 51.1b summarizes a literature search of publications that appeared in ISI Web of Science using a selected keyword for the topic of "oral cancer nano*" over the past 10 years. The significance of nanomedicine in the HNC management is steadily growing with the expectation of novel applications will be translated clinically.

In this chapter, we introduce current key concepts of nanomedicine along with recent innovations having the potential to address HNC.

51.2 Nanomaterials in Nanomedicine

Over the past few decades, nanomaterial-based vectors made of various materials such as metal and metal oxides, dendrimers, carbon, lipids, polymers, and quantum dots have been used for addressing challenging issues in HNC research [17, 21–36]. The pharmacological utility of micro/nanoparticle-based therapeutic techniques has been used dated back in late 1960s by Speiser for drug delivery purposes and for vaccines [37]. However, it was in 1975 that Rigdorf proposed the possibility of polymer micro/nanomaterials as drug delivery vehicle in anticancer models. He envisioned the unique capability of polymer-based delivery of cancer therapies as water-insoluble drugs which could be made water soluble by introducing drug-solubilizing moieties into the polymer that enhance the biocompatibility and degradability [38].

Nanoparticles for pharmaceutical purposes can be defined as solid colloidal particles ranging in size from 1 to 1000 nm. They consist of macromolecular materials (a colloidal carrier, particulate dispersions, or solid particles) and can be used therapeutically as drug carriers, in which the active principle (drug or biologically active material) is dissolved, entrapped, or encapsulated or to which the active principle is adsorbed or attached [39].

51.3 Unique Characteristics of Nanoparticles

Nanotechnology truly represents a new age of medicine with the ability to design biologically compatible particles with appropriate size match that can work within the lock-and-key system typical of biological molecules or completely bypass biologic hurdles with innovative strategies. At the nanoscale, physical and chemical properties of nanoparticles can be controlled by altering the spatial confinement of electrons, which directly depend on the particle composition, size, shape, degree of aggregation, and local environment. Over the past two decades, it was discovered that many metal and semiconducting nanomaterials attain unique and unusual properties due to the larger proportion of surface atoms compared to their bulk entity. Modifications in various parameters such as spatial confinement of electrons and phonons are attainable by changing the size and shape of particles, and this has resulting effects on the exhibited behavior of the particles' physical properties, electric field, magnetism, and phonon excitation. Novel effects are seen based on the particle size, shape, and composition, making them tunable in some settings to specific wavelengths of the electromagnetic spectrum. Noble metal nanoparticles exhibit LSPR effect; quantum confinement occurs in semiconductor particles or noble metal quantum clusters, while others exhibit paramagnetism, superparamagnetism, superparamagnetism [40–42], etc. Physics has opened opportunities for applications in nanomedicine using techniques such as resonance light scattering, photoacoustic imaging, multiphoton imaging, Raman and fluorescence spectroscopy, photothermal and magnetothermal heating of nanoparticles, high-resolution molecular imaging, and so forth [21].

Given the myriad of nanotechnologies, the potential can be demonstrated using GNPs as an example. GNPs exhibit a strong surface plasmon resonance associated with the modification in the confinement of electrons during the transition of metal from their bulk stage to nanoregime. Because of the poor penetration power of lower energy electromagnetic waves on a metal surface, the excitation of plasmons is only caused by the surface electrons of bulk metals. This results in the formation and propagation of alternating positive and negative charges along the x and y directions (surface) of the metal–dielectric interface, which decays momentarily in the z direction (Fig. 51.2) [43, 44]. At the nanoscale, electrons are confined to a finite volume of the nanoparticle. During exposure of GNPs with electromagnetic radiation of appropriate wavelength, the conduction band electrons near a metal–dielectric interface get excited and undergo a collective coherent oscillation of free electrons relative to the lattice of positive nuclei at the frequency of the incident light. This creates a localized surface plasmon as the electrons resonate together. This electron oscillation around the nanoparticle surface creates a dipole that can switch along the direction of the electric field of the light [13]. This enhanced field is several orders of magnitude above the incident field, which brings about novel properties for the particles.

51.3.1 Potential Attributes of Gold Nanoparticles

GNPs have been proposed for a myriad of applications in nanomedicine due to their extremely small size that is well matched in size to biological molecules, facile surface chemistry allowing conjugation with various ligands for biofunctionalization, larger surface to volume ratio to allow concentrated delivery of therapeutic agents, and apparent low toxicity [46–48]. Manipulating GNP size and surface functionality has allowed early success to achieve both passive and active targeting of tumors (will be discussing later in details).

51.3.2 Nanoparticles for Drug Delivery

Designing nanoparticle-based drug delivery strategies can lead to the development of several novel cancer treatment modalities. In nanoparticle-based drug delivery strategy, drug molecules can be incorporated to the nanoparticle during the

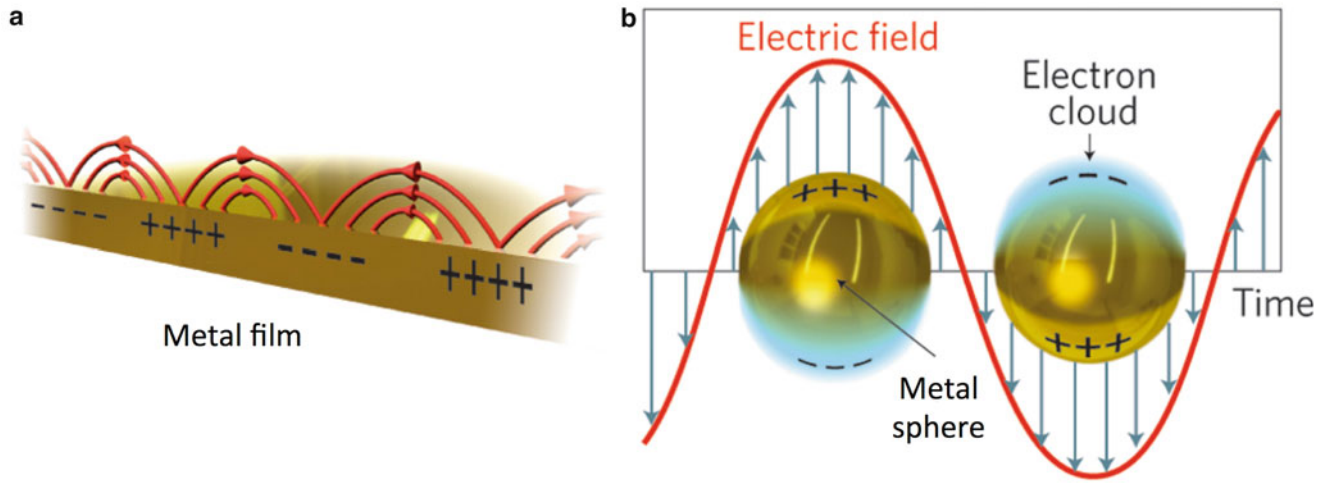

Fig. 51.2 Plasmonic nanoparticles show unusual optical properties that are different from their bulk analogue. (**a**) Excitation of surface plasmon on metal film results in the formation of alternating positive and negative charges, which propagate in the x and y directions along the metal–dielectric interface. (**b**) Localized surface plasmons in metal nanospheres [45] [Adapted from Juan, M. L.; Righini, M.; Quidant, R.: Plasmon nano-optical tweezers. Nat Photon 2011, 5, 349-356. With permission from Nature Publishing Group]

time of synthesis or post-synthetically by direct functionalization (metal nanoparticles) and/or by adsorption/absorption (nonmetal, macromolecule, etc.) techniques. In general, enhanced solubility of drug molecules and their release rate through desorption, diffusion, and degradation can be achieved by apt chemical functionalization of the nanoparticles [49]. Site-specific targeting of nanoparticles can be achieved by attaching various targeting ligands to the surface of the nanoparticles that can enhance the therapeutic efficacy by targeted delivery of drugs in a tissue- or cell-specific manner. The nanoparticle administration can be done by various routes including oral, intravenous, nasal, parenteral, intraocular, etc.

Apart from that, nanoparticle-based platforms can be used in theranostics by combining multimodal capabilities and simultaneous diagnosis, therapy, and real-time monitoring of therapeutic efficacy. Nanocarriers offer many advantages over free drugs as they can prevent the premature degradation of molecules, evade the immune system, and avoid premature intravascular clearance.

Ideally, a nanocarrier should deliver the drug to the tumor site with minimal loss of their dose volume, drug activity, and therapeutic efficacy while reducing host morbidity to healthy tissue. Current nanoparticle-based targeted delivery strategy has been mainly classified into passive and active targeting [9, 15, 50, 51]. In the passive targeting technique, nanoparticles without having any tumor-specific targeting moiety accumulate at tumor site through enhanced permeability and retention effect (EPR) (Fig. 51.3). Due to their malformed nature, solid tumors tend to have leaky vascular that allows inflow of molecules and particles. Shielding nanoparticles and attached moieties from the immune system with immunopassivation techniques, such as coating with polyethylene glycol, allows for increased circulation time. Choosing nanoparticles of the correct charge and size allows avoidance of other clearance mechanisms such as the kidney, liver, and reticuloendothelial system. Due to the increased vascular permeability and poor lymphatic drainage in tumors, nanoparticles can penetrate through malformed spaces in the microcapillaries and become sequestered at the tumor sites. However, the poor diffusion efficiency of many drugs or moieties that could be carried by nanoparticles therapeutically, and the absence of EPR effect in certain tumors, makes this method challenging. Overcoming these barriers is an ongoing active field of research to balance the physical and biological barriers while carrying therapeutic or imaging agents.

Actively targeting tumors is another avenue of attack. Nanoparticles can be conjugated with targeting agents, such as antibodies specific to proteins more highly expressed in tumors than healthy tissue, peptides, small molecules, etc. which can actively bind to target molecules on the tumor as a result of the binding properties of the targeting ligands on the nanoparticle surface (Fig. 51.3). These include EGFR/Her1, cyclic RGD (cRGD), galactose, glycyrrhizin, bisphosphonates, and (S,S-2-(3-(5-amino-1-carboxypentyl)-ureido)-pentanedioic acid) (ACUPA) and have been employed for active tumor targeting of folate receptor, endoglin (CD105), prostate-specific membrane antigen (PSMA), epithelial cell adhesion molecule (EpCAM), etc. [9, 52] on the cancer cell surface. Most techniques must rely on a sequential process involving both passive via the EPR effect and active targeting.

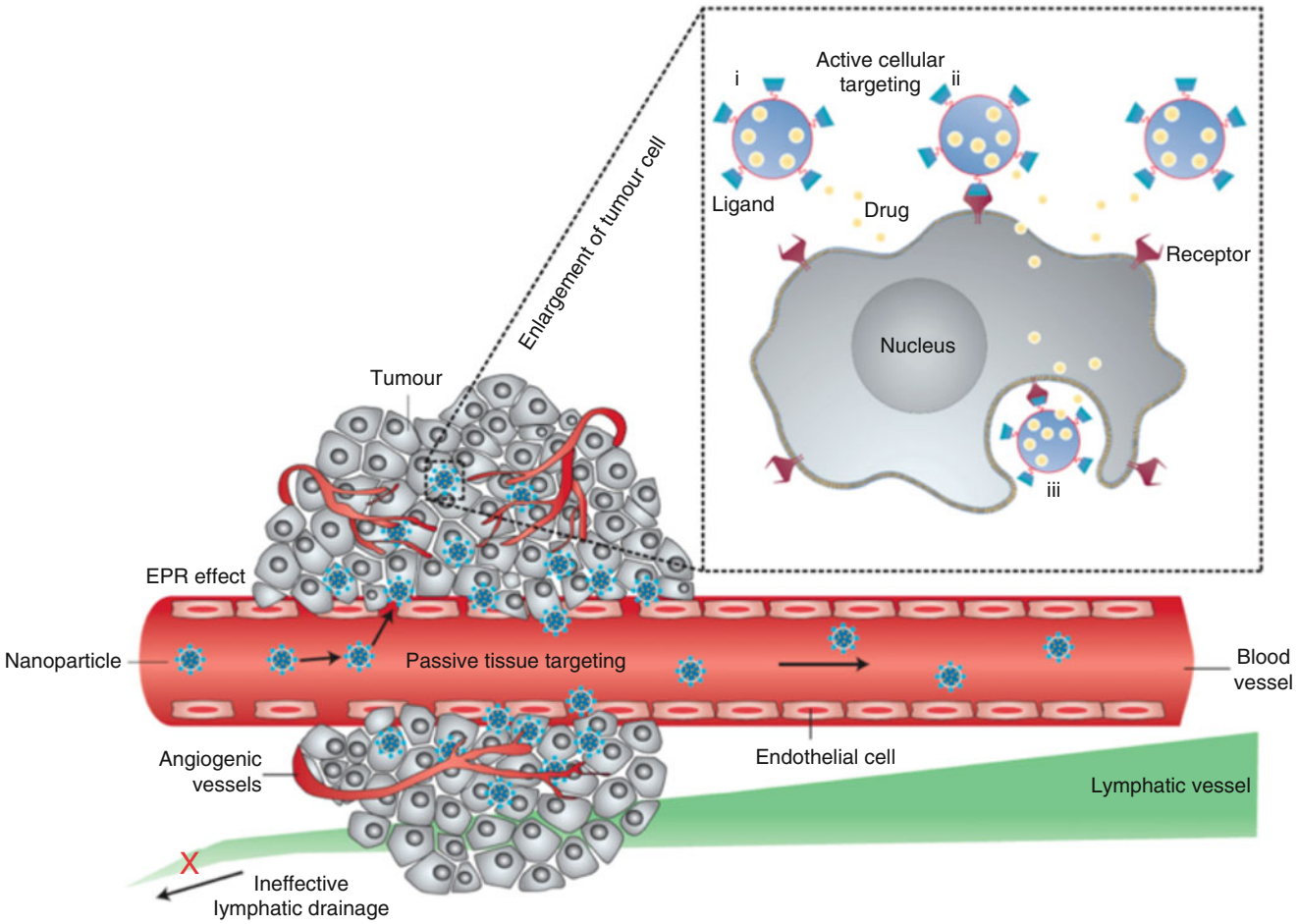

Fig. 51.3 Nanoparticles can passively target tumors through preferential passage through larger interendothelial junctions, which are key characteristics of the irregular tumor vasculature. Nanoparticles can actively target tumors by functionalizing them with targeting agents, such as antibodies that can preferentially bind with the antigen overexpressed in tumors than healthy tissue [15] [Adapted from Peer, D.; Karp, J. M.; Hong, S.; Farokhzad, O. C.; Margalit, R.; Langer, R.: Nanocarriers as an emerging platform for cancer therapy. Nat Nano 2007, 2, 751-760. With permission Nature Publishing Group]

51.3.3 Nanomedicine-Based Approaches to Head and Neck Cancer

This section has been divided into three categories, which include the various drug delivery vehicles used in HNC treatment and diagnosis, various nanoparticle-based therapeutic platforms being explored in the treatment of a variety of HNC, as well as diagnostic enhancement techniques. A pictorial representation of all these aspects is given in Fig. 51.4.

Nanoparticle-based delivery vehicles are the materials which can carry multiple drugs and/or imaging agents so as to enhance their local concentration at tumor site inside the body and trigger the controlled release of the cargo molecule within them when bound to the tumor sites. A broad spectrum of innovative nanoparticle-based delivery vehicles has been developed recently by the nanotechnologists for addressing various challenges in HNC. Here, we specifically mention few of those delivery vehicles used in immediate therapy and for multimodality techniques.

51.4 Drug Delivery Vehicles

Nanotechnology is under investigation of vehicles for delivery of drug and therapeutic molecules. Nanotechnology shows particular promises in aiding delivery of non-druggable drugs such as those insoluble in biological conditions or too toxic for the human host. Drugs and molecules can be entrapped, encapsulated, attached, or dissolved in nanoparticles. Several types of molecular nanocarriers have been reported such as polysaccharides, proteins, biocompatible/biodegradable polymers such as polyethylene glycol, poly(γ-benyzl-L-glutamate, poly(D, L-lactide), poly(lactic acid), poly(D, L-glycolide), chitosan, gelatin, and so forth [33]. Nanomaterials made of metals, dendrimers, liposomes, or micelles can also be exploited for drug delivery. Nanoparticle formulations of drugs or molecules can be used to dissolve insoluble drugs, avoid degradation, by pass the immune system, reduce host toxicity, and improve tumor delivery via the EPR effect. There is some early data sug-

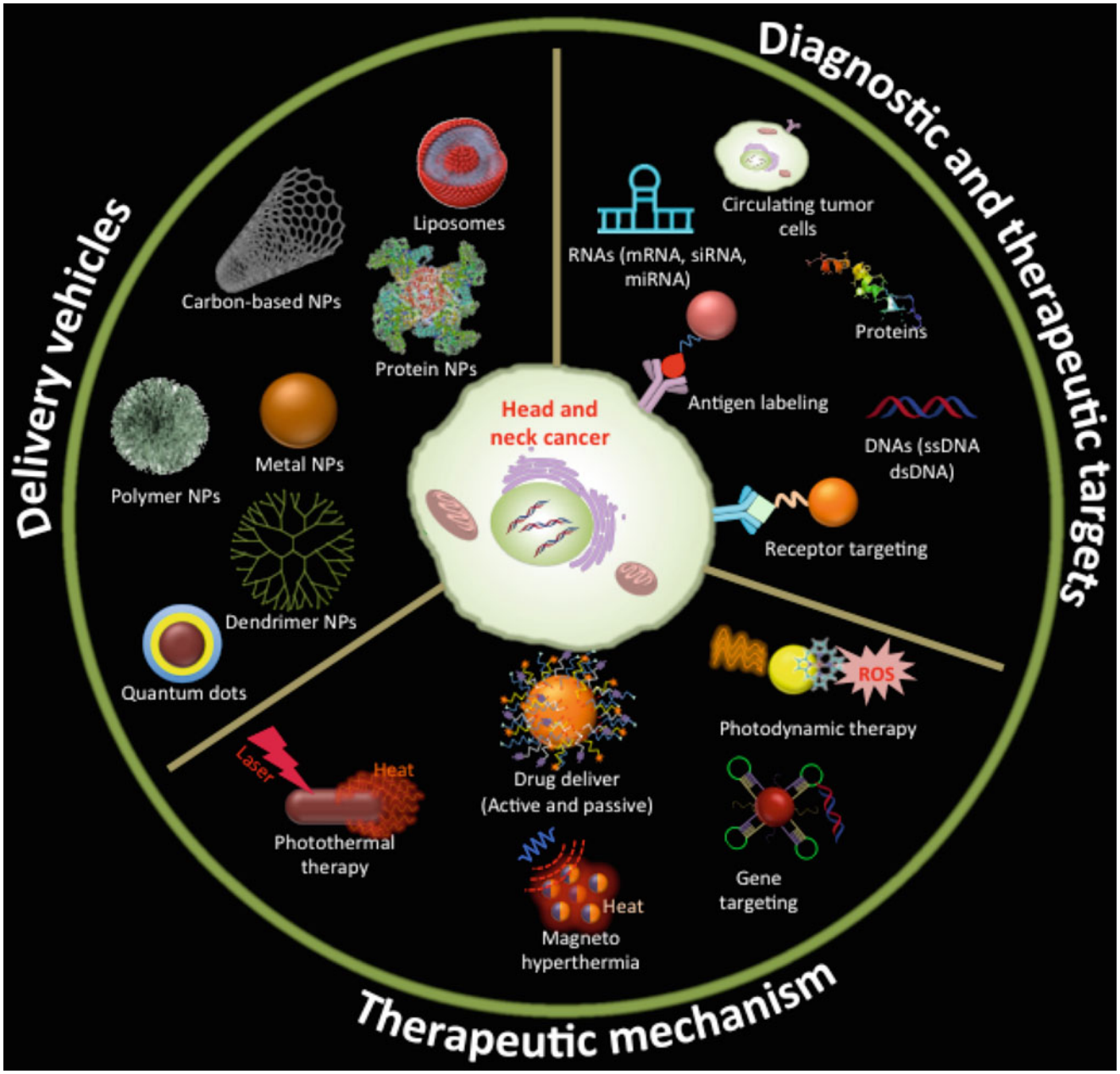

Fig.51.4 Schematic showing various delivery vehicles, diagnostic and therapeutic targets, and therapeutic mechanisms involved in nanotechnology-based treatment modalities in HNC

gesting that nanoparticle formulations may help prevent eliciting drug resistance mechanism in cellular responses [53]. Koziara et al. found that paclitaxel bound in emulsifying wax nanoparticles applied to human adenocarcinoma cell line appeared to avoid activating p-glycoprotein pump, a chemoresistance mechanism of some cancers. Paclitaxel is used with a solvent commonly used in paclitaxel formulations, but it is known to be highly allergenic and requires high-dose steroids and antihistamine premedication prior treatment. By formulating paclitaxel in an albumin nanoparticle (nab-paclitaxel), the solvent Cremophor EL® is avoided and higher doses are delivered to the tumor. Damescelli et al. demonstrated in a pilot study in humans that nab-paclitaxel administered with selective intra-arterial catheterization demonstrated clinical response in 78 % of oral tongue carcinomas [54]. Currently, nab-paclitaxel is used in human breast cancer and in conjunction with gemcitabine for pancreatic cancer [55]. Other strategies using copolymers bound to herpes simplex virus thymidine kinase [56] and cisplatin-loaded polyethylene glycol have been assessed in oral cancer models and demonstrated some effect. In the cisplatin model, renal toxicity was also reduced [57]. However, issues with toxicity of some polymer systems and scalablity of polymer-based products still limit current clinical use. Details of various nanomaterial-based platforms used in HNC treatment have been given in Table 51.1.

Table 51.1 Details of various nanomaterial-based platforms used in HNC treatment

Nano-platform	Type of cancer	Treatment type	Targeting moiety	Application	Type of study	Ref.
Magnetic	Nasopharyngeal, laryngeal, and HNC	Hyperthermia and photodynamic therapy	Folate receptor, integrin β1, intratumoral injection	Imaging and therapy, magnetic resonance imaging, immunohistochemistry and an immunofluorescence	In vitro and in vivo	[25, 58, 59]
SWNTs	Head and neck squamous carcinoma	Drug delivery and electrochemical immunosensor	EGFR, interleukin-6	Imaging, therapy, breath testing using nanoscale artificial nose	In vitro and in vivo	[27, 60, 61]
Carbon	Head and neck squamous cell carcinoma	Drug delivery vehicle	Cetuximab	Targeted therapy	In vitro and in vivo	[62]
Dendrimer	Head and neck squamous cell carcinoma	Drug delivery	Folate receptor	Targeted therapy	In vitro and in vivo	[26]
Gold	Head and neck squamous cell carcinoma	Photothermal therapy, photodynamic therapy, and drug delivery vehicle	EGFR, A9 antigen	Optical imaging, X-ray-based computed tomography, and targeted therapy	In vitro, in vivo, and clinical and preclinical trials	[17, 18, 63–65]
Lipid	Head and neck squamous cell carcinoma	Gene delivery	RNA	Deliver therapeutic microRNAs	In vitro and in vivo	[28]
Polymer	Head and neck squamous cell carcinoma and salivary glands	Drug and gene delivery and photodynamic therapy	Scavenger receptors, RNA	Targeted therapy, Radioprotection using siRNA-based gene silencing	In vitro and in vivo	[31, 66–68]
Protein	Head and neck carcinoma	Gene delivery	Gene	Adenoviral gene therapy	In vitro and in vivo	[69]

51.4.1 Metal Nanoparticles

Metallic nanoparticles have long attracted interest as a promising material in nanomedicine. They were recognized in early 1970s when Faulk and Taylor showed the possibilities of immunogold labeling using nano-bioconjugates [70, 71]. Since then, metallic nanoparticles, especially gold, have garnered significant attention toward the diagnosis and treatment of HNC owing to their unique properties such as plasmon absorption and scattering. GNPs, in particular, are exciting because they have low toxicity and can be easily synthesized and functionalized with proper ligands. They exhibit unique optical properties in biologically relevant windows of the electromagnetic spectrum, which can be tuned by manipulating their size and shape. Based on the LSPR effect, the plasmonic enhancement of incident light can be exploited as optical probes for early detection of oral cancer and photothermal therapy of HNC and many other cancers. The color of the light scattered or absorbed is tunable over the visible range for gold nanospheres and the near-infrared region with gold nanorods (GNRs). Further the brightness of the light is extremely intense, allowing for single nanoparticle detection. El-Sayed et al. demonstrated a simple and inexpensive plasmonic technique to distinguish the oral cancer cells from noncancerous cells [18]. Here, the monoclonal anti-epidermal growth factor receptor (anti-EGFR) antibody-conjugated spherical GNPs showed specific, homogenous, and enhanced binding affinity to the surface of two malignant oral epithelial cell lines (HOC 313 clone 8 and HSC-3) than to the nonmalignant epithelial cell line (HaCaT), which is mainly attributed to the overexpressed EGFR on the cytoplasmic membrane of the malignant cells (Fig. 51.5a). This specific and homogeneous binding resulted in a significantly sharper LSPR absorption

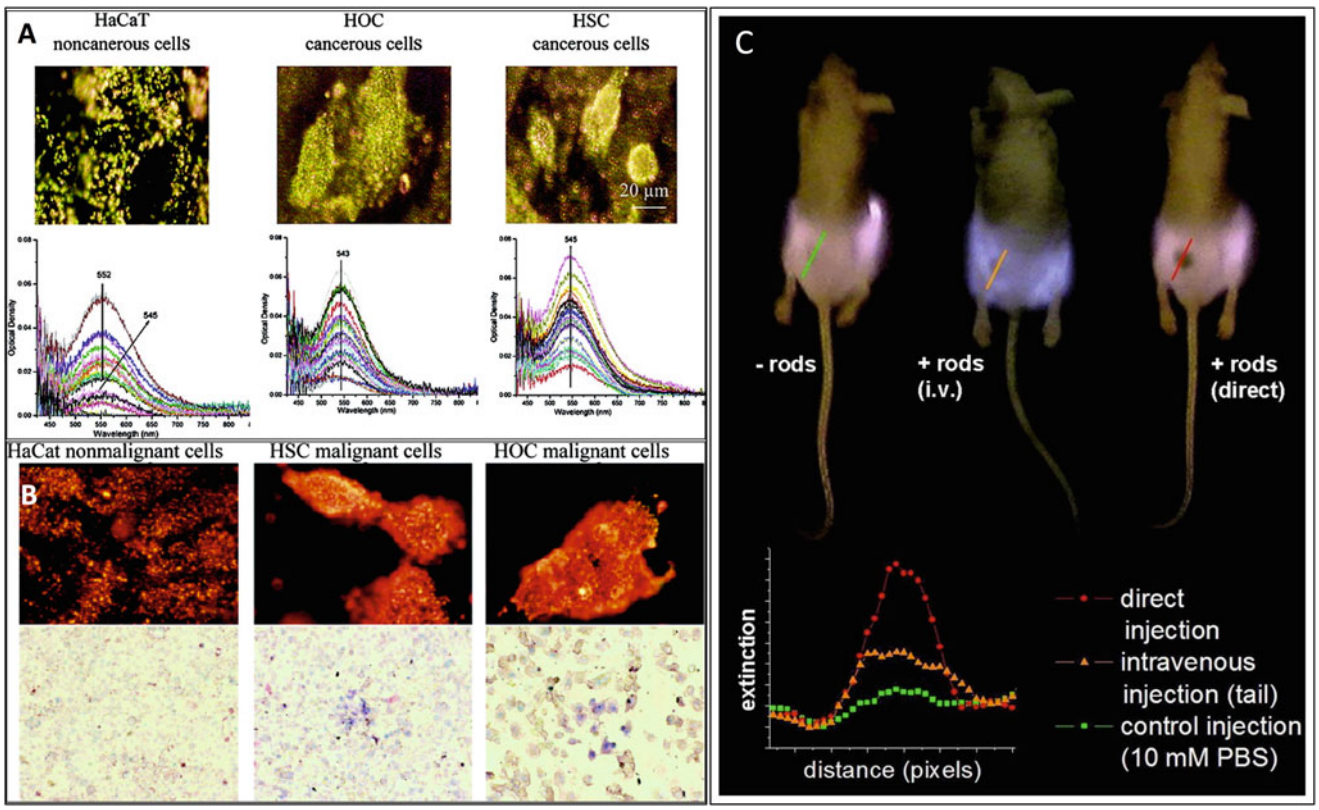

Fig. 51.5 (**a**) *Top panel* shows the light scattering images and microabsorption spectra of HaCaT noncancerous cells (*left column*), HOC cancerous cells (*middle column*), and HSC cancerous cells (*right column*) after incubation with anti-EGFR antibody-conjugated GNPs. *Bottom panel* shows the absorption spectra measured for 25 different single cells of each kind [18]. (**b**) Light scattering images of anti-EGFR/Au nanorods after incubation with cells for 30 min at room temperature (*top panel*). Selective photothermal therapy of cancer cells with anti-EGFR/Au nanorods incubated (*bottom panel*) [17]. (**c**) NIR transmission images of mice prior to PPTT treatments. Inset shows intensity line scans of NIR extinction at tumor sites for control (*green square*), intravenous (*yellow triangle*), and direct (*red circle*) administration of pegylated GNRs [72] (**a**) Reprinted from El-Sayed, I. H.; Huang, X.; El-Sayed, M. A.: Surface Plasmon Resonance Scattering and Absorption of anti-EGFR Antibody Conjugated Gold Nanoparticles in Cancer Diagnostics: Applications in Oral Cancer. Nano letters 2005, 5, 829-834. With permission from American Chemical Society. (**b**) Reprinted from Huang, X.; El-Sayed, I. H.; Qian, W.; El-Sayed, M. A.: Cancer Cell Imaging and Photothermal Therapy in the Near-Infrared Region by Using Gold Nanorods. Journal of the American Chemical Society 2006, 128, 2115-2120. With permission from American Chemical Society. (**c**) Reprinted from Dickerson, E. B.; Dreaden, E. C.; Huang, X.; El-Sayed, I. H.; Chu, H.; Pushpanketh, S.; McDonald, J. F.; El-Sayed, M. A.: Gold nanorod assisted near-infrared plasmonic photothermal therapy (PPTT) of squamous cell carcinoma in mice. Cancer Letters 2008, 269, 57-66. With permission from Elsevier

band with a redshifted maximum in the cancer cells compared to that observed when added to the noncancerous cells. Further, the unique binding affinity of anti-EGFR functionalized nanoparticles toward the HSC-3 cancer cell surface has been used to demonstrate the utility of GNRs, which can absorb and scatter strongly in the NIR region (650–900 nm), for simultaneous molecular imaging and photothermal cancer therapy (Fig. 51.5b) [17].

In vivo experiments further demonstrated the potential of this technique as a photothermal therapy agent. A portion of the incident light on a GNP is absorbed and converted to heat. At the nanoscale this transition produces a lot of heat for the small amount of particles. Using an oral squamous carcinoma model in mice, the average HSC-3 tumor growth in nu/nu mice treated with pegylated GNRs administrated through direct injection and intravenous administration demonstrated inhibition of growth over a 13-day period (Fig. 51.5c) [72]. Various surface functionalizations of GNRs have been proposed using other targeting molecules such as folate receptors [73] and phosphatidylcholine [74], and these also render the HNC cells highly susceptible to photothermal damage when irradiated along the nanorods' longitudinal surface plasmon resonance (even at a lower laser fluences).

Similar antibody-conjugated GNRs were also used to detect HNC in tissue-like phantoms and in vivo through a new detection method utilizing the diffusion reflection (DR) measurement based on the absorption coefficient differences between cancerous and normal tissues following targeted GNRs' injection [75, 76]. This study showed that the measured reflectance between a source and detector on the measured sample surface was proportional to the absorption of the GNR, which demonstrates the high sensitivity of diffusion reflection measurements to the absorption differences between the GNR-targeted cancerous tissue and normal, noncancerous tissue.

More recently, a new and an innovative theranostic technique called quadrapeutics [77–79] was introduced by Lapotko et al., which is more efficient than conventional chemo and radiation therapy against aggressive, drug-resistant head and neck tumors. This technique utilizes both the acoustic diagnostics and guided intracellular delivery of antitumor drug (liposome-encapsulated doxorubicin, Doxil) in one rapid process, namely, a pulsed laser-activated plasmonic nanobubble (PNB). Quadrapeutics technique involves three steps. In the first step, GNPs conjugated with liposomal drug and cancer-specific antibody get endocytosed via receptor-mediated endocytosis into the cancer cell and form an intracellular nanocluster aggregate. In the second step, low-energy near-infrared laser pulse will be applied to the nanoparticle-targeted cancer cells, where the NIR laser will be absorbed by the nanoparticle to produce plasmonically enhanced localized heat. At the same time, surrounding liquid evaporates into an expanding and collapsing vapor nanobubble called "plasmonic nanobubbles" (Fig. 51.6). These nanobubbles can mechanically destruct the cell or eject the drug into its cytoplasm by breaking the liposome and endosome. This enhances the local doses of the chemotherapy drug. In the third step, a low dose of X-ray radiation will be aimed at the tumor, which will amplify inside the cancer cells, by the radiosensitizing capability of gold nanoclusters [77]. Plasmonic nanobubble-mediated technique could increase the therapeutic efficacy of the standard drug by more than tenfold compared to chemotherapy alone and eliminated >80 % of the drug-resistant head and neck squamous cell carcinoma tumor within 1 mm of tissue depth in a fast single treatment.

The unique capability of plasmonic nanoparticles to enhance the Raman scattering efficiencies of adsorbed molecules (surface-enhanced Raman scattering (SERS)) has been utilized for various applications in HNC research [19, 80–82]. Based on this technique, biocompatible and nontoxic nanoparticles made of GNPs functionalized with polyethylene glycol, ScFv antibody, and Raman reporter molecule (malachite green) have been utilized for in vitro and in vivo tumor targeting and detection (Fig. 51.7) [80]. This ScFv antibody recognizes the EGFR, which is overexpressed at the tumor site. The SERS spectra collected from the tumor site showed distinct Raman bands corresponding to the reporter molecules present on the antibody-conjugated targeted SERS tag. However, nontargeted SERS tag did not show the characteristic SERS signals at the tumor site. More recently, El-Sayed and coworkers have developed a targeted plasmonically enhanced single cell Raman spectroscopic technique to visualize the entire cell cycle and mitosis in HSC-3 cell line from their molecular perspective [19, 81]. Apart from this, this technique has been utilized to study the cell death mechanism and drug efficacy in HNC cells [83, 84]. This technique utilizes the nuclear-targeted GNPs functionalized with PEG molecules, RGD, and NLS. While RGD peptide facilitates the endocytosis of the nanoparticles into the cytoplasm via receptor-mediated endocytosis pathway, NLS targets the particles toward the nuclear region inside the cells [19, 85].

51.5 Dendrimeric Nanoparticles

Dendrimers are three-dimensional branched macromolecules having a diameter varying from 2.5 to 10 nm. A wide variety of drug molecules can be physically trapped inside the voids, which allow the encapsulation of hydrophilic, hydrophobic, or even amphiphilic compounds as guest

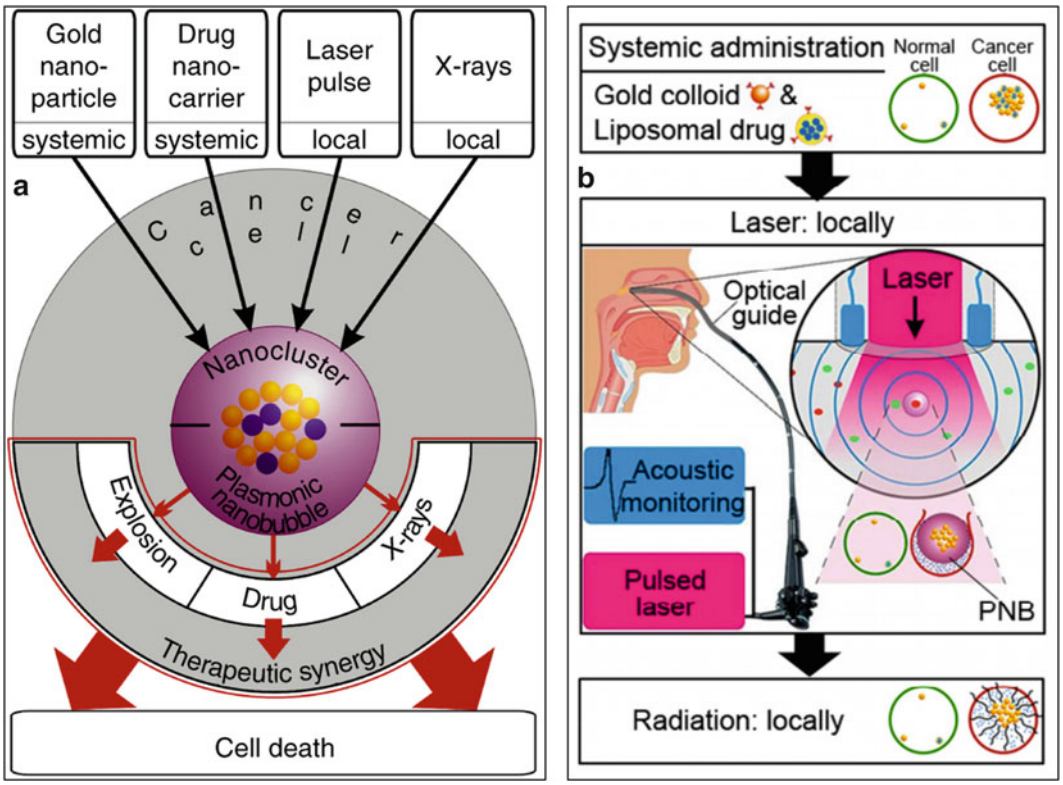

Fig. 51.6 (**a**) Principle of the quadrapeutics, where GNPs, encapsulated drugs, low-energy short laser pulses, and X-rays are administered in a simple three-step protocol [78]. (**b**) Schematic showing clinical application of quadrapeutics, where antibody-conjugated GNPs and liposomal drugs are delivered systemically to form nanoclusters in cancer cells and in the next step the laser pulse applied locally via an endoscope to selectively generate in cancer cells plasmonic nanobubbles [77]. (**a**) Adapted from Lukianova-Hleb, E. Y.; Ren, X.; Sawant, R. R.; Wu, X.; Torchilin, V. P.; Lapotko, D. O.: On-demand intracellular amplification of chemoradiation with cancer-specific plasmonic nanobubbles. Nat Med 2014, 20, 778-784. With permission from Nature Publishing Group. (**b**) Adapted from Lukianova-Hleb, E. Y.; Lapotko, D. O.: Nano-Quadrapeutics rapidly detects and destroys squamous cell carcinoma of the head and neck. Head & Neck 2015 [Epub ahead of print] with permission from John Wiley & Sons

molecules within a dendrimer [86]. This has been widely used in nanomedicine as a drug carrier as many drug molecules can be attached to them through encapsulation and covalent conjugation.

In a unique study, acetylated fifth-generation dendrimers conjugated to the folic acid (targeting moiety) and the methotrexate (therapeutic moiety) were administered to three different groups of mice, which were inoculated with UM-SCC-1, UM-SCC-17B, and UM-SCC-22B cancer cells. The control group had tumors grown from HNC, which did not produce the folic acid receptor, and the other two experimental groups had tumors grown from human head and neck tumors that expressed moderate and high levels of the folic acid receptor. Mice were injected with targeted therapy, free methotrexate, or saline control and monitored for drug efficacy and toxicity. Researchers tested their dendrimer-based formulation in three different groups of mice. The control group had tumors grown from human head and neck tumors that did not produce the folic acid receptor. The two experimental groups had tumors grown from human head and neck tumors that expressed moderate and high levels of the folic acid receptor. Mice receiving the equivalent of three times the normally lethal dose of methotrexate, delivered on the dendrimer nanoparticle, experienced none of the weight loss normally associated with methotrexate therapy. More importantly, dendrimer-delivered therapy produced marked gains in therapeutic response even in the mice whose tumors produced only moderate levels of folic acid receptor [26].

51.6 Carbon Nanoparticles

Carbon-based nanoparticles for cancer detection and treatment are under study. Various biologically active molecules such as proteins, peptides, DNA, etc. functionalized onto a wide range of carbon-based nanoparticles such as nanotubes, fullerene, nanodots, grapheme, etc., have resulted in the

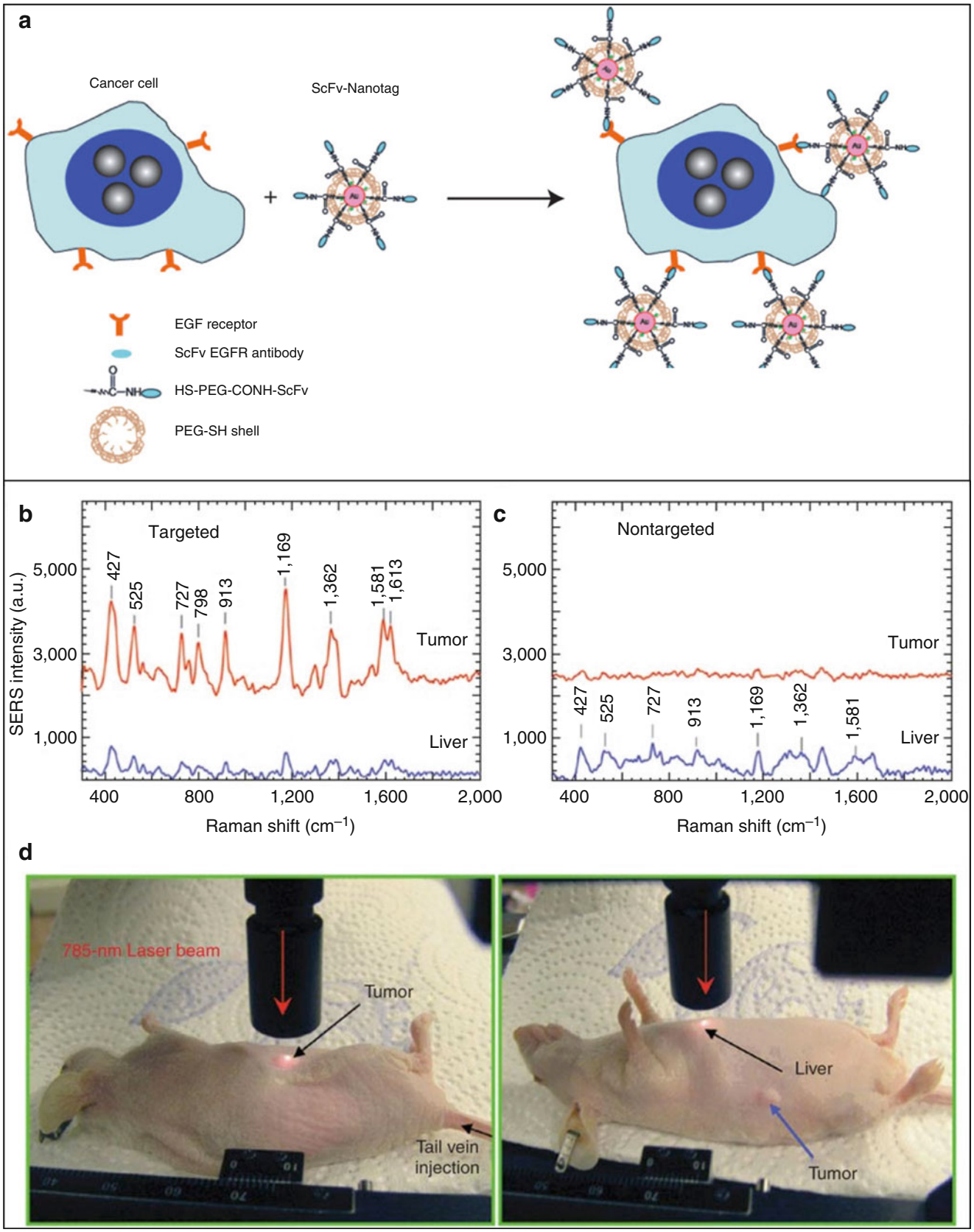

Fig. 51.7 (**a**) Schematic showing targeting of functionalized nanoparticles to the cancer cell surface. Covalent conjugation of an EGFR-antibody fragment occurs at the exposed terminal of the hetero-functional PEG. (**b**, **c**) SERS spectra collected from the tumor and the liver locations by using (**b**) targeted and (**c**) nontargeted nanoparticles. Here, two nude mice bearing human head and neck squamous cell carcinoma received 90 μL of ScFv EGFR-conjugated SERS tags (targeted) or pegylated SERS tags (nontargeted) via tail vein. SERS spectra were collected 5 h after injection. (**d**) Photographs showing a laser beam focusing on the tumor site or on the liver location. In vivo SERS spectra were collected from the tumor site (*red*) and the liver site (*blue*) [80] [Adapted from Qian, X.; Peng, X.-H.; Ansari, D. O.; Yin-Goen, Q.; Chen, G. Z.; Shin, D. M.; Yang, L.; Young, A. N.; Wang, M. D.; Nie, S.: In vivo tumor targeting and spectroscopic detection with surface-enhanced Raman nanoparticle tags. Nat Biotech 2008, 26, 83-90. With permission from Nature Publishing Group]

development of carbon-based drug delivery vehicles, imaging, and treatment modalities in cancer research [87, 88].

The hollow cavity and extremely large surface to volume ratio in carbon nanotube (CNT) can be used to load large amounts of chemical species. Single-walled carbon nanotubes (SWNTs) functionalized with quantum dot (Qdot), EGF, and cisplatin can be selectively taken up by head and neck squamous carcinoma cells that often overexpress EGF receptors [27]. Confocal fluorescence microscopy showed that SWNT–Qdot–EGF bioconjugates could internalize very rapidly into the cancer cells, while limited uptake was observed for control cells without EGF. A significant regression in the tumor growth was observed in mice, which is treated with targeted SWNT–cisplatin–EGF relative to non-targeted SWNT-cisplatin. Interleukin-6 (IL-6) has an important role in the immune, inflammatory, and angiogenic responses associated with squamous cell carcinomas of the head and neck. SWNT forests with attached capture antibodies (Ab1) for IL-6 were used in an electrochemical sandwich immunoassay protocol using enzyme label horseradish peroxidase (HRP) to measure very low ($\leq$30 pg mL^{-1}) and elevated cancer-related levels of IL-6 in HNC [60]. Haick et al. have designed a nanoscale artificial nose based on an array of SWNT sensors capable of distinguishing between HNC and healthy controls as well as HNC from lung cancer [61]. These results were validated by the comparative analysis of the chemical composition of the breath using various other techniques such as gas chromatography in conjunction with mass spectrometry.

51.7 Polymeric Nanoparticles

Polymeric nanoparticles are another novel drug delivery vehicles extensively used for biomedical applications. These materials are made of both synthetic polymers, such as poly(lactic acid) (PLA) and poly(lactide-coglycolide) (PLGA), and natural polymers, such as chitosan and collagen [89]. Polymeric nanoparticles can be embedded with imaging or therapeutic payloads and can specifically deliver at the tumor sites [89, 90]. Poor solubility and rapid degradation of drug molecules such as hydroxycamptothecin (HCPT) is a critical issue in the treatment of HNC. An amphiphilic block copolymer micelle nanoparticle derived from poly[ethylene glycol]-poly[gamma-benzyl-L-glutamate] (PEG-PBLG) showed enhanced antitumoral effect than open ring-carboxylated HCPT entity against oral squamous cell carcinoma in vivo [91]. Polymeric nanoparticles have been also used in cell-targeted nanomedicine approach in HNC models for delivering photosensitizer for photodynamic therapy [68, 92], drug delivery [31], siRNA delivery [66, 67], etc.

51.8 Nanotherapeutic Strategies

51.8.1 Nanoparticles for Enhanced Radiation Therapy

Even though radiation therapy (RT) is an important treatment modality used in HNC, the inherent antiapoptotic mechanism makes them radioresistant, which yield poor therapeutic efficiency and tumor recurrence. This can be eliminated by enhancing the efficiency of RT and by sensitizing tumor cells to undergo apoptosis at reduced radiation dosages, which can limit the damage to healthy tissues [93]. Studies have shown that targeted GNPs can selectively enhance the efficiency of radiation therapy in squamous cell carcinoma and hence enhanced tumor cell killing efficiency [94–96]. This technique mainly relies on the radiosensitization property of gold (high-Z materials) due to its excellent X-ray absorbing capability and subsequent formation of high photo/Auger electron fluence within the tumor, which can induce greater physical damage to the tumor tissues [97]. This technique has been successfully demonstrated in vivo on radiation-resistant and highly aggressive mouse head and neck squamous cell carcinoma model, SCCVII, where the mice-bearing subcutaneous SCCVII tumors were irradiated with X-rays with and without prior intravenous administration of nanogold having 1.9 nm diameter gold core [95]. AuNP-mediated RT was more effective at 42 Gy than at 30 Gy compared to controls without gold. Apart from gold, recent studies show that ~5 nm size gadolinium-based nanoparticle made of gadolinium oxide core with a polysiloxane shell functionalized by diethylenetriaminepentaacetic acid can act as efficient in vitro radiosensitizers at energy of 660 keV on head and neck squamous cell carcinoma cells [98]. The physical events associated with the interaction of X-rays with high-Z nanoparticles have been summarized in Fig. 51.8.

51.8.2 Plasmonic Photothermal Therapy

Plasmonic photothermal therapy (PPTT) is a minimally invasive therapeutic strategy than chemotherapy or surgery, where resonant photon energy absorbed by the plasmonic nanoparticle will result in rapid nonequilibrium heating at the surface of the metal nanoparticles [99, 100]. Subsequently, the heat dissipates to the surrounding medium of the nanoparticle via energy exchange between the electrons and the lattice phonons as well as phonon–phonon coupling (Fig. 51.9) [101]. This results in a local temperature increase sufficient enough to damage and destroy cancer cells. For this technique, nanoparticle having absorption in the NIR region is desirable, as most biological tissues absorb visible light but

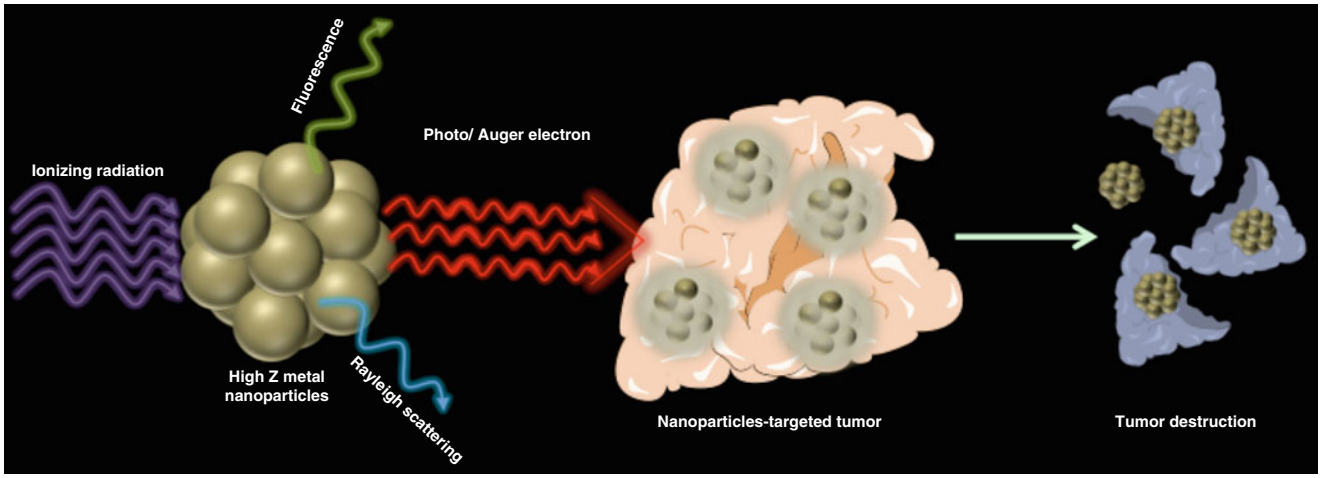

Fig. 51.8 Interaction of ionizing radiation with high-Z metal nanoparticles and subsequent formation of high energy secondary radiation within the tumor. This radiation dose enhancement inside the tumor tissues loaded with high-Z metal nanoparticles can efficiently destruct the tumor tissues

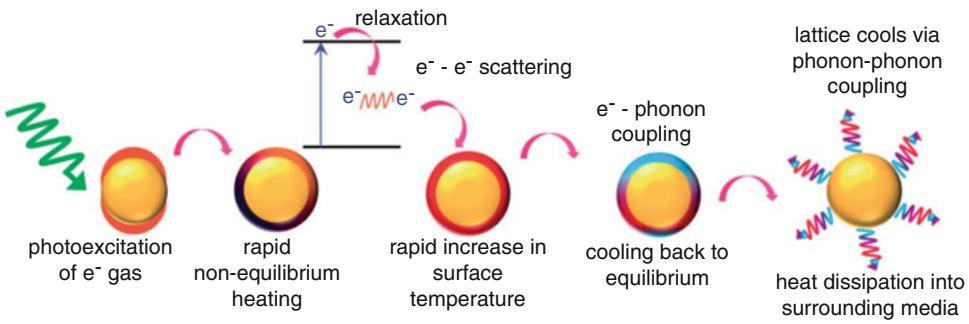

Fig. 51.9 Schematic describing the principle of photothermal light to heat conversion by plasmonic nanostructures [101] [Adapted from Webb, J. A.; Bardhan, R.: Emerging advances in nanomedicine with engineered gold nanostructures. Nanoscale 2014, 5(6): 2502-2530. With permission from Royal Society of Chemistry]

exhibit minimal light absorption from tissue chromophores and water in this range, and hence tissue penetration can be maximized. Gold nanoshells are one of the first nanoparticles exploited for the investigation of role of plasmonic nanoparticles in photothermal therapy [102]. Due to the large absorption cross sections of Au nanoshells, the absorbed photons are converted into phonons and can increase the temperature. Halas's group has performed a range of in vivo studies with them for demonstrating high survival rates after treatment in mice, and phase-I clinical trials began for HNCs in 2008 [64]. El-Sayed's group has widely explored this technique as an efficient treatment modality for addressing HNC. Their studies on HSC cells showed that anti-EGFR-functionalized GNRs can specifically target HSC cells than healthy HaCaT cells and can be used simultaneously for molecular imaging and photothermal cancer therapy [17].

51.8.3 Gene Therapy

Radioprotection of normal tissues during the radiation therapy is a critical issue of the standard therapeutic radiation treatment for patients with HNCs. An alternate method to reduce this side effect is to use efficient radioprotection strategies capable of protecting healthy tissue against radiation damage during RT. Gene therapy has been considered as an emerging technique with widespread applications in treatment of HNC and various other cancers. The major challenges in gene therapy are to deliver therapeutic genes to target tissues, improve transfection efficiency, and protect the antisense oligonucleotides such as siRNA, miRNA, etc. from degradation. Even though viral-based gene delivery vectors showed high transfection efficiency, their preparation techniques are very complex, have many serious potential risks, and show immunogenicity [103, 104]. Organic and inorganic

nanoparticle-based gene delivery vectors are promising materials in this context, as they show improvement of bioavailability with low immunoreactions, excellent adsorption capacity, high loading, targeting and delivery efficiency, and minimal damage to the DNA or RNA [104–106].

Recently, a nanoparticle-based drug delivery vector has been developed for the targeted delivery of small interfering RNA molecules (siRNA) for the treatment of HNC, which is being tested in human clinical trials [36]. In this study, a cyclodextrin-based polymeric nanoformulation carrying siRNA, capable of protecting siRNA from degradation, successfully targeted to the ribonucleotide reductase subunit M2 (RRM2). RRM2 plays a critical role in tumor progression and in the development of drug resistance. Initial in vitro studies on head and neck squamous cell carcinoma showed that the cancer cells took up this siRNA incorporated nanovector and resulted in the knockdown of RRM2 through an RNA silencing mechanism, which strongly inhibited cancer cell growth. In vivo studies on mouse xenograft model of HNC after intravenous injection of siRNA-loaded nanovector significantly downregulated the production of RRM2 for at least 10 days without any adverse effects or changes in body weight during the course of therapy. Further studies to unravel the mechanism involved in RRM2 knockdown in HNC tumor suppression revealed that RRM2 suppression significantly reduces the Bcl-2 protein expression by their degradation and identified their colocalization with RRM2 in HNC. This resulted in the induction of mitochondria-mediated intrinsic apoptosis [107].

Another important target for reversal of radiation resistance is the EGFR, which has been overexpressed in many squamous cell carcinoma of the head and neck [108]. EGFR plays an important role in regulating the cell proliferation and differentiation. Anti-EGFR treatments can enhance the therapeutic activity of radiation therapy. Administration of poly(lactic-co-glycolic acid) (PLGA) nanoparticle-encapsulated antisense EGFR oligonucleotides to SCCVII squamous cells showed decrease in the expression of the EGFR and enhanced radiosensitivity by the inhibition of EGFR-mediated mechanisms of radioresistance [109]. More recently, siRNA delivery in HNC has been achieved by a new kind of super carbonate apatite (sCA) nanoparticles. This nanoparticle consists of inorganic ions, which can accumulate specifically in tumor cell and can easily achieve endosomal escape [110].

51.8.4 Photodynamic Therapy

Photodynamic therapy (PDT) or photochemotherapy is a highly specific anticancer treatment modality especially for the treatment of highly aggressive and recurrent cancers, which involves cell destruction by means of toxic singlet oxygen and/or various other reactive oxygen species that are produced as a result of sequence of photochemical and photobiological processes. The formation of singlet oxygen or reactive oxygen species (ROS) is initiated by the excitation of a photosensitizer by the exposure of a specific electromagnetic radiation in the visible or near-infrared (NIR) region and its interaction with tissue oxygen. However, light-associated toxicity limits its clinical applications. As an emerging material, nanoparticles can overcome most of the limitations of classic photosensitizers in PDT [25, 111, 112]. The large surface to volume ratios can significantly enhance the amount of photosensitizer molecules that can be delivered to the target cells. Apart from that, nanoparticles may prevent the premature release of photosensitizer, which may cause the inactivation of the drug by plasma components, and enhance the nonspecific accumulation in normal tissues.

The toxicity associated with PDT can be significantly reduced by the use of nanoparticles. It has been demonstrated that iron oxide nanoparticles conjugated with fibronectin-mimetic peptide and a second-generation PDT drug can be efficiently used as a PDT vector with minimal toxicity compared to conventional PDT. Studies showed that targeted iron oxide nanoparticles can accumulate in xenograft tumors with higher concentrations than non-formulated Pc 4, which yielded size reduction of head and neck squamous cell carcinoma xenograft tumors more effectively than free Pc 4 [25]. Moreover, combination therapy can enhance the anticancer efficacy of both drugs via synergistic effects. It has been reported that polymer-based core–shell nanoparticles encapsulated with cisplatin and the photosensitizer pyrolipid can be used for combined chemotherapy and photodynamic therapy [111]. The polymeric nanoparticle can release cisplatin and pyrolipid in a triggered manner synergistically and showed superior potency and efficacy in tumor regression in head and neck cancer SQ20B xenograft murine model.

51.9 Diagnostic Enhancement Techniques

Nanoparticles have found usefulness for enhancement of standard imaging modalities. It is known that gold can induce strong X-ray attenuation. The enhanced X-ray attenuation property and unique physiochemical properties of GNPs have been utilized to demonstrate the in vivo CT molecular imaging capability of immuno-targeted GNPs, which can selectively and sensitively target head and neck tumors [65]. These gold nanoprobes targeted to cancer cells showed a distinguishable X-ray attenuation, which is not typical for healthy tissues. As an alternative imaging technique, photoacoustic imaging has shown tremendous potential in cancer cell imaging [113]. This technique relies on the conversion of electromagnetic energy into acoustic pressure waves [114]. In cancer diagnosis, nanoparticles serve as photo-

acoustic imaging contrast agents, which can deeply penetrate the tissue and selectively bind to cancer cells.

Since a change in the size/shape and aspect ratio of GNPs determines which wavelengths of light generate the greatest LSPR effect, the GNPs are optically tunable. The unique and tunable optical absorption properties of anti-EGFR-conjugated GNRs have been used for electively targeting oral cancer cells, and photoacoustic molecular imaging has been achieved both in vitro and in vivo with contrast enhancement of up to 10 dB and 3.5 dB, respectively [115].

Magnetic resonance imaging (MRI) is another noninvasive or minimally invasive imaging technique that could provide enhanced spatial resolution when compared to other imaging techniques. The viability of this technique in precise identification of cancer can be achieved by using targeted paramagnetic or superparamagnetic nanoparticle-based contrast agents [116, 117]. These include various nanomaterials made of metals (gold, silver, and cobalt) or metal oxides (Gd_2O_3, Fe_3O_4, TiO_2, and SiO_2). Perturbation of magnetic field around these nanomaterials when they are exposed to an external magnetic field causes faster water proton relaxation inside the tissues, which enables the detection with MRI. A nanoformulation made of phospholipid-based phosphorescent nanomicelle functionalized with gadolinium has been used for combined MRI and optical (near-infrared phosphorescence) imaging of head and neck tumor [118].

Cetuximab-conjugated GNRs exhibited a visual increase in contrast from tumor tissues after topical administration of targeted GNR and performing a two-photon-based near-infrared narrowband imaging (NBI) [119]. Near-infrared NBI could image narrow wavelength bands to enhance contrast from plasmonic particles in a wide-field portable and noncontact device that is clinically compatible for real-time tumor imaging and tumor margin demarcation.

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Head and Neck Quality Assurance 2014

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Abstract

Quality assurance (QA) in complex head and neck cancer trials is essential. The need for QA is made more relevant with trials comprised of multiple end points, worldwide participation, and increasing use of adaptive strategies/advanced technology to validate/verify outcome analyses. Integration is necessary for tissue analysis, biomarker assessment, imaging, radiation therapy, chemotherapy, and/or targeted therapy for patients with new diagnosis, relapse, and second head and neck malignancies.

Credentialing, data acquisition, management, review, and archive processes must be flexible and consistent for real-time review and validated results. Central to these comprehensive processes is a robust informatics platform for daily operation, data integrity, and communication. The ability to query well-constructed data repositories of clinical information, radiation

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and medical oncology, tissue, biomarker, and imaging objects is important to answer current and future questions. These libraries are extraordinary teaching resources.

Imaging, tissue, and biomarker analyses are key components of head and neck trials. Radiation therapy is a core treatment strategy, and trials will continue to study acute/late effects, tumor control, radiation dose-volume constraints, target definition, recurrence, and second malignancies.

QA remains the most invaluable construct to trial management. Protocol-compliant management provides consistent care through which new paradigms of care can be established and validated.

Keywords
Clinical trial • Quality assurance • Informatics • Biomarkers • Real-time review • Radiation therapy • Imaging • Credentialing

52.1 Introduction

Quality assurance (QA) in modern head and neck cancer clinical trials is an essential component of clinical trial (protocol) management made more relevant with the increasing use of advanced technology in radiation therapy (RT) and imaging. The need for QA is coupled with the increasing need for availability of the tissue for biomarker analysis. This places an ever-increasing importance on tissue acquisition at the time of primary diagnosis and treatment relapse and linking this information with imaging and treatment objects for outcome analysis. Each facet of clinical trial data management requires careful attention to detail to insure the integrity of trial results and conclusions. Data acquisition processes for trial management must be nimble yet complete to meet all trial objectives including the retrospective use of information for validation of therapy for the agencies responsible for therapy approval, e.g., the US Food and Drug Administration (US FDA). Informatics systems must be comprehensive for data storage and constructed in a manner for easy information retrieval and query function to answer questions that may not have been anticipated at the time of trial design. Modern trials have multiple important end points including tissue analysis, biomarker assessment, imaging, RT, chemotherapy, and/or targeted therapy all fully integrated with patient outcome for trial analysis. Modern head and neck clinical trials are adaptive in design to accommodate the rapidly changing landscape of targeted therapies. Aside from the complexity of trials for patients with new diagnosis of head and neck malignancy, studies will be available for relapse patients and patients with second head and neck malignancies identified after successful treatment of their initial disease. These patients, in particular, are challenging as previous therapies, including RT, place potential restrictions on the re-treatment strategy, therefore positioning tissues of limited self-renewal potential at risk for injury in spite of optimal treatment planning efforts. Accordingly, as clinical trials mature, they require many disciplines to harmonize in an integrated manner for successful trial completion. As a result, clinical trials are becoming more complex with multiple end points under simultaneous evaluation for trial conduct. QA processes must be complete yet respect current limitations placed on health-care systems for data acquisition and management.

Knowledge is and remains a continuum. As we seek to escalate primary protocol therapy and attempt re-treatment protocols moving forward, we will learn and optimize strategies for RT dose-volume constraints and use imaging tools to validate primary and secondary tumor targets including response to treatment. We are learning how to attenuate therapy in parallel with improvements in targeted therapy, especially for patients where we have concerns of exceeding known current dose-volume tolerance limitations. We are learning more from imaging, genomics, and proteomics fully validated by patient outcome. We are learning how to contour our targets better with advanced technology imaging tools, and we are drawing normal tissue volumes with much more accuracy and consistency than in the past. The increased availability of image guidance is insuring accurate daily treatment potentially decreasing the size of planning target volumes for both tumor and normal tissue. Recent cooperative group head and neck protocols have used response to induction chemotherapy and *human papillomavirus* (HPV) status to define protocol parameters such as dose and volume reduction of RT based on response to induction chemotherapy. Therefore, within one study, validation of HPV status, response to induction chemotherapy, and dose-specific RT QA must be done on each patient in real time to insure that the results of the study are interpreted with confidence.

QA is of increasing importance in clinical trials. New therapies and new integrated therapeutic combination therapy must be validated in a timely and thorough manner. Protocol-compliant management provides consistent care and discipline by site and study investigators for successful

trial management. Only through this mechanism can new paradigms of care be established and validated. QA programs enhance the strength and completeness of clinical trial data and insure that interpretation of the data can be completed with the best possible information. Clinical trials for cancers of the head and neck are especially challenging to complete. They are often more expensive and complex as end points require tissue for biomarker analysis and advanced technology imaging to define tumor target location and treatment response. RT treatment objects include intensity modulation, which will require a site credentialing process and review of target volume definition. Patient outcome data will need to be readily available to provide appropriate information for adaptive protocol strategies. There is always a temptation to limit QA data acquisition for cost and process; however, if data acquisition processes are oversimplified, limited ambiguous data is open to multiple venues of interpretation that cannot be validated with incomplete databases. If one of the objectives is to identify new forms of therapy with participation of agencies responsible for therapy approval, validated QA processes are required and should be considered standard of care for trial management.

52.2 The Argument for Quality Assurance

There is ample evidence demonstrating the importance of QA in clinical trials. In historical trials, patient care imaging and RT treatment objects were collected on a rolling basis and evaluated by study investigators after closure of the trial in order to prepare data for publication. The data was not used for direct real-time intervention during the course of the study. Data was collected via hard copy mechanisms thus unable to be viewed in real time or by multiple investigators in a simultaneous manner. Pediatric Oncology Group (POG) protocol 8725 evaluated patients with advanced Hodgkin lymphoma. Patients received eight cycles of hybrid chemotherapy. After completion of chemotherapy, patients were randomized to receive RT to all sites of disease defined on imaging at presentation prior to therapy. On initial evaluation without benefit of QA review, the evidence did not support the addition of RT. However, the Quality Assurance Review Center (QARC) performed a secondary analysis of the protocol information [1]. As seen in Fig. 52.1, if patients were treated to target volume compliant to study, there was a statistically significant survival advantage for patients treated with RT. If patients were treated with RT to target volumes not compliant to study objectives, their outcome was identical to those patients treated with chemotherapy alone. The deviations from study compliance were nearly all due to not including sites of disease defined at presentation in the RT treatment field. This information implied that if RT was to be incorporated into the treatment plan for the patient, all sites of disease defined at presentation needed to be incorporated into the RT treatment field. Patterns of failure review supported this position. The additional issue identified was that RT treatment objects needed to be reviewed prior to the initiation of RT in order to insure compliance to study and consistent application of RT during the course of the study. This issue was first tested in POG 9426. This protocol evaluated the role of response-adapted therapy in early-stage Hodgkin lymphoma. In this study, patients were treated with two cycles of chemotherapy. If site investigators determined that the patient had a rapid early response to chemotherapy, the patient was treated with RT directed to an involved field. If the patient was not deemed to have a rapid early response to therapy, the patient would receive two more cycles of chemotherapy and involved field RT. The data has recently been published, and patient outcome with attenuated therapy assuming rapid early response to chemotherapy was outstanding [2, 3]. Pretreatment review of RT treatment objects significantly improved compliance to study guidelines [3]. However, in this study, site investigators assessed response to chemotherapy as a real-time event. Central review of the assessment of response to chemotherapy was performed after the study was completed. The central review of response

Survival According to Treatment* (POG 8725)

Treatment	5 year Relapse Free Survival (%)
Arm 1: Chemotherapy Alone	85
Arm 2: Chemotherapy + RT:	
Appropriate RT volume	96
Major & Minor RT Deviations	86

*Only patients who were in complete remission at the end of chemotherapy

Relapse free survival indicating significantly better results when the radiation therapy was in accordance with protocol specifications

Fig. 52.1 POG 8725 survival according to treatment [Adapted from FitzGerald TJ, Bishop-Jodoin M, Bosch WR, Curran WJ, Followill DS, Galvin JM, Hanusik R, King SR, Knopp MV, Laurie F, O'Meara E, Michalski JM, Saltz JH, Schnall MD, Schwartz L, Ulin K, Xiao Y, Urie M. Future vision for the quality assurance of oncology clinical trials. Front. Oncol. 2013; 3:31. doi: 10.3389/fonc.2013.00031. With permission from Frontiers Media]

disagreed with site investigators in 50 % of patients, implying a need to also validate the imaging assessment component to the clinical trial as well as address issues associated with the design of RT treatment fields [4].

The Pediatric Oncology Group (POG) and the Children's Cancer Group (CCG) merged to form the Children's Oncology Group (COG) in 2000. COG protocol AHOD0031 was the first protocol to fully integrate real-time review of both imaging and RT treatment objects for protocol compliance in intermediate-risk Hodgkin lymphoma. The protocol was designed in a risk-adaptive manner with more attenuated therapies assigned for patients deemed with a rapid early response to chemotherapy. The objectives were to insure that response assessment and RT treatment field design were compliant to study. The schema for the study is in Fig. 52.2. The imaging and RT QA were excellent for this study, and four-year results of the trial have been recently published [5]. Review of the failure patterns suggests that the few patients that failed on study were in sites of previous disease, and if treated with RT, the site of failure was within the RT treatment field, not in a marginal or distant area of treatment [6]. Building upon this platform of data management and imaging/RT QA processes, COG launched a study of high-risk Hodgkin lymphoma, AHOD0831, which placed emphasis on chemotherapy with RT delivered to sites/regions that did not fully respond to chemotherapy. This was a unique situation as not all areas that harbored disease at presentation were uniformly included in the RT treatment field post-chemotherapy. The fields of treatment were determined by response to chemotherapy. A detailed review of treatment response in all sites of disease was used to design the field of treatment in a uniform manner. The study has completed accrual and follow-up images including relapse/site of failure imaging are being collected for outcome analysis.

Today's clinical trials are complex. We now integrate advanced technology imaging and RT treatment objects into protocol strategies including analysis of outcome at intermediate time points for both secondary randomization study objectives and to accommodate for adaptive treatment strategies of the protocol therapy. With hundreds of sites and investigators participating in clinical trials, we potentially invite ambiguity in data interpretation when there is asymmetry in defining response between study and site investigators. Individual protocols are now addressing subsets of patient populations that were imbedded in more generic disease-based clinical trials. Examples include triple-negative breast patients, HPV-positive/HPV-negative head/neck patients, and other populations with unique features within various diseases requiring clinical trials. International

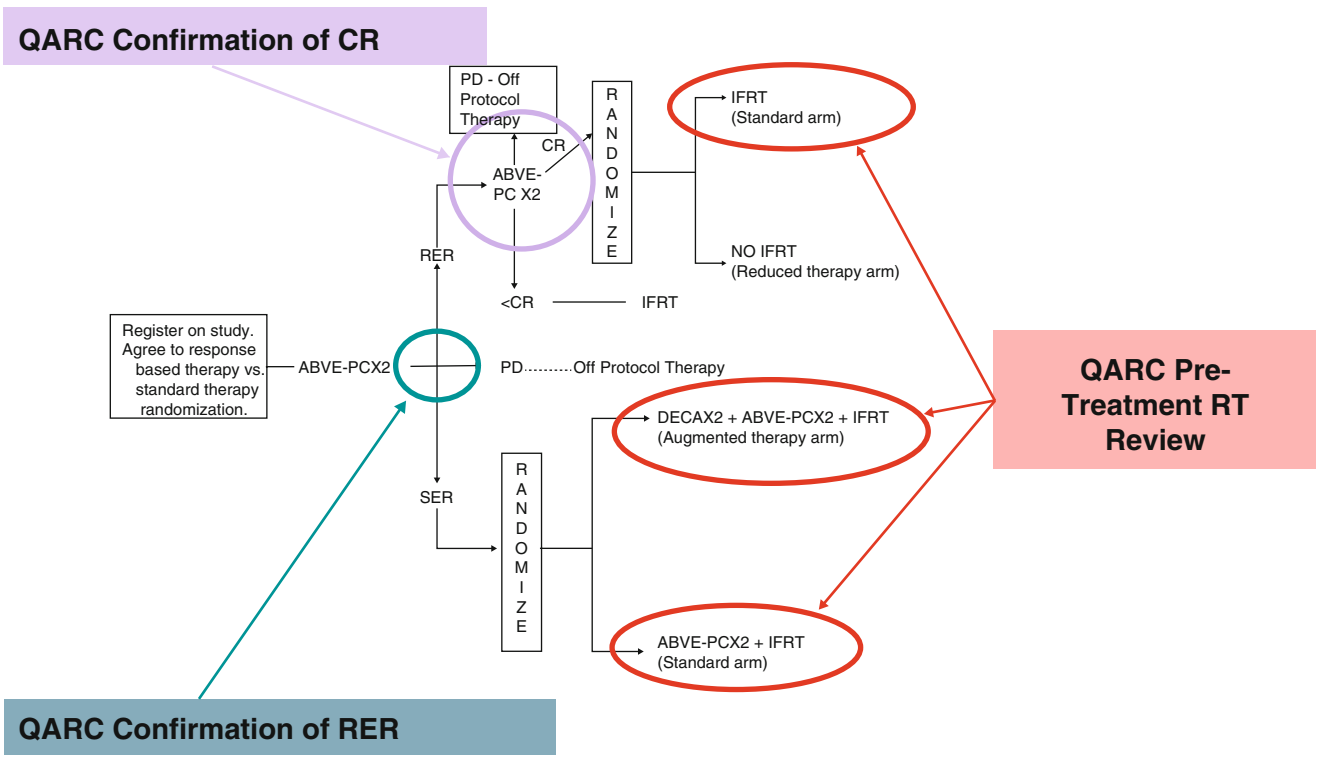

Fig. 52.2 COG AHOD0031 schema with real-time review points [Adapted from FitzGerald TJ, Bishop-Jodoin M, Bosch WR, Curran WJ, Followill DS, Galvin JM, Hanusik R, King SR, Knopp MV, Laurie F, O'Meara E, Michalski JM, Saltz JH, Schnall MD, Schwartz L, Ulin K, Xiao Y, Urie M. Future vision for the quality assurance of oncology clinical trials. Front. Oncol. 2013; 3:31. doi: 10.3389/fonc.2013.00031. With permission from Frontiers Media]

participation will be required to meet accrual objectives including institutions less familiar with the QA process, thus augmenting the need to a robust QA plan.

The asymmetric interpretation of data between site and study investigators became evident in the clinical trial evaluating the use of hypoxia agent, tirapazamine, in head and neck cancer. This phase 3 trial randomized patients to receive tirapazamine with cisplatin/RT. The trial was intended to validate previous favorable phase 2 data in clinical trials [7]. The RT targets were designed to treat all areas of gross tumor at presentation to 7000 cGy. The clinical trial had significant international participation (Fig. 52.3). Study credentialing was accomplished by questionnaire and completion of a two-dimensional RT treatment plan. Volumetric imaging was beginning to be used at an enterprise level as the study was designed and initiated. Intensity modulation was not permitted on the study. Because this was an international trial, the decision was made to perform a central interventional review within three days of beginning RT. On central review, imaging and RT material from 208 patients were thought not to be study compliant at the time of interventional review. Investigators adjusted 89 patients, and the adjusted objects were found to be study compliant at the time of final review by study investigators. Investigators chose not to adjust treatment fields for 108 patients, and nearly all were found to be noncompliant to study guidelines (Fig. 52.4). Because of the number of plans that did not meet study objectives at the time of interventional review, the deviations were rereviewed to reassign a deviation score as to whether or not the deviation was clinically relevant, specifically if there was gross tumor not covered by protocol dose. A clear pattern arose from the review (Fig. 52.5). If patients were treated in a study-compliant manner de novo at the time of interventional review, survival was 80 %. If the institution made an adjustment after the interventional review or the noncompliant plan on rereview was not deemed to be clinically significant, patient survival was 70 %. This finding was statistically significant. If the plan on interventional review was not adjusted to meet study guidelines or on rereview felt to be of clinical significance, patient survival was less than 50 % ($p = <001$).

This data defined the clear need for a strong QA program for complex clinical trials. The objective of the trial was to test a prospective novel chemotherapy agent for head and neck cancer. Because of varied investigator interpretation of imaging and different applied strategies to target definition based on imaging and applied RT, the deviations on study likely had significant influence on trial outcome possibly negating the influence of tirapazamine on patient care. The cost associated with the clinical trial was significant; therefore, QA processes to achieve successful execution of clinical trials were clearly needed to make certain the data was valid. The need for such processes quickly became self-evident.

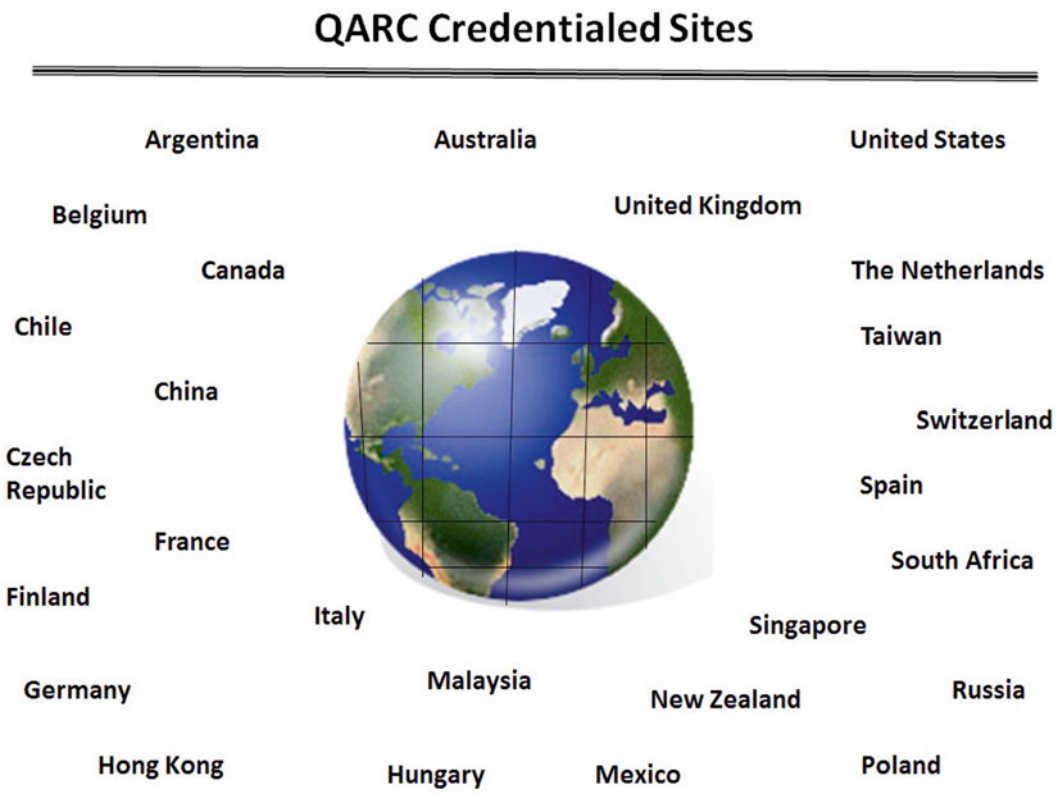

Fig. 52.3 International participation in the TROG 02.02, HeadSTART trial

QARC Review Category	TMC Compliance Status			Total
	Compliant	Noncompliant	Not Evaluable	
No plan submitted	109	32	25	166
Modification(s) not required	402	81*	7	490
Modification(s) required and made	89	0	0	89
Modification(s) required and not made	12	95	1	108
Total	612	208	33	853

- Abbreviations: TMC, Trial Management Committee; QARC, Quality Assurance Review Center.
- ↵* For 69 patients, incomplete plans were submitted initially and the deviations were introduced subsequent to QARC review.

Fig. 52.4 Results of the interventional and TMC compliance reviews in the TROG 02.02, HeadSTART trial [Reprinted from Peters LJ, O'Sullivan B, Giralt J, et al. Critical impact of radiotherapy protocol compliance and quality in the treatment of advanced head and neck cancer: Results from TROG 02.02. J Clin Oncol. 2010;28(18):2996-3001. With permission from American Society of Clinical Oncology]

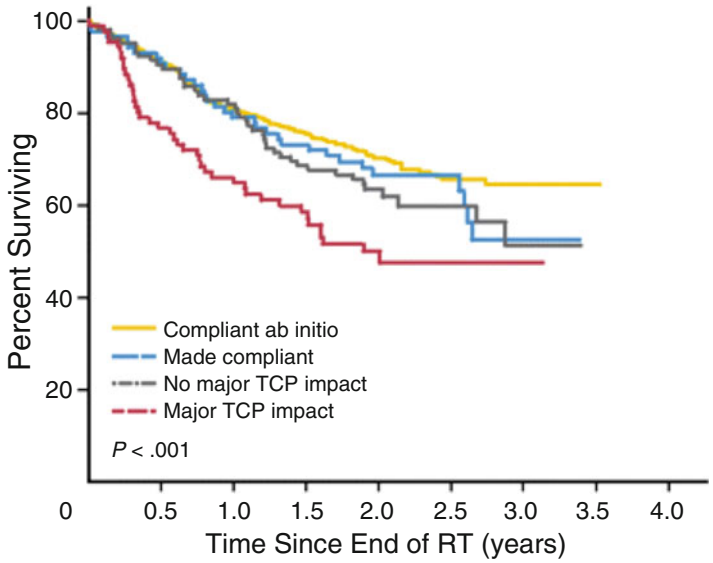

Fig. 52.5 Overall survival by deviation status in the TROG 02.02, HeadSTART trial. (1) Compliant from the outset ($n=502$), (2) made compliant following a review by the Quality Assurance Review Center ($n=86$), (3) noncompliant but without predicted major adverse impact on tumor control ($n=105$), (4) noncompliant with predicted major adverse impact on tumor control ($n=87$). Overall $P<.001$. Pair-wise tests: not statistically significant except for cohort 1 versus cohort 4 ($P<.001$), cohort 2 versus cohort 4 ($P=.041$), and cohort 3 versus cohort 4 ($P=.006$). *TCP* Tumor control probability, *RT* radiotherapy [8] [Reprinted from Peters LJ, O'Sullivan B, Giralt J, et al. Critical impact of radiotherapy protocol compliance and quality in the treatment of advanced head and neck cancer: Results from TROG 02.02. J Clin Oncol. 2010;28(18):2996-3001. With permission from American Society of Clinical Oncology]

Knowledge remains a continuum under constant change and reevaluation. The practice of radiation oncology has changed considerably over the past 15 years moving from two-dimensional therapy to intensity modulation with image guidance. Institutions worldwide are at various time points in their collective ability to acquire new technology and, more importantly, are not always uniform in learning how to apply technology. Participation in clinical trials and the QA process can be naively interpreted as onerous and cumbersome. A more thoughtful approach is to view clinical trial credentialing and QA as part of what we need to achieve to improve our daily practice for patient care and assure that institutional processes are consistent with evolving standards of care. Arguments that QA is not needed because (1) deviations occur in daily practice and (2) deviations will be equally distributed are tepid and weak. The tirapazamine trial has shown that deviations can have a powerful negative effect on the conduct and outcome of a clinical trial, and QA is the primary vehicle we use to insure that we can place trust in the validity of the data and thus believe the results.

Opportunities for process improvements can become lost without a strong QA process in place. The Cancer and Leukemia Group B (CALGB—now Alliance for Clinical Trials in Oncology) ran an innovative series of clinical trials

in breast cancer in the early Adriamycin era demonstrating benefit for Adriamycin and then successfully demonstrating the utility of dose-dense escalation of chemotherapy. These series of clinical trials were a significant part of the breast cancer committee treatment portfolio of CALGB from 1988 to 2000. As part of trial design, the decision was made not to acquire or review data on radiation management. It was felt at the executive level that local therapy did not affect patient survival; therefore collecting information on local management was not crucial for outcome analysis in these adjuvant therapy trials. Evidence became available in 1997 that local therapy for breast cancer had a significant impact on patient survival [9]. Today, we have several protocols evaluating the extent of axillary surgery and the role of axillary RT in patients with breast cancer. There is renewed interest in more comprehensive regional RT for the care of these patients. If we had collected RT data with patterns of failure on previous CALGB clinical trials, this could be correlated with axillary RT treatment dose and target volume, thus driving how current protocols could be written. This would have included knowledge of normal tissue constraints including risk of injury to important structures including the chest wall, lung, heart, large vessels, and brachial plexus. Unintentionally, we created a 20-year knowledge gap in this important area of target definition and RT dose constraints. Current studies are investigating the extent of regional therapy and struggle to define normal tissue study end points and are inconsistent in defining these points. An archive of past treatment guidelines with volumetric review would significantly aid current investigators and provide an extraordinary resource to facilitate guidelines for modern studies. There are numerous examples where significant confusion has complicated clinical trial execution. In the CALGB experience for Adriamycin dose escalation, trials were initiated to evaluate the role of Taxol in patient care. The trial became an intergroup trial and more than 3000 patients were entered on the study [10]. Despite the complexity of the project, Dr. Carolyn Sartor and colleagues formed a working group in order to collect RT treatment data on patients enrolled on this particular trial as the data suggested a benefit to patients receiving Taxol [11]. Dr. Sartor and her group supported by the QARC were able to collect RT information on the patients submitted through the CALGB. The investigators determined that patients receiving Taxol also had a trend to receive RT, therefore confounding the primary end point of the study. Because RT guidelines were not imbedded in the study, the investigators on retrospective review found extraordinary disparity in radiation dose delivery, volumes of tissue treated, and nonuniform radiation dose to target. These issues confounded further analysis of the data. Building upon data generated from the National Surgical Breast and Bowel Project (NSABP), the American College of Surgeons Oncology Group (ACOSOG) embarked on clinical trial Z0011 which evaluated more limited axillary surgical staging in patients with breast cancer. Study guidelines required that no intentional regional RT be delivered. However, the RT data was not acquired or reviewed. Jagsi and colleagues acquired the RT information in retrospect on patients treated on this study and found a significant disparity between protocol guidelines and treatment execution with a significant percentage of patients receiving intentional regional treatment, contrary to study objectives [12]. These examples highlight several key points in clinical trial execution. It is important to collect and archive data. We cannot always anticipate how information will be used or the value of the information during trial execution. However the archive becomes invaluable when we need to ask questions of modern trials that can be facilitated through history. If we become minimalists in data acquisition, we miss opportunities for information validation. Another salient point is the fact that although guidelines were clearly defined in the study, the lack of a data acquisition strategy and accountability facilitated noncompliance with guidelines. A standardized data acquisition and QA platform imbedded into clinical trials insure that the appropriate information is available for investigator review, and the results of the study can be validated. Potential areas of noncompliance need to be addressed early in the execution of the study in order to insure study credibility.

Fairchild and colleagues performed a critical review of seventeen multicenter protocols including one patterns of care study from 1980 to 2012 that provided specific details concerning RT protocol compliance [13]. Specific disease sites included head and neck, breast, lung, pancreas, blood andlymph systems. In seven trials, failure rates were significantly higher after adequate versus inadequate RT. Five of nine and two of five trials reported worse overall and progression-free survival, respectively, after less than adequate RT. One reported a significant correlation and two reported nonsignificant trends toward increased toxicity with noncompliant RT. This data again supports the use of QA program for clinical trials.

On a recent review of a paper generated through data at QARC concerning the impact of centralized radiotherapy review upon protocol compliance in Hodgkin lymphoma, a reviewer had the following comments at the time of decision for publication. “The paper established a standard for clinical trial research testing the value of RT and demonstrated that the time, money, and effort of performing RT data review are mandatory if the overall study results are to be believed. The study demonstrated the importance of physician education in order to improve performance and limit deviations on study for improved study compliance. It is clear when interventional review modifications were performed, protocol deviations were nearly eliminated.” These statements, made by a reviewer on a paper detailing QA methods and showing that centralized RT review is not only feasible, but is capable of successfully averting potential deviations, capture the essence of why QA must remain imbedded in clinical trial processes.

52.3 Informatics

Essential to the core mission of clinical trial, QA for head and neck cancer is a robust informatics platform that can accommodate the multifaceted needs of modern clinical trials. The epicenter of the management system is the protocol patient database that links to all of the applications and data archives used in daily operation for data processing, data integrity, and communication between the multiple aspects of clinical trial management. Data validation, regulatory compliance, and integration with sponsor and cooperative group data centers are essential informatics functions as protocol information needs to be shared and made available to the organizations and regulatory agencies essential in the trial conduct.

The informatics system needs to bring together the complete information required for clinical trial management including all relevant clinical information, pathology objects, imaging, RT treatment objects, chemotherapy treatment plan, and validation of treatment with longitudinal review of outcome including imaging of relapse. The system provides access to all clinical demographics with study-specific elements assembled in a uniform format for review. Clinical investigators need to have the real-time capability of reviewing objects, annotating images, and communicating evaluations through this system. Query functions and standard reports are incorporated into functionality allowing investigators and users facile navigation through patient information and records.

Protocols moving forward will make use of adaptive strategies for patient care. This will include changes in treatment strategy based on patient response to therapy during study. This requires that real-time review of information, including biomarkers and imaging, be readily available for investigator and compliance review. The mechanisms for review must be nimble and user friendly for protocol compliance and provide timely feedback to study/site investigators. Inquiries concerning staging and eligibility often require same-day evaluation feedback to the site investigator in order to expedite entry into study. The multiple media tools enable study investigators to review eligibility objects including biomarkers and imaging at the same time to move care forward in a timely manner. This process can determine which study a patient may be best suited for care. The same process and informatics tools can be used to review response to therapy and navigate discrepancies in real time between site and study investigators. These strategies can facilitate and promote participation from international sites as the tools have no geographic boundary.

The Imaging and Radiation Oncology Core (IROC) is the imaging and radiation oncology QA vehicle for the NCTN. IROC is composed of the QA centers at IROC Houston (the former Radiological Physics Center—RPC), IROC Ohio (the former Cancer and Leukemia Group B—CALGB Imaging Core Lab), IROC Philadelphia (RT) (the former Radiation Therapy Oncology Group—RTOG QA Center), IROC Philadelphia (Imaging) (the former American College of Radiology Imaging Network—ACRIN Core Lab), IROC St. Louis (the former Image-guided Therapy Center), and IROC Rhode Island (the former Quality Assurance Review Center—QARC).

Within this coordinated program, each center maintains an internal informatics system with many similar features including imbedded platforms for protocol development, site identification/resources, credentialing, data acquisition, case management, case review, data transfer for the NCTN, and data archive. Each has specific user-friendly function tailored to each segment of the NCTN as needed for each center. Because each system is used for real-time review and problem solving, user-friendly query function is available for protocol analysis both during the study and after study completion. Data is indexed and tailored to respective user groups. Each system employs control for 21 CFR Part 11 compliance and ICH-GCP adherence. Elements in the records are audited to track changes. Secure audit trails can be made available for agency review. Each of these steps is essential for data management and insures that all information can be stored and retrieved in a timely and protocol-compliant manner. Web-based tools enable immediate access to clinical trial information and objects. This promotes harmonization between protocol objectives and protocol treatment execution which insures protocol-compliant therapy.

52.4 Tissue and Biomarkers

Tissue management is crucial for clinical trial conduct. It is essential to have sufficient volume of tissue as well characterized as possible in order to provide the highest quality support for the clinical trial. Management of tissue is generally reserved for tissue banks whose laboratories can support the needs of tissue storage and analysis of data. These core laboratories provide support for collection of tissue, triage and processing of tissue for histopathology, generation of microarray platforms, and immunohistochemistry. Research specimens can consist of snap-frozen tissue, archival or fresh tissue blocks, cells consisting of tumor and/or tumor-associated lymphocytes, peripheral blood, and paraffin-embedded tissue. Microdissection of submitted tissue is often needed for extraction of ribonucleic acid (RNA) and RNA-based molecular assays. Tissue storage is important as new tools for tissue and patient outcome evaluations become available.

The field of biomarkers is rapidly evolving. Predictive factors can be clinical or biological (not caused by or are treatment related), are observed at baseline, and are statistically associated with outcome including normal tissue toxicity. *Human papillomavirus* (HPV) may be an important

predictive biomarker moving forward in the head and neck cancers. Selected single nucleotide polymorphisms (SNP) may become important in this patient population. Response markers are defined as therapy-related changes in biomarkers that are related to treatment outcome at the individual patient level. These markers may be used to define therapy intensity or interventions for toxicity in an individual patient. Suggested head and neck markers for normal tissue toxicity include tumor necrosis factor beta (TNF-beta) and interleukin-1 alpha (IL-1α). End points are characteristics that are used to assess treatment outcome in a population of patients. These can include clinical (symptom-/disease-free status) or imaging-driven review.

For cancer of the head and neck, approximately 20 % of squamous cell cancers contain genomic deoxyribonucleic acid (DNA) from HPV, in particular HPV-16. It is generally found in cancers of the tonsil and less often in the hypopharynx and oral cavity. There is evidence suggesting that head and neck cancers exhibiting HPV carry a more favorable prognosis. High-risk HPV-16 and HPV-18 encode two oncoproteins (E6 and E7) which influence cellular transformation and cell cycle control. These patients appear to develop cancers via a multistep process with loss of heterozygosity of 17p, and specific point mutations occur in 50 % of patients with cancers of the head and neck. Over 90 % of cancers of the head and neck overexpress epidermal growth factor receptor (EGFR) which may correlate with a poorer outcome in selected patients. Epstein-Barr virus is associated with cancers of the nasopharynx. Each of these markers may become important tools for categorizing outcome in the future [14–16].

Microarray technology has permitted gene expression profiling at the RNA level in most expressed genes. This is accomplished by hybridizing an array of known sequences with labeled cRNA reverse transcribed from sample RNA. DNA microarrays are designed to examine areas of chromosome deletion/amplification or chromosomal methylation. These technologies have demonstrated that premalignant lesions such as leukoplakia have stronger resemblance to invasive cancers than normal controls. Although not yet fully validated or vetted, these biomarkers may become vehicles to develop clinical trials of the future where aggressiveness of therapy could be tailored to specific biomarkers. These will be equally important for more traditional squamous cell cancers of the head and neck and other cancers including salivary gland and other more rare tumors requiring clinical trials. Candidate biomarkers currently include HPV, EGFR, and vascular endothelial growth factor (VEGF) markers as well as specific polymorphisms which have promise in predicting patient outcome.

As one would anticipate, the story relative to candidate biomarkers for patients with the head and neck has become complex, confusing, and often ambiguous with conflicting information at present. HPV and p16 status may overlap in some patients and be discordant in others. Although there was information suggesting that EGFR therapy provided benefit to patients treated with RT for definitive intent as well as patients treated with chemotherapy for metastatic disease, a recent trial (RTOG 0522) did not show additive benefit of EGFR-targeted therapy for definitive patients treated with chemo-radiotherapy. This issue remains unresolved in clinical trials with ambiguous results in both the HPV-positive and HPV-negative patients. Several recent trials did demonstrate increased rates of acute toxicity which is now more evident than the time of the original publication [17, 18] demonstrating benefit to targeted therapy with RT. EGFR has also been measured in healing mucosa with no clear relationship between expression of EGFR and normal tissue tolerance. As more targeted therapies including treatments driven toward PIK3CA and RAS mutations and the mTOR pathway become part of clinical trials, processes will need to be in place to rapidly correlate candidate biomarkers with clinical outcome [19–27].

Informatics systems will need to be designed to meet this purpose if we are to successfully analyze tissue biomarkers with patient outcome. Many biomarker assays and microarray objects can be stored as Digital Imaging and Communications in Medicine (DICOM) standard compatible objects and therefore can be archived with imaging/RT objects for rapid real-time query function. This will permit adaptive clinical trial strategies to mature in clinical protocols. Strategies such as this will be essential in moving forward as we attempt to validate new targeted therapies and biomarkers in clinical trial design.

52.5 Imaging

Imaging has become an essential component to the conduct of clinical trials for cancer of the head and neck. Advanced technology imaging is now a mandatory component for staging patients with head and neck malignancies. Imaging is used to define the extent and volume of the tumor burden, the target for RT, the presence/absence of metastatic disease, and the disease response/progression. These end points are essential for clinical trial management and have significant influence on trial design and execution.

Many advanced technology imaging platforms are now used routinely in head and neck clinical trials. Computer tomography (CT) is the imaging platform used for most RT planning systems. These images can be obtained with and without intravenous contrast. Most institutions prefer not to image with contrast for planning in case of a patient's reaction to contrast while secured in a department-specific immobilization device. Imaging objects used as part of staging and target definition can be fused into planning studies to facilitate target definition and insure that all areas of abnormal tissue can be incorporated into the intended RT treatment field. Advanced technology imaging including positron emission

tomography (PET) and magnetic resonance imaging (MRI) help define high-risk regions and, as part of follow-up, help adjudicate response to therapy. Often advanced technology imaging better defines regions of gross tumor as well as extension into tissues not always easily seen on CT including the cartilage and bone, thus improving our ability to define targets and treat appropriately.

PET-CT has become an important imaging tool in clinical trials. For head and neck trials, the CT component is fused with the metabolic component for a volumetric study of distribution of specific PET tracer compounds, the most common of which is [18F]-fluorodeoxyglucose (FDG). Fusion of the studies is essential for accurate target location, and fusion of the PET-CT objects helps secure the extent and location of gross tumor. This is particularly useful in defining the perimeter of gross tumor, identifying a suspicious second primary tumor, and locating clinically involved lymph nodes which may be below size criteria for identifying them as tumor (Figs. 52.6 and 52.7). With rare exception, PET-avid regions of interest are considered disease and RT treatment planning is altered based on the review of the study. Credentialing institutions for participating in clinical trials involves both phantom dosimetry and review of each case to be certain that both the amount and timing of tracer administration and time for individual completion of imaging comply with study guidelines. Because there are various vendors for PET studies, QA review requires that all information be loaded into a single viewer and standardized uptake value (SUV) units be re-calibrated in a single system for protocol review. Data suggests that compliance for these requirements is in excess

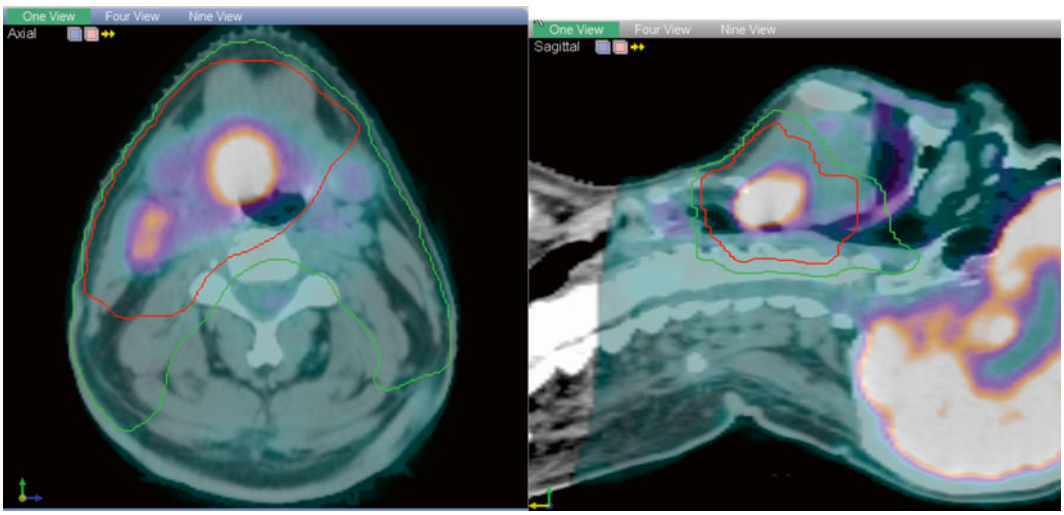

Fig. 52.6 A fused dataset of a pretreatment PET and radiation planning scan with target contours defined [Courtesy of Jeff M. Michalski, MD]

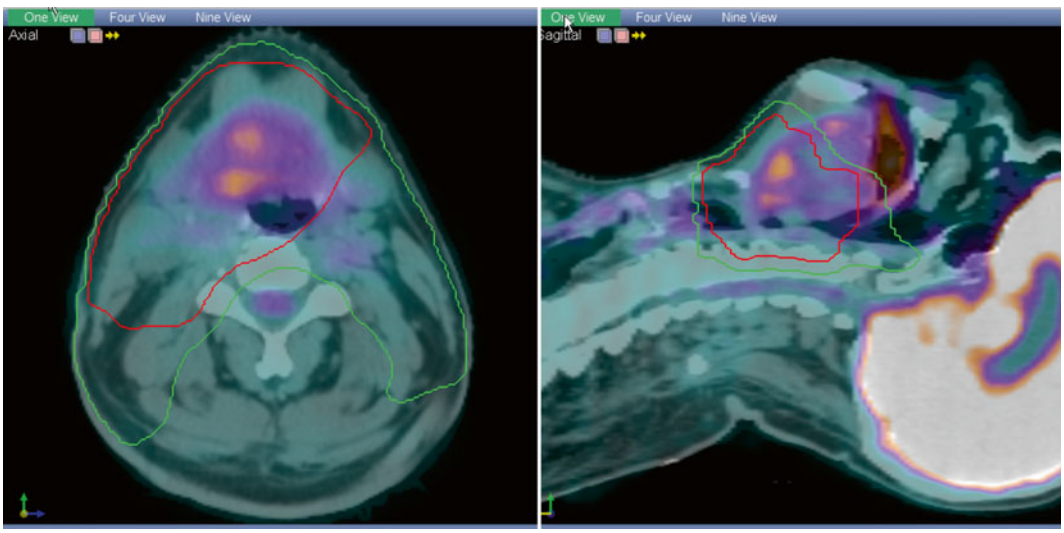

Fig. 52.7 Demonstrates the response to chemoradiation therapy on the posttreatment PET-CT superimposed upon the RT planning scan [Courtesy of Jeff M. Michalski, MD]

of 95 % on most studies. Future protocols will evaluate the role of alternate PET tracers including amino acids, misonidazole (hypoxia), and thymidine (DNA synthesis).

MRI is also playing a valuable role in imaging patients with head and neck malignancies. The strength of MRI resides in the definition of the extent of soft tissue disease as well as better definition of the interface between bone and soft tissue including less commonly seen malignancies such as Ewing's disease and soft tissue sarcoma for pediatric and adult patients. MRI may be less helpful in determining absence of nodal involvement. Protocols are written with specific guidelines for sequence parameters with contrast. Credentialing involves phantom measurements for MRI-specific protocol questions and review of submitted images on the first patient for protocol questions that are not MRI specific.

While there has been more widespread acceptance of PET-CT for the evaluation of the patient with head and neck cancer, on the horizon is the development of PET-MR where various metabolites can be viewed with standard and novel PET tracers. These sequences may better define tumor targets and response to treatment in a manner not previously captured in clinical trials [28].

Imaging will remain an essential component to the management of clinical trials for patients being treated for cancers of the head and neck. Imaging serves to validate clinical staging which on occasion may be subject to variable interpretation by on-site investigators with imaging serving as a bridge between site and study investigators. Because clinical trials for these patients will require international participation for large phase 3 studies, imaging will remain the common ground vehicle to insure appropriate patient entry, staging, and response to treatment for trial validation.

52.6 Radiation Therapy

RT remains a core component of care for patients with head and neck cancer. It is used for definitive clinical trials and clinical trials evaluating postoperative management.

Several components are required for successful RT clinical trial execution. Institutions need to be credentialed to participate in clinical trials. Credentialing can take many forms and can be tailored to the specific needs of trials. For example, many trials for head and neck patients permit the use of intensity modulation for treatment execution. As this technology is becoming more worldwide in acceptance and utilization, phantom credentialing may be indicated if the trial is asking a specific question of intensity modulation and requires validation that intensity modulation can be delivered with the anticipated precision required for treatment execution [29, 30]. The need for this service was underscored by colleagues from IROC Houston who noted a less than 70 % passing rate of institutions submitting data for head and neck phantoms during their first submission of data. As can be seen in Fig. 52.8, the passing rate has increased each year over time. However, in spite of the fact that the phantom has been irradiated 1700 times by 1033 RT institutions, the passing rate, even in more modern times, has only increased above 90 % on two occasions. This reflects the changing environments within institutions and the need to maintain excellence in our discipline as personnel and equipment change and evolve within institutions. A few of the reasons for failure included incorrect dosimetry data and complex modeling of the ends of multileaf collimators as suggested by Cadman and colleagues [31]. With increasing participation in clinical trials by the international community, hard validation through phantom irradiation

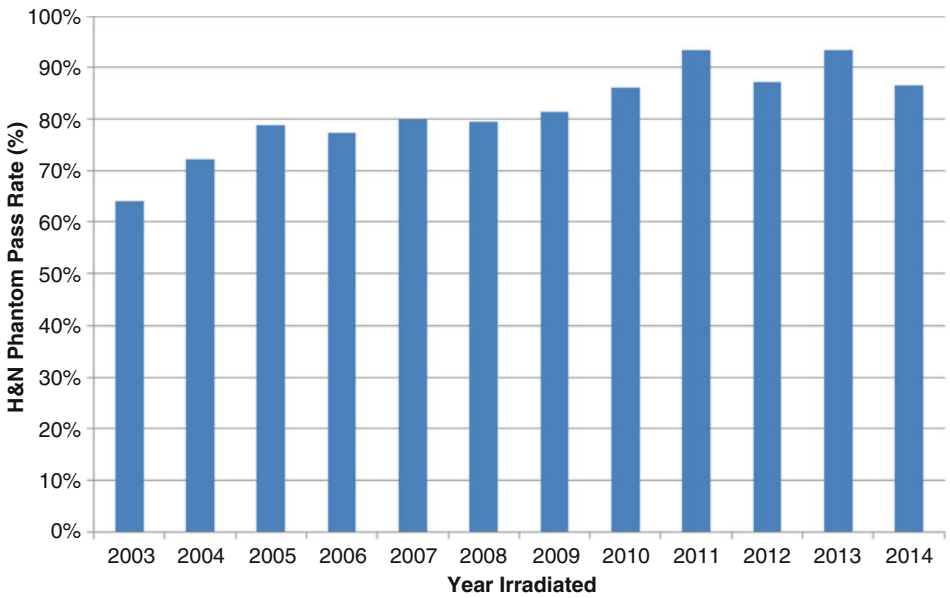

Fig. 52.8 The IMRT head and neck phantom passing rate for the past 12 years of its use by the IROC Houston QA Center [Courtesy of David S. Followill, PhD]

remains an outstanding QA tool. As indicated by Dr. Followill, the head and neck phantom remains the most requested phantom at IROC Houston.

Acquiring advanced technology equipment for RT treatment execution and clinical trial participation requires time and effort to develop the appropriate degree of expertise for clinical trial participation. Validating this expertise through the phantom process insures that appropriate systems are in place for making certain that complex treatments can be executed in a trial-specific manner. If the trial is not asking a specific question of intensity modulation, case credentialing may be a more optimal choice in order to insure that targets can be drawn correctly and submitted to the QA center through the appropriate mechanism. It is important not to limit or provide barriers to study accrual; however, moving forward it remains likely that RT protocol data for clinical trials will be submitted for QA through digital media. This will require that informatics systems be designed in a flexible format to support data acquisition of both imaging and RT treatment data through multiple digital media. This has several advantages for clinical trial management. The first is that information can be received and formatted in a manner that can be reviewed simultaneously by multiple reviewers in the same format at the identical time, therefore permitting real-time intervention as needed in order to insure compliance to study guidelines. The importance of this process was underscored in the clinical trial managed by the Trans Tasman Radiation Oncology Group (TROG). Referenced in the previous section, investigators from more than 30 countries around the world participated in the trial. Because much of the data on this trial was acquired in a non-digital format, the decision was made by the clinical trial management team to perform an interventional review after the first 3 days on treatment as it was felt that a real-time review with worldwide participation was not feasible. As seen, patient survival on study was directly related to the quality of the plan, and there was a difference in survival even when a plan was adjusted as part of the interventional review, implying that the best outcome was achieved when the plan was compliant with protocol objectives de novo. The use of multiple media for data submission permits more institutions to participate thus promoting study accrual.

These processes have significant ramifications for clinical trial processes. The trial evaluating tirapazamine was not intended to test RT treatment objectives. The RT was designed to be part of the foundation of the trial with randomization of a specific chemotherapy agent being the primary test point of the study. The deviations in RT contributed to generating uncertainty in the study outcome promoting the need for QA in clinical trials such as this. Each deviation is meaningful to study design and trial outcome. The cost of clinical trials would certainly decrease if each enrolled patient was (1) appropriate for the study and (2) their treatment objects were study compliant. Modern QA processes need to provide informatics platforms to insure, as best as possible, that these two objectives can be met. The need for real-time review of RT planning objects via a central review process was underscored in the study. Modern platforms insure that objects can be reviewed by study investigators worldwide prior to patient entry on study and treatment delivery.

52.7 Problems in Contouring

As we increase the utilization of volumetric RT treatment planning, tumor and normal tissue structures are contoured, and volumes of the structures are created. This has permitted increased dose to tumor target with potentially decreased dose to normal tissues. Organs at risk are defined for each head and neck protocol, and treatment planning efforts are performed to attempt to meet the constraints defined on each study. Many structures are drawn with relative ease and readily outlined with secure definition using computer tools. Others are more elusive in definition and require considerable effort with inconsistent ambiguous results among investigators. Prior to surgery, chronic disease associated with muscle-wasting syndromes, variant anatomy, and image artifact makes contouring precision more challenging. Although gaps in definition will improve as technology evolves, this will continue to be a process of learning. There also remains considerable variability among radiation oncologists in defining tumor targets and normal tissue organs at risk. Even what is perceived as simple can defy definition including the beginning and end of an organ. This affects volume and needs to be defined in the study. Advanced technology imaging will need to be vetted with sound clinical evaluation to be certain that what is defined as disease on imaging does represent disease. As we adjust targets for treatment and apply conformal avoidance to normal tissues, patterns of failure studies are suggesting we may have overcompensated our efforts to spare normal tissue, and patients are failing in regions of conformal avoidance.

Feng and colleagues who were experts in contouring head and neck anatomy jointly drew head and neck organs at risk for 10 patients, each on three separate occasions, 1 week apart. The study demonstrated measureable variability in contouring normal tissue anatomy with pharyngeal constrictor muscles appeared to be the most variable between investigators. Another study demonstrated more pronounced inter-clinician variation in drawing of the parotid and brain stem, both affecting radiation dose plan optimization when performing conformal avoidance [32].

Investigators have noted changes in patient anatomy during treatment of patients on protocols for head and neck cancer which can create ambiguity in daily patient setup

including alternation in neck contour for lymph nodes responding to RT. This can be associated with weight loss during treatment; however, selected organs can change during radiation treatment. There are several reports demonstrating that parotid glands can decrease in size during RT. This remains true even in situations where the parotid structures are intentionally kept at relatively low dose through conformal avoidance. Change in size can influence mean parotid dose by as much as 20 %. Investigators have documented a change in volume by as much as 40 % during a treatment course. Han and colleagues suggested that the parotid glands through serial measurement decreased in size by 0.21 cm^3 per treatment day. These changes suggest the strong need for adaptive planning for selected normal tissues during clinical trials especially for trials with specific end points evaluating normal tissue tolerance [33].

Certain normal tissues do not lend easily to volume definition. Injury to the carotid artery is becoming more visible, especially in patients who are being re-treated. Although the artery can be easily visualized, it remains less clear if a larger volume should receive an intermediate dose or a smaller volume should receive a higher dose. This is very important in protocols evaluating therapy post-neck dissection as well as re-irradiation. The brachial plexus has been well described in several atlases; however, in head and neck protocols, the structure has multiple definitions. It is challenging to characterize the plexus as a volume, and often study investigators identify the structure as a point object lateral to the vertebral body, generally at C6. The objective is to limit the dose to this structure if possible providing there is no disease at level 4. Many radiation oncologists feel the area of most concern is where the confluence of nerves coalesces as a single structure inferior to the lateral third of the clavicle. This is the area in the care of the breast cancer patient where anterior and posterior fields are used to treat regional disease. The general consensus is that the plexus cannot be easily defined for a dose-volume constraint; however, areas of the plexus should be avoided for hot spots. The spinal cord constraint is generally limited to 50 Gy to 1 % volume of the true cord.

For tumor targeting, integrating metabolic and anatomic imaging best defines all tumor targets as well as the likely extent of the primary disease. Most investigators define three tumor-associated target volumes generally referred to as low risk (microscopic disease), intermediate risk (microscopic disease in close approximation to gross disease), and gross tumor with margin. Each region would have a clinical target volume (CTV) with a planning target volume based on institutional protocol, immobilization platform, and image-guidance strategy.

Contouring targets will remain very important to clinical trials in radiation oncology. The platforms and planning systems provide opportunity to apply radiation dose in a uniform manner between investigators and institutions. Because digital objects can be transferred in real time to study QA investigators, pretreatment review of objects and contours can be performed to make certain objects are defined and applied per study guidelines.

52.8 Quality Assurance: Surgery/Medical Oncology

QA programs in surgery and medical oncology generally consist of facility inventories, site education, investigator credentialing, and periodic peer review audit. This has led to several programs and clinical trials to make treatment delivery processes in these two essential areas more uniform in execution. While audits and education processes have been in place for medical oncology, QA processes are relatively new in the surgical disciplines. Although senior surgical investigators have graciously lent their time for off-site and telephone discussion, applying peer review within surgery has only recently been invited as part of protocol QA programs. More surgical disciplines are becoming incorporated into clinical trial programs, and as such, peer review processes are currently being identified. These consist of teaching videos, web-based seminars, simulation procedures, and retrospective audits. Otolaryngology investigators of the European Organization for Research and Treatment of Cancer (EORTC) recently published their experience in chart review audits of patients with laryngeal cancers treated on a clinical trial [34]. As anticipated, they identified gaps in treatment initiation and reporting of data from a surgical and pathology perspective. This review has established a paradigm for process improvements in the next iteration of clinical trials. This is important as surgical questions of the future will include sentinel lymph node mapping and robotics; therefore, training programs and QA processes will be important as we advance technology into clinical trials. The audit system has worked well for medical oncology in the past, and compliance scores can be assigned by appropriate timing and dose of chemotherapy as well as completion of all appropriate follow-up data including toxicity profiles. The same processes will be followed for targeted therapies as they mature in clinical trials.

52.9 Future Clinical Trials

Head and neck cancer will remain a strong area for clinical trials moving forward. Diseases of the head and neck can be disabling and cause significant alteration in patient function and well-being. The late effects of treatment can have significant lifetime consequence. Tumor control remains suboptimal, especially for patients with advanced disease at presentation. There are considerable opportunities to study

process improvements for better tumor control, target definition, and amelioration of acute and late effects of management. Future studies will need to include patients with recurrent cancer and second malignancies. These patients are exceptionally challenging as target definition and understanding late effects management are incomplete. Radiation dose-volume constraints have not been vetted in this population. Even with a positive outcome for tumor control, these patients remain at exceptionally high risk for late effects which are challenging to heal and manage.

Each phase of the clinical trial needs to be well managed. Imaging and biomarker analysis will need to be thorough and complete to be certain the correct patient is entered on the correct study. The availability of real-time central review of objects, whether mandatory or optional, will help facilitate entry onto the correct study and optimize the care of the patient. Clinical evaluation, metabolic imaging, and biomarker status for HPV and p16 will influence the manner of treatment of a non-smoking young patient with an early-stage lesion of the oral cavity (therapy limited to surgery) as opposed to an older patient with more traditional risk factors. Each patient needs to be studied as there is significant value in acquiring all information concerning patient care and outcome with respect to tumor control and normal tissue outcome. The information will include imaging, tissue, chemotherapy/targeted therapy information, and RT treatment objects both at the time of trial entry and at relapse. We do not always know or understand all of the questions we should ask at the time of the development of the clinical trial charter. The data repository for the clinical trial needs to house all necessary objects to permit query function for questions not anticipated at the time of trial development. Robust query functions permit near-immediate review of objects during or after trial completion to assess outcomes and unanticipated events. Robust query function and data input improve the quality of the questions asked and the responses to the queries.

Because of the literal explosion of information concerning cell signaling pathways, angiogenesis, cell cycle check points, and cell adhesion molecules, clinical trials moving forward for patients with head and neck cancers need to be adaptive and flexible enough to manage multiple moving parts in a harmonized manner. Trials will need to be designed to assess response and outcome to several targeted therapies in a synchronized manner. Standard trial design may become archaic due to the number of therapies needed to be tested in parallel. A robust number of pathways will need to be evaluated in a timely manner within the parameters established by the trial charter.

For these reasons, QA remains the most invaluable construct to clinical trial management. Each phase of the QA, from site credentialing, biomarker validation, imaging quality and interpretation, and chemo-radiotherapy treatment execution, has to be accurate and precise if the outcome of the trial is to be believed and adopted by the general oncology community. Too much is at stake to permit clinical trials that do not have data in place to validate trial outcome. Costs of trials, especially involving biomarkers and imaging, are significant and we cannot afford to lose information on patients as we move to adaptive platforms. To complete adaptive integrated clinical trials with the appropriate number of patients accrued, all QA processes must be robust and compliant to guidelines for successful trial conduct. The QA centers and tissue banks share the responsibility of making certain the processes in place are both nimble and comprehensive. The processes must not limit accrual or be perceived as a barrier to research. However, the processes must function in a validated manner and be available for audit for compliance to guidelines. This is important as there are times sponsors request using clinical trial data in a retrospective manner to repurpose data for targeted therapy for unanticipated outcomes. This can only succeed if processes for trial conduct are constructed in a manner that data can be acquired, archived, and made available in a manner compatible with regulatory guidelines including the FDA.

Of equal importance, robust informatics platforms and well-constructed data repositories become outstanding teaching vehicles. They become an electronic library with resources that can be repurposed as information evolves. Tissue banks become extraordinary resources for biomarker analysis that have yet to be identified. These information sanctuaries ultimately become vehicles to insure that our knowledge moves forward and we do not relive our mistakes of the past.

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