James A. Radosevich *Editor*

Head & Neck Cancer: Current Perspectives, Advances, and Challenges

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Contents

Chapter 1
Overview of "Head & Neck Cancer: Current Perspectives, Advances, and Challenges"

James A. Radosevich

Content

Abstract Cancers arising in the Head & Neck region are a complex group of diseases which require equally complex approaches to diagnose and treat. There is a common misconception that these are self inflicted cancers due to life style choices such as the use/abuse of alcohol and tobacco products. This volume is intended to help educate the reader about the many facets of these diseases and to provide a broad overview of this discipline. While this volume is written such that it can be understood by readers of all levels of education, it still has the content and details that professionals seek in order to stay abreast of this changing field. It should be refreshing to readers to find a volume like this one which explains in great detail many aspects of cancer biology and treatment methodologies, many of which can be applied to cancers arising throughout the body, in a way that is easily understood. In a similar fashion, readers should walk away with a sense of having their preconceived notions of Head & Neck cancer permanently changed, based on the data presented, along with thought provoking concepts that can be applied outside the field of Head & Neck cancer.

Keywords Head • Neck cancer

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1.1 Introduction

This volume starts out with a chapter exploring the evidence for Head & Neck cancer existing well before commercial tobacco and alcohol, (two of the longest linked causative agents to these diseases), were available. In some cases, both considerable temporal and geographical separation existed for these two causative agents, yet there is evidence in the records for patients presenting with Head & Neck cancer back to antiquity. We then explore the current modern state of the frequency and distribution of these diseases in various patient populations. It is important to understand who gets these diseases so that we can target screening and prevention programs, which is the next topic to be discussed.

We then take a step back to explore the human anatomy of the head and neck region, and address the pertinent anatomical sites as they are grouped in segments that are important to the treatment and diagnosis of these diseases. This chapter lays the foundation, for locating the exact anatomical structures in which these tumors arise, and is applicable for all of the remaining chapters. The first application of the anatomical review is presented in the next chapter, which outlines how to perform a proper patient examination to determine if a patient has Head & Neck cancer.

Some patients that are screened do present with abnormalities. In the subsequent chapters, we learn that not every nodule and abnormality is Head & Neck cancer, how to differentiate what they could be, and the follow-up actions that need to take place. We then explore the pathological presentations of the spectrum of disease states that are related to Head & Neck cancer. These need to be understood in order to make the proper diagnosis of lesions that are in fact cancerous. Two chapters are directed at delving into the pathology of the most common type of Head & Neck cancer, followed by a chapter on rarer tumors. We then address how a special branch of pathology, cytopathology, connects with screening efforts, and initial diagnosis of Head & Neck cancers, along with its link to traditional pathology.

Using the pathological background that is presented, we use that background to start to explore the link between Head & Neck cancers and cervical cancer. One may wonder why this is important and/or relevant in a book focused on Head & Neck cancer, but the answer is simple and not realized by many outside the field. Cancers arising in these two sites share considerable overlap in their biology, pathology, viral associations, and many other connections, such that there is a growing body of scientific literature that uses them interchangeably and/or simultaneously in the same scientific manuscript. Discoveries at all levels from basic research to diagnosis and treatment, readily flow from one cancer site to the other. It is ironic, that in light of these strong overlapping similarities of the cancers arising in these two anatomical regions, that funding agencies resist funding research projects that are not dedicated to their particular anatomical region. We learn from this chapter that policy makers, researchers, and funding agencies would benefit patients presenting with these tumors, keeping in mind that an advance made for one disease site is an advance made for the other.

The next several chapters discuss the role that viruses play in Head & Neck cancers, as well as the complex interplay of various microorganisms, host genome expression, and a number of other factors that promote tumor growth. We then explore the role of nutrients in not only the prevention of Head & Neck cancer, but also its role in helping patients recover from their tumors, as well as its link to survival.

The next several chapters are directed at helping the reader to understand what considerations are taken into account in order to produce a treatment plan for patients with Head & Neck cancer. This is followed by chapters that define the role of medical oncology in treating this group of tumors, as well as one that outlines the role of surgical interventions. We then take a look at how diagnostic technologies are applied to more accurately stage and assist the treatment team in treating Head & Neck cancer patients. Considerable time is spent on why some diagnostic methods are better in particular situations, and how the technologies work. This leads us to the next most common treatment, radiotherapy, and how it is applied to these patients.

One technology that lends itself very well to the treatment of Head & Neck cancers is the use of various lasers. In this chapter, and a related chapter that uses compounds activated by laser light, we see how these once exotic technologies are becoming more commonplace in the arsenal of methods to treat Head & Neck cancer.

We then explore the reconstruction of the patient that has been scared both physically and mentally by these diseases and/or as a result of their treatments. We also look at the most common complications of the treatments used on these patients. This is done with the thought that if one knows what negative outcomes can result from a given treatment course, those facts can help guide treatment planning on a patient by patient basis to best avoid them. We then turn to the mental healing that some patients need and highlight for health care providers and family members the mental issues that may be burdening these cancer patients. As with other cancers, these patients struggle with the mental burdens of their possible loss of function, disfiguration, quality of life, and possibly shortened life span. How practitioners and family members can address these issues are covered in this chapter.

A chapter is presented to demystify how cancer drugs and clinical trials are conducted. Having a clear understanding of the overall process by patients, practitioners, and family members will help to clarify the misconceptions related to investigational drugs. This leads us to a chapter describing how currently used drugs work, as a well as a new promising agent to treat Head & Neck cancers. Since cancer is really an immune deficiency disease (because the patient's immune system cannot keep the tumor growth subclinical), we explore a chapter on the immune system and how that has led to a class of antibody-based treatments.

Mitochondria are small organelles within both normal and tumor cells. They are in part responsible for the energy production of the cell. Comparatively new research findings are pointing to this organelle as being a key element in the development and progression of Head & Neck cancer. Drugs directed at acting on key elements to alter the function of mitochondria in tumor cells have recently entered into human

clinical trials. A chapter highlighting the importance of this new body of work, and how it relates to Head & Neck cancer, is presented.

No volume on Head & Neck cancer would be complete without addressing the genetic aspects of these diseases. Similarly, the emerging role of biomarkers as tools to diagnose and as treatment targets are discussed. The comparatively new field of microRNAs is defined, and their possible roles in Head & Neck cancers are outlined.

Finally, we end this volume with the idea that the future is now, with the reduction of a dream to reality. It has long been hoped that early, easy, and affordable methods would be developed to screen patients and identify those patients at early stages of oral cancer, when these diseases are much more amenable to treatment. The use of saliva as a readily available biofluid is being using to detect different types of biological markers to identify early stage cancers. It is anticipated that these advances will propel similar technologies to the market place, and forever change the way Head & Neck cancer patients are treated.

It is essentially impossible to cover every aspect of Head & Neck cancer, as each of the chapters in this volume could be book in and of themselves. That being stated, it is hoped that the reader will gain a broad view of the many overlapping facets related to Head & Neck cancer and be more versed in this complex field after reading this book.

Chapter 2
A Disease Without History? Evidence for the Antiquity of Head and Neck Cancers

William J. Pestle and Michael Colvard

Contents

Abstract There has been a long-running debate in anthropological, archaeological, and medical literature regarding the prevalence of cancer in various ancient human populations. At one extreme, some scholars have claimed that past human societies had rates of cancer roughly equivalent to those seen among modern peoples; at the other extreme, some researchers have effectively claimed that cancer is a disease of modernity. The present study aims to shed further light on this topic, at least insofar as cancers of the head and neck are concerned. A review of ancient art, medical texts, and paleopathological reports revealed somewhat discordant accounts of the age, geographical distribution, and prevalence

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of head and neck cancers. While representations of these neoplastic conditions in art are relatively rare and patchy in geographic distribution, descriptions of suspect lesions in ancient medical texts are rather more widespread, if unevenly distributed geographically, and the paleopathological record was found to contain surprisingly abundant evidence for cancers of the head and neck, especially as compared to what are, in modern societies, more ubiquitous cancers of the breast, lung, or prostate. While establishing the absolute prevalence of any of these conditions in antiquity is impossible, the present work establishes that cancers of the head and neck have long been present, and perhaps even prevalent, in human societies.

Keywords Head and neck cancer • Paleopathology • Archaeology • Artistic representations of disease • History of medicine

Abbreviation

H&NC Head and neck cancer

2.1 Introduction

Evidence for the antiquity of the term "cancer" is indisputable. Hippocrates, writing in the fifth century B.C., used the term 'καρκίνος' (crab/the astrological sign of the Crab) in reference to the texture and shape of a tumor in the breast of a female patient from Abdera, thereby giving rise (through Latin transliteration) to the contemporary English terms 'cancer' and 'carcinoma' [64]. While establishing the history of the recognition and naming of cancer is thus a fairly easy task, determining the antiquity, let alone the prevalence, of any specific class of cancer, in the present case head and neck cancer (hereafter H&NC), is rather more complicated. While we know, for instance, that in the nineteenth century, two American Presidents (Ulysses S. Grant and Grover Cleveland) and a German Emperor (Frederick III) suffered from, and in two instances died as a result of, H&NC, identifying the frequency of the conditions in the more remote past requires a more concerted effort. In the following pages, three classes of evidence, artistic/representational, historical, and paleopathological, are examined in an attempt to determine the age, geographical distribution, and past frequency of H&NC. While this last task is undoubtedly the most fraught, it is hoped that this chapter will demonstrate that H&NC is not solely a condition of the modern age or lifestyle, and that the pain and suffering that they bring have long been a scourge to the human species.

2.2 A First Approximation of the Antiquity of Cancer Writ Large

In an excellent review of the history and distribution of cancer (human and non-human alike), Luigi Capasso identifies the earliest evidence for neoplasm in fossil fish remains dating to the Upper Devonian, around 350 million years ago, with a smattering of additional cases recorded in a variety of fossil vertebrate taxa spanning the Paleozoic, Mesozoic, and Cenozoic eras ([24]:4–6). Within the hominid lineage (the evolutionary line that includes humans and related/ancestral species since its divergence from the line that produced chimpanzees), only a very small number of (often disputed) neoplasms have been identified in fossilized remains. The earliest possible example comes from a 1.5 million year old Kenyan *Homo erectus* mandible that exhibits a lesion that has been variously identified as Burkitt's lymphoma [106], an ossifying sarcoma [121], or simply a bony callus subsequent to a fracture or other periosteal response [101]. Otherwise, a possible meningioma in a 35,000-year-old German Neanderthal parietal bone may represent the sum total of the identified cases of cancer in hominids prior to the appearance of anatomically modern *Homo sapiens* [36].

Turning the focus to our species, the question at hand is, "whether cancer is truly a disease of modern society or whether it may be regarded as part of human heritage from the earliest times," ([79]:843)? The seminal texts on paleopathology seem somewhat at odds regarding the prevalence of neoplastic conditions in antiquity. Calvin Wells, a physician and one of the founders of the science of paleopathology, noted, "Today the common carcinomata—cancer of the stomach, bowel, lung, breast, uterus and many other organs—kill millions of people every decade. Evidence of the disease from early burial grounds is rare," ([134]:73). Conversely, Don Brothwell, another of the dons of the discipline, notes, "It has been stated by a number of previous workers that tumors are rare in skeletal collections…one of the points I wish to emphasize in this survey is the likelihood that the scarcity of tumors has been *overemphasized* in the past," ([19]:320, italics in original).

More recently, treatments on the history of cancer have become somewhat more aligned in arguing that neoplasms were far less prevalent in humanity's ancient past, a difference that is most often attributed to the ubiquity of carcinogenic substances in the modern world. For instance, Zimmerman and colleagues note that, "cancer was a rare disease in antiquity…the current high incidence of cancer is due to a factor or factors present in the modern industrialized world," ([141]:500). This refrain is taken up most recently by David and Zimmerman, who contend that, "the minimal diagnostic evidence for cancer in ancient remains indicates the rarity of the disease in antiquity. Carcinogenic environmental factors have been linked to up to 75% of human cancers, and the rarity of cancer in antiquity suggests that such factors are limited to societies that are affected by modern lifestyle issues such as tobacco use and pollution resulting from industrialization." ([39]:731). The drumbeat for this position is not wholly unanimous, however, as Nerlich and colleagues

[84] have argued quite convincingly on the basis of their recent multi-modality study of cancer in two ancient and one modern populations:

> malignant tumors were present in spatially and temporarily different populations over the last 4,000 years with an age- and gender-adjusted frequency not different from Western industrial populations of c. 100 years ago. Therefore, we conclude that the current rise in tumor frequencies in present populations is much more related to the higher life expectancy than primary environmental or genetic factors, ([84]:197).

Moreover, several recent reviews of neoplasms in non-human primates (e.g. [2, 7, 9, 13, 20, 33]) have shown that these conditions are not just present, but surprisingly widespread in our closest evolutionary relations. That neoplastic conditions would be present, if not prevalent, in both modern humans and non-human primates but not ancient humans violates the basic principle of parsimony.

These finding, among others, have continued to stoke the fires of this argument (e.g. [40, 48]), with no resolution in sight. For now, at least, this debate must be considered a draw pending further information. However, as will be discussed below, in the case of the H&NC, there is telling evidence for *bona fide* antiquity, if not widespread prevalence. Before discussing those findings, however, the nature of the evidence and materials employed merits description.

2.3 Lines of Evidence

This work documents the history and prehistory of H&NC using three distinct lines of evidence: artistic representations, historical documentation, and paleopathology. Given their disparate natures, each of these classes of data has quite distinct strengths and weaknesses. The discussion that follows focuses in particular on the fortes and the limitations of each class of evidence vis-à-vis the identification of ancient cases of H&NC.

2.3.1 Artistic Representations

The first class of evidence for ancient H&NC employed herein is collectively referred to as "artistic representation". This term is construed quite broadly here as to encompass both what we might think of as "traditional" artwork (painting, sculpture, etc.) as well as other forms and media that might not immediately be recognized or categorized as "art". Included in this latter category are such varied human representations as numismatic portraiture (faces/busts on coins) and pre-Columbian South American portrait vessels, pottery vessels made in the shape of human faces or bodies. In all of these instances, artistic representation of oral/facial tumors provide us with insights into ancient/pre-modern conceptions of disease and infirmity, as well as raising intriguing questions regarding the motivation for such portrayals. As with historical descriptions of various cancers, artistic representations of cancer

give us insights into soft tissue manifestations that are most often absent from the paleopathological record. That being said, the drawbacks to using such evidence in reconstructing the timing and geographical distribution of ancient H&NC should be evident. Specifically, the interpretation of artistic representations of disease is limited by at least three factors.

First, as with historical references in medical texts (see below), the representation of possible neoplastic lesions in art is most often consistent with both cancerous and non-cancerous (e.g. infectious) diagnoses. Given the lack of figure legends in ancient artwork, attributions of cancers in such media are thus contingent. Second, for most ancient societies, the anatomical and medical knowledge of the artist making the representation under analysis must be viewed as somewhat suspect or incomplete. In societies where the actual medical practitioners ostensibly lacked what would be characterized in modern terms as basic anatomical and medical knowledge (see below), it is hard to believe that artists or craftsmen would be much better off. Finally, unlike medical practitioners (ancient or modern) who are ostensibly bound to some notion of (culturally mitigated) reality, artists are more often free to depict idealized rather than actual forms and/or to meld the natural and supernatural in their work. Thus, we should not necessarily take seriously the presence of a tumor on a depiction of a human head if that head also exhibits some sort of combination of human and animal attributes, as is often the case in pre-Columbian Amerindian ceramic figures and stone sculpture.

2.3.2 Historical Records

As mentioned in the introduction to this work, the historical documentation of something called cancer is quite ancient and, as will be discussed below, widely geographically dispersed. The descriptions of cancerous lesions provided in ancient medical treatises fill an obvious gap in our base of knowledge and provide a perspective on soft tissue lesions that paleopathology does not afford the modern observer. A legitimate question remains, however, as to whether every, or even most, historical mention of cancer ought to be taken as writ and with equal credibility. While blindly attributing every "swelling" described in ancient medical texts as bona fide malignancies would be foolhardy, several historical texts provide rather more specific descriptions of lesions and conditions that are almost indisputably cancerous. While historical reference can thus provide us with a degree of specificity that paleopathology cannot, attributions derived from historical sources are limited by at least three factors.

First, ancient texts written in languages that are, at best, distantly related to modern language are prone to mistranslation, especially in the case of medical/technical jargon. Even those languages with direct relationship to modern tongues can present non-trivial issues of translation, with idiomatic terms and false cognates being particularly problematic. For instance, the corpus of ancient Greek terms describing possibly cancerous lesions is expansive (including, most commonly, καρκίνος,

οἴδημα, and φῦμα, in addition to a host of less often used terms), ambiguous, and does not bear a one-to-one relationship to modern diagnostic terminology [94–96]. Similarly, the *Sushruta Samhita*, the encyclopedic Sanskrit medical text of the 1st millennium B.C. Indian surgeon Sushruta, names and describes numerous possibly cancerous conditions of the mouth and throat (e.g. *Alasa*, *Adhijihwa*, *Mahasaushir*, and *Arbudam*, to name but a few), making the tasks of direct association with contemporary categories of disease onerous if not impossible ([119]:397–398).

Second, many ancient medical descriptions of lesions are vague enough as to be consistent with a variety of cancerous and non-cancerous etiologies. For instance, the sixteenth century B.C. Egyptian medical text known as the Ebers Papyrus [42] describes numerous possibly cancerous lesions that fall under terms generally translated as "swelling" or "tumor" [16]. The neoplastic origin of most of these are, however, often regarded with some skepticism and, "modern readers have usually interpreted such descriptions simply as swellings, leprosy or perhaps varicose veins", ([39]:729).

Third, and most importantly, any evaluation of a given ancient cancer diagnoses must be considered within the context of the anatomical, medical, and scientific knowledge of the society that produced it. While Hippocrates and Galen are rightly recognized for their precociousness in the recognition of cancer, their chosen explanation of the mechanism for its occurrence, an excess of black bile, serves to limit somewhat the modern utility and comparability of their observations and should serve to remind us to interpret their findings with some caution [86, 137].[1] Likewise, while Traditional Chinese Medicine (TCM) treatises like the *Huang Ti Nei Ching Su Wên* (composed sometime between the fourth and first century B.C.) contain extremely early and accurate descriptions of cancer [66, 128], the explanations of pathogenesis (yin/yang or *wuxing* imbalance) are discordant with modern Western understandings of the topic [21]. Finally, the great Arab scientific and medical minds of seventh to twelfth centuries A.D. were hamstrung in their anatomical knowledge by religious prohibitions on human dissection ([137]:15). None of this is meant to disparage the various ancient or non-Western understandings of health and medicine, but rather is intended to introduce a note of caution in the non-critical application or interpretation of ancient diagnoses of cancer.

2.3.3 Paleopathology

Paleopathology (literally the study of ancient disease) is a multi-disciplinary field of study with a history that stretches back only to the late nineteenth or early twentieth century. Combining aspects of archaeology, physical anthropology, and medicine, paleopathology endeavors to identify the traces of disease and traumatic injury in

[1] The humoural theory of disease (cancer included), it must be noted, was not only the state-of-the-art of the ancient Mediterranean world but continued to dominate medical thinking on the origins and treatment of cancer until the nineteenth century when it was finally replaced by Müller and Virchow's cellular theory of cancer.

preserved ancient human remains (most typically skeletal, but in some instances mummified remains). The value of paleopathology to modern medicine is the temporal depth that it can provide, "those who confine their research entirely to diseases as they exi[s]t at the present moment are operating in a two-dimensional plane: paleopathology adds a third dimension. It is like the difference between monocular and binocular vision." ([35]:151). The conclusions derived from paleopathological research are, however, rendered somewhat contingent by the following five factors, several of which are particularly germane to the present study of ancient H&NC.

First, the state of human remains as they appear today rarely, if ever, faithfully represents the appearance of those remains in life. The preservation of human remains in archaeological contexts is the exception rather than the rule, so a stark minority of the remains of past individuals exist today in any recognizable form. Thus, to begin with, the sample of remains available to us today may or may not accurately represent the population from which they are drawn thereby calling into question reconstructions of past disease prevalence. Even in those instances where remains have survived the rigors of time and burial, a whole suite of biological, chemical, cultural, and physical processes (collectively referred to as taphonomic processes) can serve to alter the gross, microscopic, and compositional nature of bone to the point where pathological recognition becomes impossible. Furthermore, in some cases, these very same processes can alter bone in manners that are startlingly similar to bona fide pathology or trauma, producing so-called pseudopathologies ([6]:11–17).

Second, even in those instances where human remains survive in (relatively) unaltered condition, additional bias may be introduced by differences in the rates of their discovery/excavation and study. Put simply, not all regions of the world are or have been of equal interest to archaeologists, and the public and forces within discipline have tended to privilege the study of remains/materials from certain regions (e.g. Egypt) over others. Even in those instances where steadfast efforts at excavation and study have been made, inherent biases in the preservation and recovery of, for instance, males versus females or adults versus subadults can color or distort paleopathological reconstruction of past disease processes [126].

Third, the identification and attribution of specific disease or neoplastic processes from skeletal remains, in particular, is sharply limited by the non-specific appearance of many bony lesions. Lacking tumorous tissues, which in all cases except extreme mummification are likely to be lost [139], all that remains as evidence in bone (if bone was indeed affected) will fall into the fairly limited repertoire of non-specific osseous reactions (osteoblastic versus osteoclastic/osteolytic) ([115]:2). Making a disease/cancer specific diagnosis from such evidence is often difficult and/or speculative, particularly in the case of soft tissue or metastatic carcinomas, but even sometimes in the case of primary osseous tumors (especially when taphonomic and pseudopathological changes are taken into account).

Fourth, the interpretation of the prevalence of any past disease is complicated by a three issues (demographic nonstationarity, selective mortality, and hidden heterogeneity), which are jointly referred to as the "osteological paradox" [138]. The issue of selective mortality is of particular relevance to the present discussion, in that, for

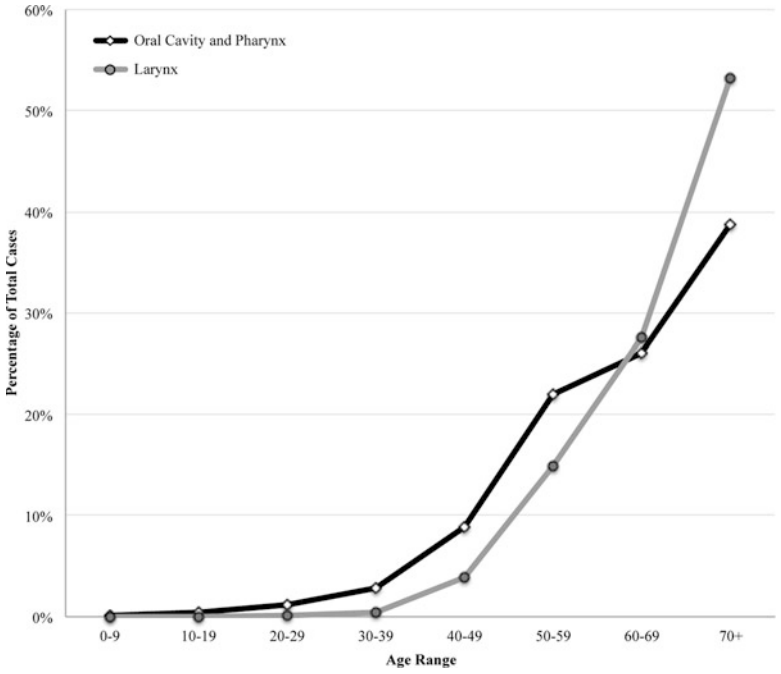

Fig. 2.1 Head and Neck Cancer prevalence by age cohort (Based on SEER/NCI Cancer Statistics Review 1995–2008)

example, if we were to identify a particular neoplastic lesion on the skeleton of a 20–30 year old (after [138]:344), we might be inclined to attribute greater risk of said neoplasm to individuals of that age range than to individuals between 40 and 50 years of age. What such interpretation fails to take into account is that the only 20–30 year olds we observe in a skeletal sample are, by definition, those individuals that died in that age range. As such, they were not representative of the mortality risk inherent to that age range (all the 40–50 year olds were once between 20 and 30 too), but rather of the mortality risk of the deceased individuals alone.

Finally, there remains the issue that the direct comparison of ancient and modern populations, particularly when it comes to the matter of disease prevalence rates, is generally ill advised. Besides the issues of the osteological paradox (discussed above), there are many differences between populations of the ancient and modern world in regards to numerous other variables that contribute to overall health and disease risk. To give but one example, stark differences in life expectancy between ancient and modern societies make any comparison of cancer prevalence between the two groups fruitless. Without getting too immersed in the debate about ancient life expectancies (see, for example, [26, 31, 130]), it can be postulated that the average life expectancy in almost every ancient society was several decades shorter than the 2008 U.S. life expectancy of 78.7 years. As seen in Fig. 2.1, the prevalence of two

forms of H&NC increases dramatically with age, to the extent that over 85% of oral cavity and pharyngeal cancers and over 95% of laryngeal cancers are found in individuals 50 years or older (U.S. data [65]). If individuals in past populations weren't living (on average) past 50 or 60 or 70 years, significant numbers of past H&NC cases would be, for lack of a better term, invisible to the modern researcher. To compare the prevalence rates of such diseases between two such disparately structured populations (to say nothing of differences in diet, health care screening, activities, psycho-social factors, etc.) would thus be fruitless and prone to misinterpretation.

2.4 Findings

In order to assess the presence and/or ubiquity of H&NC in the ancient world, three parallel reviews of three distinct data sets were performed. First, we surveyed archaeological and art historical literature in search of artistic representations of possible cranio-facial neoplasms. To augment these artistic/representational data, a review of ancient medical literature (primary documents and relevant secondary sources) was also conducted. Finally, in order to evaluate the "true" paleopathological prevalence of H&NC, we undertook an exhaustive review of the relevant archaeological, anthropological, and paleopathological reports. The somewhat discordant and surprising results of these reviews are as follows.

2.4.1 Artistic Representations of H&NC

An opportunistic review of the pertinent literature revealed only a very few, admittedly ambiguous, examples of possible head and neck neoplasms. A few of these are, however, rather more convincing.

Among the earliest (600 B.C.-A.D. 350), and most impressive of these artistic representations is a small ceramic figure made by people of the Tumaco-La Tolita culture of present-day Colombia and Ecuador. The proper left cheek of this figurine (Fig. 2.2) exhibits, "a big facial mass, rounded with edges and ulceration…. A deviation of the mouth suggests compromise of the facial nerve. A tumor of the maxillary sinus seems a probable diagnosis," ([12]:189). Bernal and Briceno [12] appear to suggest that this is not the only example of tumors represented in the Tumaco-La Tolita materials they observed.

Roughly contemporary (Han Dynasty (202 B.C.-A.D. 220) and later) Chinese representations of the god Nan-ji-xian-weng or Shou Xing depict, in a variety of media, an elderly man with prominent bossing of the forehead (Fig. 2.3) [32]. While his appearance is similar to that of an individual afflicted by craniosynostosis, "some legends say that the frontal mass is a soft tissue tumor instead of a bony lesion. As 'Nan-ji-xian-weng' has been living for as long as the earth, the mass should be a benign slow-growing tumor," ([127]:2).

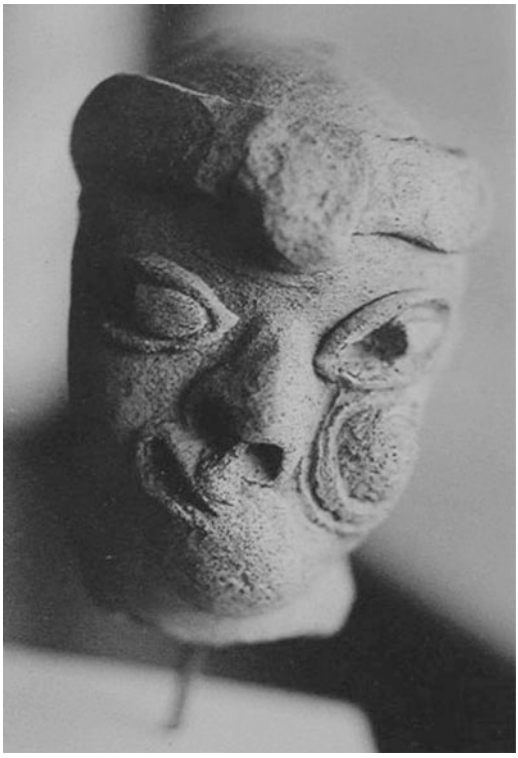

Fig. 2.2 Tumaco-La Tolita ceramic figurine displaying large facial tumor (Photo courtesy of J.E. Bernal, reproduced with permission of John Wiley and Sons)

A particularly intriguing example of ancient H&NC may be found in the coinage of the Parthian Empire (247 B.C.-A.D. 224) of Central Asia and Iran. Beginning with the Emperor Mithridates II (123–88 B.C.), numismatic depictions of the busts of five successive emperors of the Parthian royal family exhibit small blastic cutaneous lesions of the cheek or forehead (Figs. 2.4 and 2.5) [8]. Various authors have interpreted these lesions as trichoepithelioma [62], basal cell carcinomas [76], or a cutaneous lesion of Neurofibromatosis Type I (NF-1, von Recklinghausen's Disease) [122]. The apparent hereditary aspect of these lesions would seem to lend greater credence to an explanation of trichoepithelioma or neurofibromatosis.

Moving more recently in time, ceramics of the Moche/Mochica civilization of northern coastal Peru (A.D. 100–800), and other Andean cultures, provide a comparatively rich corpus of data on, in particular, cranio-facial pathology. Among others, the depictions found on these vessels provide evidence for a variety of genetic, traumatic, and infectious conditions, as well as for the treatments thereof (e.g. [22, 54, 78]). Of particular relevance to the present work are, for example, a vase (Museo Nacional, Lima, no. 1/3664) depicting an individual with a bulging tumor of/behind the proper left eye ([37]:45, 210), the broken head of a vase, now in a collection in Hamburg, with a tumor of the proper left cheek ([10]:204), and a vase depicting a man (Museo Larco, Lima, ML000452, Fig. 2.6) with a bulging localized tumor on his proper right cheek. The location of this "lesion" is, however, also consistent with a quid of coca leaf, a common pastime of both ancient and modern Andean peoples.

Fig. 2.3 Seventeenth or eighteenth century Chinese ceramic depiction of god Nan-ji-xian-weng or Shou Xing exhibiting prominent soft tissue tumor of forehead (Image AN10223001 © Trustees of the British Museum)

Fig. 2.4 Coin of Parthian Emperor Orodes II (57–38 B.C.) exhibiting blastic lesion on forehead (Image AN1099987001 © Trustees of the British Museum)

Fig. 2.5 Coin of Parthian Emperor Phraates IV (37–2 B.C.) exhibiting blastic lesion on forehead (Image AN1099837001 © Trustees of the British Museum)

Finally, a ceramic sculptural head from sixth century A.D. Remojadas culture of Veracruz, Mexico would appear to show evidence of one or more tumorous processes. According to Pirsig [93] this individual, "without a doubt shows a tumor of the left parotid gland that has also affected portions of the external ear (*although this may be an ear spool and not a tumor*) and adjacent areas of the neck." This tumor complex, in conjunction with a small round lump beneath the proper left eye has led to a diagnosis of, "a malignant melanoma of the lower eyelid with metastasis to the area of the parotid gland and external ear," ([93]:255).

2.4.2 Historical Medical Records of H&NC

In contrast to the very few artistic representations of H&NC, the canvassing of ancient medical texts revealed a somewhat larger number of lesion descriptions and/or diagnoses consistent with H&NC.[2] However, in most areas of the ancient world,

[2] It should be noted that this review of ancient medical texts is obviously biased in that only literate past societies would have left any written records of their collective medical knowledge.

Fig. 2.6 Moche ceramic effigy vessel displaying tumor of left cheek (ML000452, courtesy of Museo Larco, Lima-Perú)

described head and neck neoplasms still are far outnumbered by clearer descriptions of cancers of the breast and uterus, among others.

The earliest preserved Egyptian medical text, the Ebers Papyrus (ca. 1500 B.C.) describes a handful of lesions that are at least consistent with neoplasms. In addition to two references (cases 553 and 554) to eating ulcers (*bnwt*) of the gums or teeth (likely dental abscesses), in the papyrus' final section (the so-called Treatise on Tumours [124]), there are as many as five cases that may be read as tumors of the head or neck, although other explanations are possible [43]. The first, case 857, a *ḥnḥnt* of the throat (Fig. 2.7), is described as, "the swelling in the neck of a man (with a previous attack (of bile)). On palpation the swelling is soft, with overlying vesicles. It contains fluid. Treatment is by local applications," ([16]:37). Two other examples, cases 859 and 861, a *ḥnḥnt* and a *ḥnḥnt nt rj.t* of the throat, respectively, seem likely to have been purulent lesions given their stated association with pus formation ([124]:29–31). Case 860, a *ḥnḥnt.t nt ʿḏ* (a fatty tumor of the neck), is described as a, "glandular swelling in his neck, felt like the thymus gland. Treatment is by surgery, plus local applications," ([16]:37). Finally, case 870, a *ʿȝ.t nt šnj* (cyst/swelling) of the scalp, most likely refers to a benign cyst or localized purulent lesion ([124]:35). While the contemporary Edwin Smith Papyrus describes the surgical treatment of breast cancer numerous times, it makes no mention of any condition reconcilable with H&NC [17]. Interestingly, contemporary Mesopotamian medical tablets make no mention of cancerous conditions whatsoever ([131]:205).

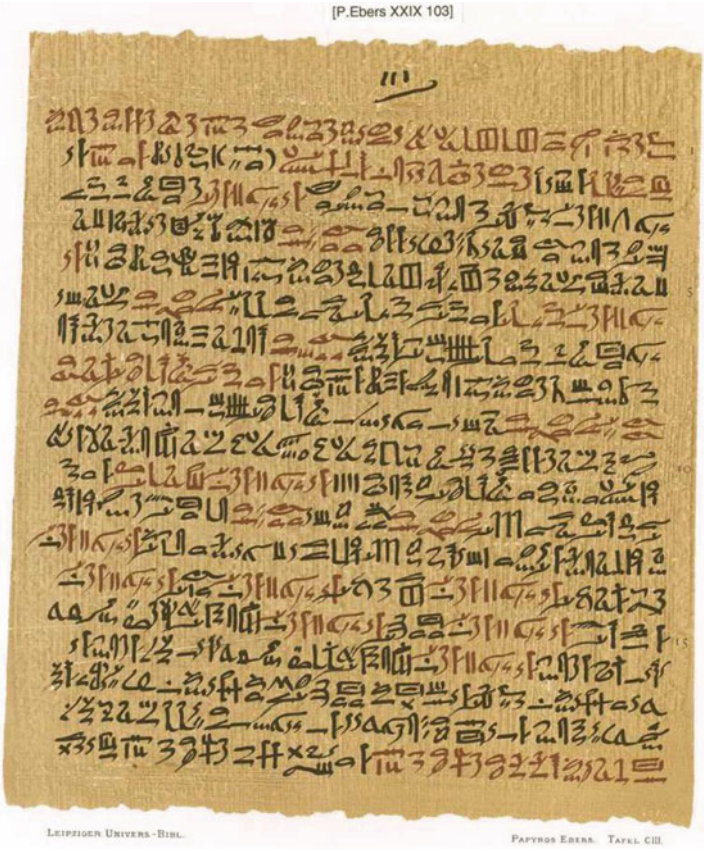

Fig. 2.7 Plate 103 of the Ebers Papyrus, describing possible head and neck tumors (Image courtesy of Universitätsbibliothek Leipzig)

On the contrary, more numerous and definitive descriptions of H&NC are found in the *Sushruta Samhita*, a mid-first millennium B.C. Sanskrit surgical text penned by the famous Ayurvedic surgeon Sushruta [14]. In Chap. 11 of the pathology section of this work, Sushruta describes the general signs, symptoms, and clinical prospects of what he calls Arbuda (tumors) and Adhi-Arbudam (metastases), while Chap. 16 is devoted specifically to oral diseases. In the latter section, a number of the conditions described would seem to match well with modern clinical presentations of H&NC [119]. Among these are: (1) the Mánsaja type (lip cancer) ([14]:102, [119]:397), (2) the Mahá-Saushira type (alveolar/palatal tumor) ([14]:103, [119]:397), (3) the Alása and Adhijihva types (neoplasms of the base and tip of the tongue, respectively) ([14]:106, 108–109, [119]:397), (4) the Arvuda type (palatal tumor) ([14]:107, [119]:397), (5) the Rohini, Śataghni, and Valása types (tumors of the pharynx and hypopharynx) ([14]:107–109, [119]:397–398), (6) the Kaphaja Rohini, Valaya, and Giláyu types (tumors of the post-cricoid/esophagus) ([14]:108–110, [119]:398), and (7) the Svaraghna type (tumor of the larynx) ([14]:110, [119]:398).

The frequency of mention and degree of detail provided for these head and neck conditions has led some to conclude that, "we may presume that oral and oropharyngeal diseases which are mentioned at great length must be much more common than a lump in the breast," ([119]:400). In the case of the Egyptian medical texts (above) and those of the Greco-Roman world (below), the converse would appear to be true. While it clearly is difficult to infer meaning and/or causality from the relative abundance of mentions of head and neck conditions, it should be noted that the chewing of betel quid, a combination of areca nut (*Areca catechu*), catechu (*Acacia catechu*), slake lime, and betel leaf (*Piper betle*), a mixture with strong carcinogenic tendencies [58, 67], is well documented in South Asia in the period of the *Sushruta Samhita*.

Somewhat more recently, one can find numerous mentions of likely cancerous pathologies and the appropriate treatments thereof in the expansive collection of Greco-Roman medical literature. Kouzis [73] and Retsas [96] have identified 15 definitive and 7 possible ancient and Medieval Greek language authors who, at one time or another, wrote on the topic of cancer. While the humoral theory of disease advanced by these authors has long since been disproven, the descriptions of (possibly) cancerous pathologies oftentimes match quite well with modern clinical appearances thereof.

Not surprisingly, the earliest of the Greek works to mention H&NC belongs to Hippocrates (460–375 B.C.), who was, "the first to deliver medicine from the bonds of mysticism and speculation by founding it on natural science and experience," ([137]:4). The Hippocratic corpus, in addition to a now-lost treatise *On Carcinosis* (Περί Καρκινώσεως), includes at least three mentions of likely H&NC. In the second book on *Diseases* [63], Hippocrates described lesions at the base of the tongue that are remarkably similar to those noted by Sushruta ([63]:242–243). In the same work, he differentiates between a series of presumably benign nasal polyps and small "carcinia" lesions (likely malignant) of the nasopharynx, "Ἕτερος φύεται ἐκ πλαγίου τοῦ χόνδρου ἐν ἄκρῳ οἷον καρκίνια," ([63]:250). Finally, treatment of similar lesions is to be found in the seventh book on *Epidemics*, in which a successful application of cautery to "carcinoma" of the pharynx is described, "Ὁ τὸ καρκίνωμα τὸ ἐν τῇ φάρυγγι καυθεὶς ὑγιὴς ἐγένετο ὑφ' ἡμέων,"([64]:404).

In his *De Medicina* [28–30], the Roman author Celsus (30 B.C.-A.D. 38) became the first to differentiate carcinoma (which, for him, referred only to malignancies) from cancer, a more blanket terms for all tumoral growths ([30]:589–592, [137]:6–7). Conditions of both types appear in the head and neck. Among the most common locations for malignancies, Celsus argued, were the face, nose, ear, and lips, "Id vitium fit maxime in superioribus partibus, circa faciem, nares, aures, labra," ([29]:128). According to Celsus, surgical remediation of these malignancies was not recommended, but excision was an option with, for instance, less aggressive cancers of the lip when alimentary function was impaired, "in labris vero, si nimium contracta sunt, usui quoque necessario iactura fit, quia minus facile et cibus adsumitur et sermo explicatur," ([30]:362). He also advised caustic treatment of nasal polyps unless they were of a cancerous, that is malignant, variety, "Polypus vero est caruncula, modo alba modo subruba, quae narium ossi inhaeret…fereque mollis est, raro dura, eaque magis

spiritum impedit et nares dilatat; quae fere carcinodes est; itaque attingi non debet," ([29]:244–246).

Galen (A.D. 131–203), the Greek-born physician to the Roman Emperors Marcus Aurelius and Commodus, who picked up the cause of Hippocrates and was instrumental in the development of Western medicine, also makes several references to possible neoplasms of the head and neck. Among these are: (1) his observation that the face, ears, nose, and lips are particularly common sites for cancerous lesions ([137]:10), and (2) his warning against any attempt at excision or cautery of tumors of the palate ([96]:50). This latter observation is emblematic of the generally conservative course of action in the treatment of tumors advocated by many Greco-Roman (and later Late Antique and Medieval) physicians [71].

2.4.3 Paleopathology of H&NC

Among the three classes of data presented here, it was the review of paleopathological cases of H&NC that yielded the most abundant evidence in favor of the *bona fide* antiquity of H&NC. For the purposes of this paleopathological review, while we took the step of categorizing all possible cases of H&NC as primary or metastatic, the original authors' attributions/descriptions of the relevant lesions/cases are presented as found in the primary source material. No effort was made to standardize the descriptive terminology of the various authors, whose work represents over a century of scholarship and medical and paleopathological knowledge. In some instances, later re-examination of supposedly neoplastic lesions precipitated their exclusion from tabulation. Given their global ubiquity and the lack of any significant health impact, instances of both button or ivory osteomas and external auditory exostoses were excluded from consideration ([6]:254–5, 375). Cases of metastatic carcinoma (of unknown and various primary origin) and instances of multiple myeloma with systemic distribution have, however, been included. Table 2.1 displays the results of this survey.

Based on the results of this literature review, it would appear that of all of the primary soft tissue cancers, cancers of the head and neck may be among the best represented in the paleopathological record both in terms of their number and their geographical distribution. As seen in Table 2.1, 123 cases of H&NC have been identified in skeletal or mummified remains. While, as discussed above, this number cannot be extrapolated into a statement about the prehistoric prevalence of these conditions, it can be examined in comparison to paleopathological findings concerning other primary soft tissue cancers. For instance, examination of countless mummies has revealed no evidence of primary cancerous lesions of the breast [140], and only a handful of possible cases of metastasized breast cancer in the skeleton have been suggested (e.g. [1]). This is not to say that H&NC were more prevalent in antiquity than were breast cancers, but instead that such conditions were present in substantial enough quantities as to be well-represented despite the types of impediments to paleopathological identification identified above.

2.5 Discussion and Conclusion

The results of these three parallel surveys of ancient H&NC are somewhat inconsistent, and yet some insights into the antiquity of this one class of cancers can nonetheless be gleaned.

On the one hand, our review of ancient art was able to identify only a handful of possible representations of cancers of the head and neck. These examples were the products of ancient societies from Latin America (Ecuador, Mexico, and Peru) and Asia (China and Iran), although this uneven distribution can hardly be construed to represent accurately the prehistoric geography of H&NC. Rather, it seems more appropriate to construe these few admittedly ambiguous examples as a tantalizing hint of the antiquity (as early as seventh century B.C.) and widespread geographic distribution of cancers of the head and neck. While specific diagnosis from such evidence is ill advised or impossible, the existence of these representations does speak to the fact that, for at least 2,500 years, and on several continents, artists were making a choice to present through their work the visages of individuals with craniofacial morphology that are in line with that which we might today associate with H&NC. Certain of these examples, in particular the ceramic head featuring a facial tumor from the Tumaco-La Tolita peoples and the possible example of metastasis from sixth century A.D. Veracruz, are particularly convincing as representations of true H&NC.

Turning to the survey of ancient medical texts, we are able to build upon and solidify the inkling of the *bona fide* antiquity of H&NC provided through the study of these ancient works of art. Ancient medical texts from three continents (Africa, Asia, and Europe), and as old as 3,500 years, would appear to bear witness to the existence of conditions that, while imperfectly described in modern clinical terms, are strikingly consistent with H&NC. The lengthy and detailed treatment of such conditions in the roughly 2,500-year-old *Sushruta Samhita* and the numerous mentions in the expansive Greco-Roman medical corpus are especially convincing of the notion that ancient medical practitioners, while less than ideally trained in modern terms, were encountering conditions in the course of their practice that are strikingly consistent with the modern clinical experience of H&NC. The ability of these practitioners to differentiate between benign and malignant processes, to recognize metastasis, and to so accurately describe the symptomology and treatability (or lack thereof) of these various head and neck conditions are to us exceptionally persuasive of both their knowledge and of the existence of H&NC in antiquity.

The most convincing evidence of the true age and even ubiquity of H&NC comes however, from the paleopathological review presented here. As stated above, 123 cases that are at least broadly consistent with a variety of cancers of the head and neck were found in the paleopathological literature. Among these 123 identified cases, 62 were likely primary head or neck neoplasms of varying type, 47 were metastatic in origin, 13 were of unclear neoplastic origin (with the most common source of uncertainty stemming from the macroscopic similarity of the bony lesions of multiple myeloma and metastatic carcinoma), and one individual exhibited

Table 2.1 Documented paleopathological cases of head and neck cancer

Continent	Country	Date	Primary/metastatic	Type/description	References
Africa	Egypt	Sixth to fifth century B.C.	?	Multiple myeloma or metastatic carcinoma	Pahl [90]
Africa	Egypt	Seventh to fourth century B.C.	?	Multiple myeloma or metastatic carcinoma	Strouhal and Vyhnánek [117]
Africa	Egypt	Seventh to fourth century B.C.	?	Multiple myeloma or metastatic carcinoma	Strouhal and Vyhnánek [117]
Africa	Egypt	Seventh to fourth century B.C.	?	Multiple myeloma or metastatic carcinoma	Strouhal and Vyhnánek [117]
Africa	Egypt	Seventh to fourth century B.C.	?	Multiple myeloma or metastatic carcinoma	Strouhal and Vyhnánek [117]
Africa	Egypt	Saitic period	?	Multiple myeloma or metastatic carcinoma	Pahl [90]
Asia	Iraq	Islamic period	?	Metastic carcinoma	Wada et al. [125]
Europe	Denmark	Medieval	?	Multiple myeloma or metastatic carcinoma	Møller and Møller-Christensen [80]
Europe	England	Twelfth to fifteenth century A.D.	?	Multiple myeloma or metastatic carcinoma	Wells [135]
Europe	England	Fourteenth to fifteenth century A.D.	?	Multiple myeloma or metastatic carcinoma	Wells [135]
Europe	Spain	Neolithic	?	Multiple myeloma or metastatic carcinoma	Fusté [49]
North America	Alaska, USA	1800–1900 A.D.	?	Metastatic lesion on mandible, sarcoma or hemangioma	Cassidy [27]
North America	Alaska, USA	First to fourteenth century A.D.	?	Multiple myeloma or metastatic carcinoma	Lagier et al. [75]

Africa	Egypt	Third to fifth dynasty	Both	Primary carcinoma of the naso-pharynx causing destruction of portions of maxillary, palatal, and pterygoid bones with metastases throughout skull	Wells [133]
Africa	Egypt	–	Metastatic	Eosinophilic granuloma?	Pahl [88]
Africa	Egypt	–	Metastatic	Metastic carcinoma	Pahl [89]
Africa	Egypt	25th dynasty	Metastatic	Possible metastatic deposit in right parietal	Isherwood et al. [69]
Africa	Egypt	3200–500 B.C.	Metastatic	Metastic carcinoma	Nerlich et al. [84]
Africa	Egypt	3200–500 B.C.	Metastatic	Metastic carcinoma	Nerlich et al. [84]
Africa	Egypt	3200–500 B.C.	Metastatic	Metastic carcinoma	Nerlich et al. [84]
Africa	Egypt	Old Kingdom	Metastatic	Metastic carcinoma	Pahl [90]
Africa	Egypt	Ptolemaic	Metastatic	Metastic carcinoma	Pahl [90]
Africa	Egypt	Ptolemaic	Metastatic	Metastic carcinoma	Satinoff [102]
Africa	Egypt	Ptolemaic	Metastatic	Metastic carcinoma	Watermann [129]
Africa	Nubia	Christian period	Metastatic	Multiple myeloma or metastatic carcinoma	Armelagos [4]
Africa	Nubia	Christian period	Metastatic	Metastic carcinoma or eosinophilic granuloma	Strouhal [114]
Africa	Nubia	New Kingdom	Metastatic	Metastic carcinoma	Nielsen [85]
Europe	Czechoslovakia	Seventh to thirteenth century A.D.	Metastatic	Metastic carcinoma	Hanakova [60], Hanakova et al. [61]
Europe	Czechoslovakia	Seventh to thirteenth century A.D.	Metastatic	Metastic carcinoma	Hanakova [60], Hanakova et al. [61]

(continued)

Table 2.1 (continued)

Continent	Country	Date	Primary/metastatic	Type/description	References
Europe	Czechoslovakia	Seventh to thirteenth century A.D.	Metastatic	Metastic carcinoma	Hanakova [60], Hanakova et al. [61]
Europe	Czechoslovakia	Seventh to thirteenth century A.D.	Metastatic	Metastic carcinoma	Hanakova [60], Hanakova et al. [61]
Europe	Czechoslovakia	Bronze Age	Metastatic	Metastic carcinoma	Hanakova [60], Hanakova et al. [61]
Europe	Czechoslovakia	Bronze Age	Metastatic	Metastic carcinoma	Hanakova [60], Hanakova et al. [61]
Europe	Czechoslovakia	Chalcolithic	Metastatic	Metastic carcinoma	Hanakova [60], Hanakova et al. [61]
Europe	England	1200–1400 A.D.	Metastatic	Metastasis of pituitary tumor	Hair et al. [57]
Europe	England	Medieval	Metastatic	Metastic carcinoma	Anderson et al. [3]
Europe	England	Saxon (449–1066 AD)	Metastatic	Numerous lytic lesions in cranial vault	Brothwell [19]
Europe	Germany	1400–1800 A.D.	Metastatic	Metastic carcinoma	Nerlich et al. [84]
Europe	Germany	1400–1800 A.D.	Metastatic	Metastic carcinoma	Nerlich et al. [84]
Europe	Germany	1400–1800 A.D.	Metastatic	Metastic carcinoma	Nerlich et al. [84]
Europe	Germany	1400–1800 A.D.	Metastatic	Metastic carcinoma	Nerlich et al. [84]
Europe	Germany	1400–1800 A.D.	Metastatic	Metastic carcinoma	Nerlich et al. [84]
Europe	Germany	1400–1800 A.D.	Metastatic	Metastic carcinoma	Nerlich et al. [84]
Europe	Germany	1400–1800 A.D.	Metastatic	Metastic carcinoma	Nerlich et al. [84]
Europe	Germany	1400–1800 A.D.	Metastatic	Metastic carcinoma	Nerlich et al. [84]
Europe	Germany	1400–1800 A.D.	Metastatic	Metastic carcinoma	Nerlich et al. [84]

Europe	Germany	1400–1800 A.D.	Metastatic	Metastic carcinoma	Nerlich et al. [84]
Europe	Poland	Tenth to twelfth century A.D.	Metastatic	Metastic carcinoma	Gladykowska-Rzeczycka [53]
Europe	Poland	Twelfth to thirteenth century A.D.	Metastatic	Metastic carcinoma	Gladykowska-Rzeczycka [53]
Europe	Russia	Tenth to twelfth century A.D.	Metastatic	Metastic carcinoma	Rojlin [99]
North America	Alaska, USA	Eighteenth to nineteenth century	Metastatic	Metastasis of pituitary tumor	Ortner [87]
North America	Alaska, USA	Sixth to sixteenth century A.D.	Metastatic	Metastic carcinoma	Steinbock [109]
North America	Alaska, USA	Sixth to sixteenth century A.D.	Metastatic	Metastic carcinoma	Steinbock [109]
North America	Alaska, USA	ca. 350 A.D.	Metastatic	Metastic carcinoma	Ortner [87]
South America	Chile	ca. 750 A.D.	Metastatic	Metastic carcinoma	Gerszten et al. [51]
South America	Peru	1000–1450 A.D.	Metastatic	Metastic carcinoma	Ortner [87]
South America	Peru	Eighth century A.D.	Metastatic	Metastic carcinoma	Allison et al. [1]
South America	Peru	ca. 400 B.C.	Metastatic	Metastasis or malignant melanoma	Urteaga and Pack [123]
South America	Peru	Pre-Hispanic	Metastatic	Numerous lytic lesions in cranial vault	Grana et al. [56]
South America	Peru	Pre-Hispanic	Metastatic	Metastic carcinoma	Steinbock [109]
South America	Peru	Pre-Hispanic	Metastatic	Metastic carcinoma	Steinbock [109]
Africa	Egypt	–	Primary	Tumour of the maxilla	Pahl [89]
Africa	Egypt	1st dynasty	Primary	Osteoangioma/Haemangioma of the skull	Pahl et al. [91]
Africa	Egypt	20th dynasty	Primary	Angioma or meningioma in right parietal	Rogers [98]
Africa	Egypt	3200–500 B.C.	Primary	Plasmacytoma	Nerlich et al. [84]
Africa	Egypt	400–600 A.D.	Primary	Nasopharyngeal carcinoma	El-Rakhawy et al. [45]
Africa	Egypt	400–600 A.D.	Primary	Myeloid epulis in left maxilla	El-Rakhawy et al. [45]

(continued)

Table 2.1 (continued)

Continent	Country	Date	Primary/metastatic	Type/description	References
Africa	Egypt	400–600 A.D.	Primary	Benign hypertrophy of nasal concha	El-Rakhawy et al. [45]
Africa	Egypt	400–600 A.D.	Primary	Benign hypertrophy of nasal concha	El-Rakhawy et al. [45]
Africa	Egypt	600 B.C.	Primary	Osteosarcoma of the orbit	Salama and Hilmi [100]
Africa	Egypt	6th–12th dynasty	Primary	Nasopharyngeal/Epipharyngeal carcinoma	Strouhal [112]
Africa	Egypt	Late dynastic	Primary	Sub-pericranial dermoid tumour/ Intradiploic epidermoid cyst	Shanks and Kerley [105]
Africa	Egypt	Late dynastic	Primary	Intradiploic epidermoid cyst/ angioma	Brothwell [19]
Africa	Egypt	Late period	Primary	Osteoangioma/Haemangioma of the skull	Pahl et al. [91]
Africa	Nubia	?	Primary	Benign tumour/dermoid cyst/ granuloma	Ingalls [68]
Africa	Nubia	"Early"	Primary	Benign orbital tumour	Elliott-Smith and Wood Jones [47]
Africa	Nubia	Fourth to sixth century A.D.	Primary	Malignant osteolytic tumor originating in nasal mucous membrane or sphenoid sinus	Derry [41]
Africa	Nubia	Christian period	Primary	Nasopharyngeal carcinoma	Strouhal [113]
Africa	Nubia	Islamic	Primary	Osteogenic sarcoma in frontal	Nielsen [85]
Africa	Nubia	New Kingdom	Primary	Osteogenic sarcoma in maxilla	Nielsen [85]
Asia	Iran	3,500–3,000 B.C.	Primary	Malignant neoplasm in area of left maxillary alveolus/palate	Krogman [74]
Europe	Austria	Neolithic	Primary	Multiple myeloma	Strouhal and Kritscher [116]

Europe	Czechoslovakia	1200–1679 A.D.	Primary	Osteosarcoma	Strouhal et al. [118]
Europe	Czechoslovakia	Seventh to thirteenth century A.D.	Primary	Multiple myeloma	Hanakova [60], Hanakova et al. [61]
Europe	Czechoslovakia	Seventh to thirteenth century A.D.	Primary	Cranial angioma	Hanakova [60], Hanakova et al. [61]
Europe	Denmark	Neolithic	Primary	Benign nasopharyngeal tumour	Brothwell [19]
Europe	England	Roman	Primary	Vault osteosarcoma or meningioma	Brothwell [19]
Europe	England	Saxon (449–1066 AD)	Primary	Naso-pharyngeal fibroma	Brothwell [18]
Europe	France	Medieval	Primary	Huge ivory osteoma	Béraud et al. [11]
Europe	France	Medieval	Primary	Malignant bone tumor in right maxilla	Dastugue [38]
Europe	France	Neolithic	Primary	Angioma in cranial vault	Billard [15]
Europe	Germany	1400–1800 A.D.	Primary	Plasmacytoma	Nerlich et al. [84]
Europe	Germany	1400–1800 A.D.	Primary	Plasmacytoma	Nerlich et al. [84]
Europe	Germany	1400–1800 A.D.	Primary	Osteosarcoma	Nerlich et al. [84]
Europe	Hungary	Medieval, tenth to eleventh century A.D.	Primary	Multiple myeloma	Nemeskeri and Harsány [83]
Europe	Italy	Iron Age	Primary	Hemangioma in left parietal	Capasso et al. [25]
Europe	Poland	Tenth to twelfth century A.D.	Primary	Multiple myeloma	Gladykowska-Rzeczycka [53]
Europe	Poland	Eleventh to fourteenth century A.D.	Primary	Cranial angioma	Gladykowska-Rzeczycka [53]
Europe	Poland	Twelfth to thirteenth century A.D.	Primary	Ameolblastoma	Gladykowska-Rzeczycka [53]
Europe	Spain	Bronze Age	Primary	Nasopharyngeal carcinoma	Aufderheide and Rodríguez-Martín [6]

(continued)

Table 2.1 (continued)

Continent	Country	Date	Primary/metastatic	Type/description	References
North America	New Mexico, USA	Thirteenth to seventeenth century A.D.	Primary	Epidermal inclusion cyst	Ortner [87]
North America	New York, USA	Thirteenth century A.D.	Primary	Multiple myeloma	Williams et al. [136]
North America	New York, USA	Fifth to tenth century A.D.	Primary	Multiple myeloma	Ritchie and Warren [97]
North America	Tennessee, USA	Late prehistoric/early historic	Primary	Multiple benign fibro-osseous tumors	Ortner [87]
North America	West Virginia, USA	Seventeenth century A.D.	Primary	Primary malignant bone tumor, osteoma, or osteosarcoma in mandibular corpus	Kelln et al. [72]
South America	Chile	1100–1200 A.D.	Primary	Giant cell tumor in mandible	Sawyer et al. [103]
South America	Chile	1200–1400 A.D.	Primary	Monostotic fibrous dysplasia in right maxilla	Sawyer et al. [104]
South America	Chile	300–600 A.D.	Primary	Rhabdomyosarcoma of right cheek	Gerszten and Allison [50]
South America	Chile	ca. 1000 A.D.	Primary	Nasopharyngeal squamous cell, paranasal sinus, facial skin, or basal cell carcinoma	Halperin [59]
South America	Peru	Inca	Primary	Vault osteosarcoma or meningioma	MacCurdy [77]
South America	Peru	Pre-Hispanic	Primary	Pituitary adenoma	Grana et al. [56]
South America	Peru	Pre-Hispanic	Primary	Scalp tumor (or nascent meningioma) and soft tissue tumor in area of left maxilla causing perforation into maxillary sinus	Moodie [81]
South America	Peru	Pre-Hispanic	Primary	Cancellous osteoma	Moodie [81]

South America	Peru	Pre-Hispanic	Primary	Large frontal tumour over left orbit	Grana et al. [56]
South America	Peru	Pre-Hispanic	Primary	Nasopharyngeal carcinoma	Wells [134]
Africa	Egypt	Byzantine	Primary?	Naso-pharyngeal epitheliomata	Elliott-Smith and Dawson [46]
Africa	Egypt	Byzantine	Primary?	Naso-pharyngeal epitheliomata	Elliott-Smith and Dawson [46]
Africa	Kenya	Lower/middle Pleistocene	Primary?	Burkitt's lymphoma, osteosarcoma, or response to trauma	Stathopoulos [106], Tobias [121], Sandison [101]
Africa	Nubia	New Kingdom	Primary?	Possible soft tissue tumor adjacent to sphenoid	El-Batrawy [44]
Europe	Denmark	Neolithic	Primary?	Malignant osteolytic neoplasm of vault	Brothwell [19]
Europe	England	Iron Age	Primary?	Tumour of the maxilla	Goodman and Morant [55]
Europe	Switzerland	Early Medieval	Primary?	Lytic tumour in region of frontal sinuses	Brothwell [19]
South American	Chile	Pre-Hispanic	Primary?	Soft tissue tumor originating in left frontal sinus (Fig. 2.8)	Present work

Fig. 2.8 Chilean pre-Hispanic cranium exhibiting soft tissue tumor originating in left frontal sinus (Specimen 12.212, Museo Arqueológico R.P. Gustavo Le Paige, San Pedro de Atacama, Chile, photograph by author)

lesions consistent with both primary and metastatic neoplasms in the head/neck region. Among the primary neoplasms, cancers of the upper respiratory tract appear rather frequently, perhaps reflecting, as Capasso and others have suggested, an increased predilection for such conditions in indoor environments heated by wood fires or other combustion sources [23, 24, 34].

Geographically, paleopathological of possible ancient H&NC were identified on at least five continents (Africa, Asia, Europe, North America, South America) and in at least 20 countries. That certain regions or countries (e.g. Egypt, the Andean countries) are particularly well represented, while an entire continent (Australia) is absent from this list is likely not a reflection of the unequal prehistoric distribution of the head and neck cancers. Instead, as discussed above, this phenomenon is likely a result of both differential preservation (Egypt and the Andes representing the extreme of organic preservation in archaeological contexts) and a highly uneven distribution of scholarly attention.

Besides the aforementioned 1.5 million year old putative example of Burkitt's lymphoma or osteosarcoma from Kenya, the oldest identified cases of H&NC from Europe date to the Neolithic Age (ca. 7000–2000 B.C.), from Africa and Asia to the middle or late fourth millennium B.C., from South America to the fifth or fourth century B.C., and from North America to the fifth century A.D. It is unclear what, if any, conclusion should be drawn from these differences in time of first appearance, especially as it is highly doubtful that any of these "earliest" recorded instances accurately represent the earliest true incidence thereof (the chance that any particular recorded example of X is the earliest example of X being quite small). It may, however, be noted that all of the observed instances of H&NC are contemporary

with, or postdate, the time of first adoption of agriculture by the various societies under study. This is not to suggest a causal link between the agricultural "revolution" and H&NC, and indeed there are other reasonable explanations for this phenomenon (the increased population and population density typically seen subsequent to the adoption to agriculture, the increased likelihood of preservation of archaeologically "younger" remains from food producing societies versus those from earlier food forager societies), but it is nonetheless noteworthy that none of the cases predate this momentous transition in human history.

While the examination of these three disparate classes of data, art, texts, and ancient human remains, presents us with some interpretative challenges and a non-trivial degree of inconsistency, the sum total of evidence would seem to speak quite clearly to two key findings.

First, the wide geographic distribution of H&NC attested to by these three distinct lines of evidence would seem to indicate that lifestyle factors alone cannot explain entirely their occurrence and/or prevalence. While certain clusters of high prevalence, for example that seen in the Indian subcontinent in the first millennium B.C., may be attributable to particular environmental factors, these surveys have found compelling evidence for the existence of ancient H&NC from five of the six inhabitable continents.

Second, in answer to the primary query that motivated this work, based on these data, it seems far more likely that cancers of the head and neck predate modernity rather than these conditions being a product of a modern world or lifestyle. All three classes of evidence speak to an earliest appearance of H&NC at least 2,000–2,500 years ago, and the paleopathological record would seem to speak to even greater time depth. The history of these conditions, it would seem, reaches far back into our human history. While direct comparisons with the rates of H&NC seen in the modern world are impossible, the findings presented here should go some significant way in demonstrating that cancers of the head and neck are not conditions of the modern age or lifestyle alone, and that the pain and suffering that they bring have long been a scourge to the human species.

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Chapter 3
Head and Neck Cancer Epidemiology and Health Services Research

Linda M. Kaste, Therese A. Dolecek, and Athanasios I. Zavras

Contents

Abstract This chapter provides an overview of the epidemiology and health services research deliberations on HNC in the US and globally. Cancers of the head and neck contribute considerable burden to the health of populations as well as demands on health care systems. Variation of the anatomical sites included in HNC yield variance in the relative ranking of HNC among cancers. Designation of risk factors has general conscious but delineating the specificity of factors for cancer cause along with disparate and changing distributions around the world may impact health care provider

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knowledge and associated practices to aid in reducing HNC burden. An additional aspect on causal factors is the challenges in creating behavioral change, such as for improving diets and nutritional intake, prevention and cessation of tobacco and alcohol use, and risky sexual behaviors. Multi- and interdisciplinary approaches are needed for prevention, early intervention, and cost-effective treatment to reduce the population and health care systems burdens.

Keywords Head and neck neoplasms • Mouth neoplasms • Epidemiology • Health services research

Abbreviations

ACS	American Cancer Society
APC	Annual Percent Change
ARCAGE	Alcohol-related cancers and genetic susceptibility in Europe study
ASR	Age-standardized rate
BMI	Body mass index
CDC	United States Centers for Disease Control and Prevention
HNC	Head and neck cancers (carcinoma)
HPV	Human Papillomavirus
HSR	Health Services Research
IARC	International Agency for Research on Cancer (a component of WHO)
INHANCE	International Head and Neck Cancer Epidemiology consortium
NHB	non-Hispanic Black
NHW	non-Hispanic White

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NAACCR	North American Association of Central Cancer Registries (source for ACS Cancer Figures and Facts 2012)
NCI	USA National Cancer Institute
SEER	Surveillance Epidemiology, and End Results (a program of the US NCI)
SCC	Squamous cell carcinoma
SCCHN/HNSCC	Squamous cell carcinoma of the head and neck
US/USA	United States of America
WHO	World Health Organization

3.1 Introduction

Head and neck cancers include an array of anatomical sites where predominately the cancer is SCC. The common cancer histology has meant that for the most part there are shared preventive and risk factors. A number of detailed reviews exist that provide basics on these factors for the USA and other countries, especially focusing on the preventive aspects of nutrition (contributions of fruits and vegetables) [78], and the leading risk factors of tobacco and alcohol and the synergy of their combined use [52, 73]. The advent of studies on the association of HPV and SCC has lead to a new body of work that has also been reviewed [20, 51, 77].

In this chapter, the definition of epidemiology is based on that from Last [45]:

> The study of the distribution and determinants of health-related states or events in specified populations, and the applications of this study to control of health problems

The definition of health services research (HSR) is also from Last [45] as defined here:

> The integration of epidemiologic, sociological, economic, and other analytic sciences in the study of health services; Health services research is usually concerned with relationships between need, demand, supply, use, and outcome of health services

A more challenging definition is that for head and neck cancer (HNC). There is variation of the application within the United States of America (USA). The National Cancer Institute (a component of the US National Institutes of Health) defines HNC as "Cancer that arises in the head or neck region (in the nasal cavity, sinuses, lips, mouth, salivary glands, throat, or larynx [voice box])" (http://www.cancer.gov/cancertopics/types/head-and-neck, accessed 11/7/11). However, for the NCI SEER program's Fact Sheets (representative of accessible US data on cancer sites), the sites available do not quite correspond. For SEER, sites physically in the head and neck region and have availability from the Fact Sheets include: esophagus, eye and orbit, larynx, oral cavity and pharynx (with reporting for the sub-site of tongue) and thyroid (http://seer.cancer.gov, accessed 04/17/12). Yet a 2005 review of head and neck cancer using the SEER database included larynx, oral cavity, tongue, lip, oropharynx, hypopharynx, salivary gland, nasopharynx and other mouth [14]. In that review

of cases diagnosed between 1973 and 2000, the ordering of most frequent to least frequent sites were: larynx (27,287), oral cavity (23,667), oropharynx (18,962), lip (9,163), hypopharynx (6,391), salivary gland (6,274), nasopharynx (3,967), and other mouth and pharynx (521).

A longer list of sites contained within HNC can be found via MedicineNet.com where the definition is:

> Head and neck cancer: The common carcinomas of the oral cavity, pharynx, and larynx as well as other tumors that affect the head and neck.
> These include:
>
> - Paranasal sinus and nasal cavity cancer
> - Lip and oral cavity cancer
> - Nasopharyngeal cancer
> - Oropharyngeal cancer
> - Hypopharyngeal cancer
> - Laryngeal cancer
> - Salivary gland cancer
> - Parathyroid cancer
> - Thyroid cancer
>
> There are also metastatic head and neck cancers in which the primary tumor where the cancer originated may or may not be known. (http://www.medterms.com/script/main/art.asp?articlekey=19411, accessed 11/7/11)

The Cancer Research website for the National Health Service of the United Kingdom presents HNC as a broad term covering 30 possible tissues and organs in the head and neck (http://cancerhelp.cancerresearchuk.org/type/head-and-neck-cancer, accessed April 22, 2012). Their basic links are: "eye cancer, nasal and paranasal sinus cancer (cancers in the nasal cavity and in the sinuses around the nose), nasopharyngeal cancer (the area that connects the back of the nose to the back of the mouth), mouth and oropharyngeal cancer (cancers of the tongue, the gums, cheeks, lip and floor and roof of the mouth), larynx or laryngeal cancer (cancer of the voice box) and oesphageal cancer (cancer of the food pipe or gullet)."

A global perspective on cancer is coordinated by IARC (International Agency for Research on Cancer, a component of the WHO) via the GLOBOCAN project (http://globocan.iarc.fr, accessed 04/17/11). The most recent report is GLOBOCAN 2008. The Fact Sheet information option of GLOBOCAN 2008 includes the top eight most common cancers among which "Oesophagus" is provided. Further discussion on GLOBOCAN 2008 reporting by cancer site is provided in subsequent sections of this chapter.

Hence, within this chapter, HNC may be inconsistently used, as the HNC definition will rely on that used by the source of reported information. Tables 3.1 and 3.2 are presented to help assess the impact of potential layers of consideration of HNC definition. The first table is based on information from GLOBOCAN 2008 for global data and the second is from the American Cancer Society for US 2012 data estimates [3]. The tables are set up to help illustrate the possible differences in data on HNC depending on different definitions of including sites from cancer registries and surveillance systems as well as for research conduct. Within the tables

Table 3.1 GLOBOCAN 2008 World incidence (number, ASR, %) and mortality (number, ASR, %) for selected cancers by sex[a]

	Men						Women						Total					
	Incidence			Mortality			Incidence			Mortality			Incidence			Mortality		
World	#	ASR	%	#	ASR	%	#	ASR	%	#	ASR	%	#	ASR	%	#	ASR	%
Lip, oral cavity	170,496	5.2	2.6	83,109	2.6	2.0	92,524	2.5	1.5	44,545	1.2	1.3	263,020	3.8	2.1	127,654	1.9	1.7
Nasopharynx	57,852	1.7	0.9	35,984	1.1	0.9	26,589	0.8	0.4	15,625	0.4	0.5	84,441	1.2	0.7	51,609	0.8	0.7
Sum A: Lip, oral cavity and nasopharynx; Approximates oral cavity and pharynx																		
Sum A	228,348	6.9	3.5	119,093	3.7	2.9	119,113	3.3	1.9	60,170	1.6	1.8	347,461	5.0	2.8	179,263	2.7	2.4
Other pharynx	108,588	3.4	1.6	76,458	2.4	1.8	28,034	0.8	0.5	19,092	0.5	0.6	136,622	2.0	1.1	9,550	1.4	1.3
Oesophagus	326,245	10.1	4.9	276,007	6.5	6.5	155,400	4.2	2.6	130,526	3.4	3.9	481,645	7.0	3.8	406,533	5.8	5.4
Larynx	129,651	4.1	2.0	70,336	2.2	1.7	21,026	0.6	0.3	11,556	0.3	0.3	150,677	2.2	1.2	81,892	1.2	1.1
Sum B: Other pharynx, Oesophagus, larynx approximates upper respiratory and digestive system																		
Sum B	564,484	17.6	8.5	422,801	11.1	10.0	204,460	5.6	3.4	161,174	4.2	4.8	768,944	11.2	6.1	497,975	8.4	7.8
Sum A and Sum B	792,832	24.5	12.0	541,894	14.8	12.9	323,573	8.9	5.3	221,344	5.8	6.6	1,116,405	16.2	8.9	677,238	11.1	10.2
Thyroid	49,211	1.5	0.7	11,206	0.3	0.3	163,968	4.7	2.7	24,177	0.7	0.6	213,179	3.1	1.7	35,383	0.5	0.5
Sum A, Sum B and thyroid (HNC)	842,043	26.0	12.7	553,100	15.1	13.2	487,541	13.6	8.0	245,521	6.5	7.2	1,329,584	19.3	10.6	712,621	11.6	10.7
Brain, NS	126,815	3.8	1.9	97,251	2.9	2.3	111,098	3.1	1.8	77,629	2.3	2.2	237,913	3.5	1.9	174,880	2.5	2.3
Sum of HNC with brain and NS	968,858	29.8	14.6	650,351	18.0	15.5	598,639	16.7	9.8	323,150	8.8	9.4	1,567,497	22.8	12.5	887,501	14.1	13.0

(continued)

Table 3.1 (continued)

	Men						Women						Total					
	Incidence			Mortality			Incidence			Mortality			Incidence			Mortality		
World	#	ASR	%	#	ASR	%	#	ASR	%	#	ASR	%	#	ASR	%	#	ASR	%
Selected comparison cancers																		
Colorectum	663,904	20.3	10.0	320,397	9.6	7.6	571,204	14.6	9.4	288,654	7.0	8.6	1,235,108	17.2	9.8	609,051	8.2	8.1
Lung	1,092,056	33.8	16.5	948,993	29.2	22.5	515,999	13.5	8.5	427,586	10.9	12.8	1,608,055	22.9	12.7	1,376,579	19.3	18.2
Stomach	640,031	19.7	9.7	463,930	14.2	11.0	348,571	9.0	5.8	273,489	6.9	8.2	988,602	14.0	7.8	737,419	10.3	9.7
Prostate	899,102	27.9	13.6	258,133	7.4	6.1							899,102	27.9	7.1	258,133	7.4	3.4
Breast							1,384,155	38.9	22.9	458,503	12.4	13.7	1,384,155	38.9	10.9	458,503	12.4	6.1
Total[b]	6,617,844	202.8	100	4,219,626	127.9	100	6,044,710	164.4	100	3,345,176	87.2	100	12.7 M	180.8	100.0	7,564,802	105.6	100.0

ASR Age-standardized rate per 100,000, % = percentage of all cancers

[a]Data Source: Ferlay et al. [28]. Available from: http://globocan.iarc.fr. Accessed on 20 Jan 2012

[b]Total = all cancers excluding non-melanoma skin cancer

Table 3.2 Based on American Cancer Society Estimates of New Cancer Cases and Deaths by Sex, US, 2012 – Cancer Facts and Figures [3] – Source: Estimated cases based on 1995–2008 incidence rates from 47 states and DC as reported by the North American Association of Central Cancer Registries (NAACCR) representing about 95% of the US population. Estimated deaths are based on US Mortality Data, 1994–2008, National Center for Health Statistics, Centers for Disease Control and Prevention

	Men		Women		Total	
	Incidence	Mortality	Incidence	Mortality	Incidence	Mortality
ACS USA	#	#	#	#	#	#
Oral cavity	17,750	3,710	8,990	1,810	26,740	5,520
Pharynx	10,790	1,730	2,720	600	13,510	2,330
Sum: Oral cavity and pharynx (OCP)						
OCP	28,540	5,440	11,710	2,410	40,250	7,850
Digestive system						
Esophagus	13,950	12,040	3,510	3,030	17,460	15,070
Respiratory system						
Larynx	9,840	2,880	2,520	770	12,360	3,650
Sum: Esophagus + Larynx = Upper Respiratory and Digestive System (URDS)						
URDS	23,790	14,920	6,030	3,800	29,820	18,720
Sum: OCP + URDS (OCPURDS)						
OCPURDS	52,330	20,360	17,740	6,210	70,070	26,570
Endocrine system						
Thyroid	13,250	780	43,210	1,000	56,460	1,780
Sum OCP + URDS + Thyroid (T) (OCPURDST)						
OCPURDST	65,580	21,140	60,950	7,210	126,530	28,350
Other cancer sites in Head and Neck						
Eye and orbit	1,310	120	1,300	150	2,610	270
Brain, NS	12,630	7,720	10,280	5,980	22,910	13,700
Sum of Head and neck: OCP + URDS + T + Eye and Orbit + Brain, Nervous system (BNS)						
HNC	79,520	28,980	72,530	13,340	152,050	42,320
Selected comparison Cancers						
Colorectum	73,420	26,470	70,040	25,220	143,460	51,690
Lung and Bronchus	116,470	87,750	109,690	72,590	226,160	160,340
Stomach	13,020	6,190	8,300	4,350	21,320	10,540
Prostate	241,740	28,170	–	–	241,740	28,170
Breast	2,190	410	226,870	39,510	229,060	39,920
Total	848,170	301,820	790,740	275,370	1,638,910	577,190

are contrasts for comparison of frequently considered HNC sites (lip, oral cavity and nasopharynx), sites anatomically adjacent that may be classified in respiratory or gastrointestinal systems (other pharynx, oseophagus/esophagus and larynx), and other cancers in the head and neck region that are contained in this publicly available level of the surveillance data. For GLOBOCAN the brain is included and for ACS the eye and orbit and brain/nervous system are captured in this last category.

Both tables also provide contrasts with comparison cancers that have major concerns: colorectum, lung and bronchus, stomach, prostate, breast and total cancers. The histological diagnoses of HNC are usually not available from public use datasets and are not addressed in this chapter.

In both Tables 3.1 and 3.2, the data demonstrate the relative burden of HNC by definition of the sites included. While the respective sites may pale in comparison with lung cancer in men, for example, the collective sum of HNC incidence in GLOBOCAN (Table 3.1) considering men exceeds the comparisons of colorectum and stomach; the sum of HNCs for women exceeds colorectum, lung, and stomach; and the sum for the total surveillance exceeds that of colorectum, stomach, prostate, and breast. The total HNC at 1,567,497 approaches that of lung at 1,608,055. Mortality shows a similar relative perspective at the global level: more men are attributed to death with HNC than are to the sites of colorectum, stomach, or prostate; more women die with HNC than with cancer of the colorectum, or stomach; and in total there are more HNC deaths than for colorectum, stomach, prostate, and breast.

A similar view of HNC in the USA is held in Table 3.2. The counts allow similar ranking comparisons as for Table 3.1. In men, the total HNC projected new case estimate for 2012 is greater than for colorectum, stomach, and since a male project is provided by ACS, for breast cancer. For women HNC is also greater in new cases than for colorectum and stomach, and the comparison is likewise for the total estimate of new cases. Considering the mortality projection, total men HNC deaths are greater than colorectum, stomach, prostate or breast; total women HNC is greater than stomach; and the total mortality projection of HNC is greater than for stomach, prostate or breast.

3.2 Basic Epidemiological Descriptions

National and international cancer surveillance systems provide the means of basic monitoring for head and neck cancers. The cancer registry systems such as those of NAACCR or SEER (USA) and GLOBOCAN (184 countries) enable ecological comparisons especially for incidence and mortality rates and their trends. SEER enables additional measurements as well, such as stage of diagnosis and 5-year survival. SEER and GLOBOCAN offer the availability of on-line data for public use through fact sheets. This access allows for easy updating on statistics as soon as information is provided on the respective websites. With permission further access to the data details may be obtained. At the time of the writing of this book chapter, the on-line data for both systems were for 2008 and the data reported here are at the general public use access. (selected Figures and Tables for data reported for year 2008 estimates in the respective sections below.)

GLOBOCAN provides the opportunity to compare the global perspective by development designation (Table 3.3). Less developed countries lead more developed on cancer incidence (ASR) for men in nasopharynx and oesphagus; for women

Table 3.3 GLOBOCAN 2008[a] Comparisons of less developed and more developed countries using estimated age-standardized incidence and mortality rates for available head and neck cancers and selected other comparison cancers from "Fast Stat" ASR (W) and proportions per 100,000

	Men				Women			
	incidence		Mortality		incidence		Mortality	
	#	ASR (W)	#	ASR (W)	#	ASR (W)	#	ASR (W)
Less developed countries								
Head and neck cancers								
Lip, oral cavity	107,739	4.5	61,231	2.7	64,133	2.6	35,734	1.5
Nasopharynx	52,939	2.1	33,737	1.4	24,566	1.0	14,666	0.6
Other pharynx	68,523	3.0	55,852	2.5	19,593	0.8	15,205	0.6
Oesophagus	262,657	11.8	223,088	10.1	137,727	5.7	115,736	4.7
Larynx	78,939	3.5	46,897	2.1	13,987	0.6	8,870	0.4
Thyroid	26,198	1.0	7,892	0.3	88,713	3.4	17,824	0.7
Brain, NS	81,222	3.2	63,638	2.6	71,222	2.8	50,251	2.0
Selected comparison cancers								
Lung	612,329	27.6	538,858	24.4	272,030	11.1	239,095	9.6
Prostate	255,058	11.9	121,895	5.6				
Breast					691,521	27.1	269,048	10.7
More developed countries								
Head and neck cancers								
Lip, oral cavity	62,757	6.8	21,878	2.3	28,391	2.3	8,811	0.6
Nasopharynx	4,913	0.6	2,247	0.3	2,023	0.2	959	0.1
Other pharynx	40,065	4.5	20,606	2.2	8,441	0.8	3,887	0.3
Oesophagus	63,588	6.5	52,919	5.3	17,673	1.3	14,790	1.0
Larynx	50,712	5.4	23,439	2.4	7,039	0.6	2,686	0.2
Thyroid	23,013	2.9	3,314	0.3	75,255	9.2	6,353	0.4
Brain, NS	45,593	5.8	33,613	3.9	39,876	4.4	27,378	2.6
Selected comparison cancers								
Lung	479,727	47.1	410,135	39.2	243,969	18.8	188,491	13.6
Prostate	644,044	61.7	136,238	10.5				
Breast					692,634	66.4	189,455	15.3

ASR (W) and proportions per 100,000

[a]Data Source: Ferlay et al. [28]. Available from: http://globocan.iarc.fr. Accessed on 20 Jan 2012

lip & oral cavity, nasopharynx, and oesphagus, More developed countries lead less developed countries on cancer incidence for men in lip & oral cavity, other pharynx, larynx, thyroid and brain as well as for comparison cancers of lung and prostate; for women more developed countries lead less developed countries on cancer incidence of thyroid and brain and for the comparison cancers of lung and breast. The two development level have equal women's cancer incidence ASR for other pharynx and larynx. Mortality also shows variations between the two development categories. The mortality ASR for men of less developed countries is higher than of more developed countries in lip & oral cavity, nasopharynx, other pharynx, and oesophagus. For women, the mortality ASR is higher in less developed countries for all head and neck

cancers listed except for brain. More developed countries have higher mortality ASR for men in larynx, brain and comparison cancers, with an equal rate on thyroid. For women, the mortality ASR is higher in brain and the comparison cancers.

The SEER public data allow for more detailed considerations as seen in Table 3.4 with 2012 estimates and summaries for 2005–2009 data. Some notable observations include that the median age of diagnosis for all the cancers considered was over 60 except for thyroid and brain; black males generally have the highest mortality rate except for thyroid and brain and for the projections of eye and orbit are shown with the lowest 5-year survival. Also, following the trends (Jointpoint-APC) including the most current year (2009) for male and females shows increasing values for oral cavity and pharynx, tongue, larynx, esophagus, and thyroid. There are decreasing trends for eye and orbit, and brain and other nervous system. Decreasing trends are seen for the comparison cancers included in this table of lung and bronchus, stomach, and colon and rectum.

3.2.1 Black Male Disparities

In the USA, the group that has been monitored with the highest incidence and poorest outcome has been Black males. They are, however, the US population group showing the most improvement in trends, such that some projected 2012 incidence rates are similar between Black and White males as seen in Table 3.4, disparities on mortality remain of great concern. A consideration for this disparity in HNC is the specific cancer site and differences with survival, Schrank et al. [75] showed with cases matched on age at diagnosis, year of diagnosis, sex, stage, surgical treatment, and radiation that survival was better for whites with anatomic subsites of oropahrynx and larynx and approached statistical significance at oral cavity but whites and blacks survival did not differ for hypopharynx. They conclude that "HPV tumor status is likely a key determinant of the disparity for black patients."

3.2.2 Global Ranking

Globally, as reported in GLOBOCAN 2008 (http://globocan.iarc.fr), the ranking of the burden of head and neck cancers among the top ten most frequent cancers is dependent upon the manner of reporting HNC. For example, if including cancer of the esophagus, the worldwide 2008 ranking among incident cancer cases for males for solely of esophagus is 6th (326,600) and oral cavity is 10th (170,900). Combining these two cancer sites brings the worldwide incidence close to that of liver cancer (ranked 5th). The driving factor for ranking appears to be among developing countries males where the burden of esophagus is at 5th (262, 600) and oral cavity is at 9th (107,700). If these two cancer sites are combined, the rate is brought close to that of liver which is ranked 3rd. Neither esophagus nor oral cavity reaches the top ten incident cancers for women worldwide, but esophagus reaches 8th in developing countries.

Table 3.4 A view of the USA from SEER data estimates for 2012 and surveillance from 2005 to 2009 using 18 SEER areas

	Incidence count			Morality count		
	# Male	#Female	# Total	# Male	#Female	# Total
Oral cavity and pharynx						
Estimate for 2012	28,549	11,710	40,250			7,850
2005–2009 Median age	At diagnosis	62 years	At death	67 years		
	Incidence rate 2005–2009	Mortality rate 2005–2009				
	Male	Female	Total	Male	Female	Total
All Races	16.1	6.2	10.8	3.8	1.4	2.5
White	16.5	6.3		3.6	1.4	
Black	15.4	5.6		5.7	1.4	
Asian/Pacific islander	11.1	5.2		3.0	1.3	
American Indian/Alaska native	10.1	5.0		3.5	1.3	
Hispanic	9.1	4.0		2.4	0.7	
Stage at diagnosis for 2002–2008	Stage Distribution %	5-year relative survival %				
Localized (confined to primary site)	32	Localized	82.4			
Regional (spread to regional lymphnodes)	47	Regional	57.3			
Distant (cancer has metastasized)	16	Distant	34.9			
Unknown (unstaged)	6	Unknown	50.5			

(continued)

Table 3.4 (continued)

	Incidence count			Morality count		
	# Male	#Female	# Total	# Male	#Female	# Total
Jointpoint trend – APC	Male and female trend	Period	Male trend	Period	Female trend	Period
	0.7	1975–1981	–0.1	1975–1983	2.4	1975–1980
	−1.1	1981–2003	−1.5	1983–2001	−0.9	1980–2009
	0.4	2003–2009	0.1	2001–2009		
Oral cavity and pharynx subsite – Tongue						
Estimate for 2012	9,040	3,730	12,770			2,050
2005–2009 Median age	At diagnosis	61 years	At death	66 years		
	Incidence rate	2005–2009	18 SEER areas	Mortality rate	2005–2009	
	Male	Female	Total	Male	Female	Total
All races	4.6	1.8	3.1	0.9	0.4	0.6
White	4.9	1.9		0.9	0.4	
Black	3.6	1.2		1.1	0.3	
Asian/Pacific islander	2.5	1.3		0.5	0.3	
American Indian/Alaska native	2.1	–		–	–	
Hispanic	2.3	1.1		0.5	0.2	
Stage at diagnosis for 2002–2008	Stage distribution %	5-year relative Survival %				
Localized (confined to primary site)	33		Localized	77.5		
Regional (spread to regional lymphnodes)	47		Regional	58.2		
Distant (cancer has metastasized)	15		Distant	32.3		

Unknown (unstaged)	5		Unknown	53.9		
Jointpoint trend – APC	Male and female trend	Period	Male trend	Period	Female trend	Period
	0.4	1975–1999	0.3	1975–1999	0.4	1975–2009
	2.2	1999–2009	2.7	1999–2009		
Larynx						
Estimate for 2012	28,540	11,710	40,250			7,850
2005–2009 Median age		Diagnosis	62 years		Death	67 years
	Incidence rate	2005–2009	18 SEER areas	Mortality rate	2005–2009	
	Male	Female	Total	Male	Female	Total
All Races	16.1	6.2	10.8	3.8	1.4	2.5
White	16.5	6.3		3.6	1.4	
Black	15.4	5.6		5.7	1.4	
Asian/Pacific islander	11.1	5.2		3.0	1.3	
American Indian/Alaska native	10.1	5.0		3.5	1.3	
Hispanic	9.1	4.0		2.4	0.7	
Stage at diagnosis for 2002–2008	Stage	Distribution	%	5-year relative	Survival	%
Localized (confined to primary site)			32			82.4
Regional (spread to regional lymphnodes)			47			57.3
Distant (cancer has metastasized)			16			34.9
Unknown (unstaged)			6			50.5

(continued)

Table 3.4 (continued)

	Incidence count			Morality count		
	# Male	#Female	# Total	# Male	#Female	# Total
Jointpoint trend – APC	Male and female trend	Period	Male trend	Period	Female trend	Period
	0.7	1975–1981	−0.1	1975–1983	2.4	1975–1980
	−1.1	1981–2003	−1.5	1983–2001	−0.9	1980–2009
	0.4	2003–2009	0.1	2001–2009		
Esophagus						
Estimate for 2012	13,950	3,510	17,460			15,070
2005–2009 Median age		Diagnosis	68 years		Death	69 years
	Incidence rate	2005–2009	18 SEER areas	Mortality rate	2005–2009	
	Male	Female	Total	Male	Female	Total
All races	7.8	1.8	4.5	7.7	1.6	4.3
White	8.0	1.8		7.9	1.6	
Black	8.9	2.8		8.2	2.2	
Asian/Pacific Islander	3.7	1.2		3.0	0.9	
American Indian/Alaska native	5.8	2,8		6.4	1.5	
Hispanic	5.0	1.0		4.1	0.8	
Stage at diagnosis for 2002–2008	Stage	Distribution	%	5-year relative	Survival	%
Localized (confined to primary site)			22			37.8
Regional (spread to regional lymphnodes)			30			19.8
Distant (cancer has metastasized)			35			3.4
Unknown (unstaged)			13			10.5

Jointpoint trend – APC	Male and female trend	Period	Male trend	Period	Female trend	Period
	0.4	1975–2009	0.8 −1.5	1975–2004 2004–2009	−0.4	1975–2009
Thyroid						
Estimate for 2012	13,250	43,210	56,460			1,780
2005–2009 Median age		Diagnosis	50 years		Death	73 years
	Incidence rate	2005–2009	18 SEER areas	Mortality rate	2005–2009	
	Male	Female	Total	Male	Female	Total
All races	5.9	17.3	11.6	0.5	0.5	0.5
White	6.2	18.3		0.5	0.5	
Black	3.3	10.1		0.4	0.6	
Asian/Pacific Islander	5.3	17.7		0.5	0.8	
American Indian/Alaska native	3.2	10.9		–	–	
Hispanic	4.2	16.0		0.5	0.6	
Stage at diagnosis for 2002–2008	Stage	Distribution	%	5-year relative	Survival	%
Localized (confined to primary site)			68			99.9
Regional (spread to regional lymphnodes)			25			97.1
Distant (cancer has metastasized)			5			53.9
Unknown (unstaged)			2			87.4

(continued)

Table 3.4 (continued)

	Incidence count			Morality count		
	# Male	#Female	# Total	# Male	#Female	# Total
Jointpoint trend – APC	Male and female trend	Period	Male trend	Period	Female trend	Period
	6.1	1975–1977	−4.7	1975–1980	6.7	1975–1977
	−6.5	1977–1980	1.9	1980–1998	−5.9	1977–1980
	2.4	1980–1997	5.9	1998–2009	2.6	1980–1997
	6.6	1997–2009			7.0	1997–2009
Eye and orbit						
Estimate for 2012	1,310	1,310	2,610			270
2005–2009 Median age		Diagnosis	61 years		Death	70 years
	Incidence rate	2005–2009	18 SEER areas	Mortality rate	2005–2009	
	Male	Female	Total	Male	Female	Total
All races	0.9	0.7	0.8	0.1	0.1	0.1
White	1.0	0.8		0.1	0.1	
Black	0.3	0.1		0.0	0.0	
Asian/Pacific islander	0.3	0.2		–	–	
American Indian/Alaska native	–	–		–	–	
Hispanic	0.5	0.4		0.0	0.0	
Stage at diagnosis for 2002–2008	Stage	Distribution	%	5-year relative	Survival	%
	–	–	–	Overall		83.1
	–	–	–	White men		82.2
	–	–	–	White women		83.4
	–	–	–	Black men		75.9
				Black women		82.5
Jointpoint trend – APC	Male and female trend	Period	Male trend	Period	Female trend	Period
	−0.3	1975–2009	−0.3	1975–2009	−2.3	1975–1985

					0.2	1985–2009
Brain and other nervous system						
Estimate for 2012	12,630	10,280	22,910			13,700
2005–2009 Median age		Diagnosis	57 years		Death	64 years
	Incidence rate	2005–2009	18 SEER areas	Mortality rate	2005–2009	
	Male	Female	Total	Male	Female	Total
All races	7.7	5.4	6.5	5.2	3.5	4.3
White	8.4	5.9		5.6	3.8	
Black	4.7	3.6		3.1	2.1	
Asian/Pacific islander	4.1	3.1		2.3	1.5	
American Indian/Alaska native	3.9	3.8		2.9	2.0	
Hispanic	5.9	4.7		3.3	2.4	
Stage at diagnosis for 2002–2008	Stage	Distribution	%	5-year relative	Survival	%
Localized (confined to primary site)			75			36.2
Regional (spread to regional lymphnodes)			16			21.8
Distant (cancer has metastasized)			2			37.1
Unknown (unstaged)			7			29.1
Jointpoint trend – APC	Male and female trend	Period	Male trend	Period	Female trend	Period
	1.5	1975–1987	1.2	1975–1989	1.6	1975–1987
	–0.3	1987–2009	–0.4	1989–2009	–0.2	1987–2009

SEER Stat Fact Sheets http://seer.cancer.gov/statfacts/html. Last accessed 22 Apr 2012

Cancer of the esophagus reaches 5th for estimated deaths worldwide due to cancer in males, and 8th for females. In developed countries, esophagus is 8th among cancer deaths for males, but in developing countries both esophagus and oral cavity are in the top ten cancer deaths for males, as 4th and 10th respectively. For women in developing countries, esophagus presents as 7th in the ranking of cancer deaths. Interestingly, brain and nervous system cancer deaths, typically not included in discussions of HNC, reach the top ten for developing countries as 9th for males and 10th for females.

Geographical regions demonstrate considerable variations in rates of cancers within the head and neck region. Particularly notable variations exist for oral cavity, pharyngeal, and oesophagus which may be major contributors to the disparities seen in Table 3.3.

3.3 Common Risk Factors of Head and Neck Cancers

Agencies, particularly governmental agencies, focused on understanding cancer in human populations are interested in compiling information on factors with established associations with cancer. Table 3.5 summarizes exposures associated with cancers of the head and neck as deemed from a global perspective by IARC [21]. Tobacco is the most frequent exposure and is classified as an exposure with sufficient evidence to be declared a carcinogenic agent for eight out of the ten sites listed in this table. Radiation exposures are the carcinogenic agents associated with the two sites where tobacco products are not included (Table 3.6).

3.4 Prevention/Interventions

3.4.1 Tobacco and Alcohol

The role of tobacco and alcohol in cancer of many sites in the head and neck has been established for decades [7]. Nuances of the independent contribution of tobacco and alcohol and their combined impact continue to be studied, with renewed interest in understanding their contributions contrasted to other agents such as HPV. The ARCAGE group considered information from ten European countries for tobacco and tobacco and alcohol attributable risks of upper aerodigestive tract cancers [4]. Together tobacco and alcohol explained 73%, which was constructed from 44% jointly, nearly 29% from smoking alone and under 1% from alcohol alone. The attributable risks varied by sex (less explained for females), cancer site (highest for hypopharyngeal/laryngeal) and geographic location (highest in central Europe). The INHANCE Consortium has tried to get understanding on variance of HNC risk by type of alcohol, such as whether there is variance in risk by beer, liquor or wine [68]. Beer and liquor

Table 3.5 Comparison cancers

	Incidence count			Morality count		
	# Male	#Female	# Total	# Male	#Female	# Total
Lung and bronchus						
Estimate for 2012	116,470	109,690	226,160			160,340
2005–2009 Median age		Diagnosis	70 years		Death	72 years
	Incidence rate	2005–2009	18 SEER areas	Mortality rate	2005–2009	
	Male	Female	Total	Male	Female	Total
All races	76.4	52.7	62.6	65.7	39.6	50.6
White	76.4	55.1		65.3	40.8	
Black	99.9	52.6		82.6	38.0	
Asian/Pacific islander	52.2	28.8		35.9	18.5	
American Indian/Alaska native	51.9	37.4		48.3	33.2	
Hispanic	40.5	25.8		30.8	14.0	
Stage at diagnosis for 2002–2008	Stage	Distribution	%	5-year relative	Survival	%
Localized (confined to primary site)			15			52.2
Regional (spread to regional lymphnodes)			22			25.1
Distant (cancer has metastasized)			56			3.7
Unknown (unstaged)			6			7.9
Jointpoint trend – APC	Male and female trend	Period	Male trend	Period	Female trend	Period
	2.5	1975–1982	1.4	1975–1982	5.6	1975–1982
	1.0	1982–1991	–0.4	1982–1991	3.4	1982–1991
	–0.8	1991–2009	–1.8	1991–2009	0.5	1991–2006
					–1.5	2006–2009
Stomach						
Estimate for 2012	13,020	8,300	21.320			10,540
2005–2009 Median age		diagnosis	70 years		Death	73 years

(continued)

Table 3.5 (continued)

	Incidence count			Morality count		
	# Male	#Female	# Total	# Male	#Female	# Total
	Incidence rate	2005–2009	18 SEER areas	Mortality rate	2005–2009	
	Male	Female	Total	Male	Female	Total
All races	10.5	5.3	7.6	5.0	2.6	3.6
White	9.3	4.4		4.3	2.2	
Black	17.0	8.7		10.3	4.8	
Asian/Pacific Islander	16.4	9.9		9.0	5.3	
American Indian/Alaska native	13.6	7.3		8.3	3.8	
Hispanic	14.4	8.5		7.3	4.3	
Stage at diagnosis for 2002–2008	Stage	Distribution	%	5-year relative	Survival	%
Localized (confined to primary site)			24			62.3
Regional (spread to regional lymphnodes)			31			27.7
Distant (cancer has metastasized)			34			3.7
Unknown (unstaged)			11			17.9
Jointpoint trend – APC incidence	Male and female trend	Period	Male trend	Period	Female trend	Period
	−1.6	1975–2009	–0.2	1975–1980	−1.5	1975–2009
			−1.8	1980–2009		
Colon and rectum						
Estimate for 2012	73,420	70,040	143,460			51,690
2005–2009 Median age		Diagnosis	69 years		Death	74 years
	Incidence rate	2005–2009	18 SEER areas	Mortality rate	2005–2009	
	Male	Female	Total	Male	Female	Total
All Races	54.0	40.2	46.3	20.2	14.1	16.7
White	53.1	39.2		19.5	13.6	
Black	66.9	50.3		29.8	19.8	
Asian/Pacific Islander	44.9	34.2		13.1	9.6	

American Indian/Alaska Native	45.2	38.0		18.8	14.6	
Hispanic	45.2	31.5		15.3	10.2	
Stage at diagnosis for 2002–2008	Stage	Distribution	%	5-year relative	Survival	%
Localized (confined to primary site)			39			89.9
Regional (spread to regional lymphnodes)			36			69.6
Distant (cancer has metastasized)			20			11.9
Unknown (unstaged)			5			33.9
Jointpoint trend – APC	Male and female trend	Period	Male trend	Period	Female trend	Period
	0.8	1975–1985	1.1	1975–1985	0.3	1975–1985
	−1.8	1985–1995	−1.2	1985–1991	−1.9	1985–1995
	1.6	1995–1998	−3.2	1991–1995	1.9	1995–1998
	−2.5	1998–2009	2.1	1995–1998	−2.2	1998–2009
			−2.9	1998–2009		

Table 3.6 Head and neck cancers of humans with IARC classified carcinogen(s)/occupations/biological agents/personal habits of preventable exposures based on Cogliano 2011 [21]

Specifically named cancer site[a]	Carcinogenic agent/occupation associated with sufficient evidence with cancer site	Carcinogenic agent/occupation associated with limited evidence with cancer site
Larynx	Asbestos dusts and fibers	Human papillomavirus type 16
	Strong inorganic acid mists	Human papillomavirus type 18
	Tobacco smoking	Sulfur mustard
		Rubber production industry
		Second hand tobacco smoke
Nasal cavity and paranasal sinus	Isopropyl alcohol production	Formaldehyde
	Leather dust	Chromium (VI) compounds
	Nickel compounds	
	Tobacco smoking	
	Wood dust	
Esophagus	Acetaldehyde associated with consumption of alcoholic beverages	Rubber production industry
	Alcohol	
	Betel quid with tobacco	
	Betel quid without tobacco	
	Smokeless tobacco	
	Tobacco smoking	
	X radiation, gamma radiation	
Pharynx	Alcohol	Asbetos dusts and fibers
	Betel quid with tobacco	Second hand tobacco smoke
	Tobacco smoking	
Nasopharynx	Chinese style salted fish	
	Epstein-Barr virus	
	Tobacco smoking	
	Wood dust	
Paranasal sinus	Radium-226 and its decay products	
	Radium-228 and its decay products	
Salivary gland	X radiation, gamma radiation	
Oral cavity	Alcohol	Human papillomavirus type 18
	Betel quid with tobacco	
	Betel quid without tobacco	
	Human papillomavirus type 16	
	Smokeless tobacco	
	Tobacco smoking	
Oropharynx	Human papillomavirus type 16	
	Tobacco smoking	
Hypopharynx	Tobacco smoking	

[a]Broad categories such as bone and skin are not presented in table and may represent additional preventable exposures associated with head and neck cancers in humans

seem comparable with raised odds that have a considerable dose response, but the association with wine appears weaker and with uncertainty.

Not only are tobacco and alcohol of concern for risk of development of HNC, consideration must also be given for the impact of these exposures, such as on survivorship, if continued after diagnosis. Mayne et al. [53] collected information from patients' diagnosed with early stage oral cavity, pharynx and larynx cancer. Retrospective histories were collected at diagnosis and the patients were prospectively followed. The previous history of alcohol and tobacco were associated with risk of dying and so was continued alcohol drinking but was not seen for continued smoking.

The global health impact of tobacco exposures, such as the current annual killing of around six million people who are either direct tobacco users or who are exposed to second-hand smoke, has lead to the WHO to prioritize tobacco (WHO http://www.who.int/tobacco/en/ last accessed 04/22/12). The WHO [82] report emphasizes MPOWER as a part of the framework for action developed as a component of the global treaty "WHO Framework Convention on Tobacco Control." The six components of MPOWER provide evidence-based tobacco control measures and are communicated as:

M for monitor = monitor tobacco use and prevention policies
P for protect = protect people from tobacco smoke
O for offer = offer help to quit tobacco use
W for warn = warn about dangers of tobacco
E for enforce = enforce bans on tobacco advertising, promotion and sponsorship, and
R for raise = raise taxed on tobacco.

A consensus report from the 2nd European Workshop on Tobacco Use Prevention and Cessation for Oral Health Professionals [70] conveys that a major challenge for oral health professionals' involvement in tobacco use cessation is inappropriate compensation. They recommend modification of treatment and billing codes to provide a structure for appropriate compensation:

State 1, basic care: This consists of the identification and documentation of tobacco use as part of a part of each patient's medical history and is included in the oral examination with no extra compensation
State 2, further basic care: This consists of a brief intervention and provision of information about support. This stage should be coded as a short preventive intervention similar to other advice for oral care
State 3, intermediate care: This stage should also be coded as a brief intervention consisting of an assessment of tobacco dependency, provision of behavioral support and provision of pharmacotherapy, if required
State 4, advanced care: This stage consists of advanced interventions by oral health professional with adequate qualification. A separate treatment code should be created for this state

The European Workshop focus on oral health professionals is warranted. While both medical and dental/oral health care professionals may not provide fully optimal guidance to their patients about tobacco use, dentists considerably lag behind physicians in their efforts for their patients about tobacco risks [5, 71]. A global perspective needs to be maintained as there is considerable variation in rates of tobacco use at the country level [79] as well as that which is seen in sub-Sahara Africa [62]. Both of these reviews accentuate the concerns about developing or low-income nations and the potential untoward impact of tobacco use.

A Cochrane Collaboration Intervention Review [13] concluded "in favour of counseling, compared with usual care or no contact. The major implications of these finding are for smokeless tobacco users in the dental settings, as we found limited evidence for the effectiveness of similar interventions for cigarette smokers." This review has been updated with a review specifically on smokeless tobacco [26] and a general update [60]. Ebbert et al. [26] concluded "Varenicline and behavioural interventions may help smokeless tobacco users to quit. Behavioural interventions incorporating telephone counseling or an oral examination are likely to increase abstinence rates." Needleman and colleagues [60] found that dental professionals remain limited users of in-office counseling for tobacco use cessation. They also found that the evidence from the literature on dental office based tobacco use cessation is still weighted towards studies focusing on smokeless tobacco which supports effectiveness and there is insufficient evidence to support cigarette smoking cessation.

A recent report from the US Office of the Surgeon General raises alarms about the current status of tobacco use in youth and young adults [80]. Smoking is mostly initiated in adolescence with 88% by age 18 and 99% by 26. A decrease in tobacco use among youth and young adults that had been seen starting around 1998 has slowed or leveled in general and the tobacco use rate is actually seen as increasing in some population groups. Additionally tobacco users are increasingly likely to use more than one tobacco product, such that among high school aged White and Hispanic males, who use tobacco products, over half are using more than one product and among high school aged Hispanic females, who use tobacco products, almost half are using more than one product.

3.4.2 HPV

The identification of HPV as a carcinogenic agent for head and neck cancer has not been without controversy. The questioning of the association has largely been about the extent to which HPV is associated with specific sites. HPV 16 has been identified with sufficient evidence for IARC to declare it as an agent for Oral Cavity and Oropharynx (Table above), although there is likely to be continued debate with regards to the specificity for "oral cavity" designation. HPV 18 with HNC is thought

to have limited evidence for the sites of larynx (also having limited evidence for HPV 16) and oral cavity.

An example of the rising concern for the impact of HPV is seen in the US work by Cole and colleagues [22]. The team assessed the 11 year period between 1995 and 2005 using the North American Association of Central Cancer Registries with analyses for 1,273,273 HNC cases by sites as HPV-associated or non-HPV-associated. The sites considered HPV-associated are tonsil including Waldeyer ring (ICD-O-3 codes C09.0–C09.9 and C142), the base of tongue and lingual tonsil (C01.9 and C02.4), and parts of the oropharynx (C10.2–C10.9).

The major findings included higher ASR for HNC incidence for sites in comparison with NH Whites for NH Black total and males, higher ASR for HPV-associated sites for total, males and females, and higher ASR for Non HPV-associated sites for total and males. Comparisons with NH Whites for Hispanics showed lower incidence for Hispanics for all NHC sites, whether HPV-associated or not, for total, males and females. A particularly interesting component was the differences in direction of HPV-associated sites annual percent change (APC) for NHB, which was negative, in contrast for all races, Hispanics, and NHW which were all positive (although Hispanics was not statistically significantly different from zero). For the Non-HPV-associated sites, all groups had statistically significant negative APCs with NHB having the largest drop in incidence [22].

The APC differences continued in contrasting age groups. For HPV-associated HNC among the cases 0–44 years of age, NHW males and NHB males had statistically significant changes but NHW was positive and NHB was negative. For 45–54 years of age the NHW and NHB males significant changes were again as in the 0–44 group, positive and negative respectively. This occurred again for 55–64 years of age, when the NHB females also demonstrated a statistically significant trend that was negative. In the oldest age group, 65+, only NHW males had a statistically significant trend and it was positive [22].

The non-HPV associate sites APC for all age groups, sexes, and race/ethnicities were all negative. Males were statistically significantly negative in all age groups. NHW and NHB females were both statistically significantly negative in age groups 45–54 and 55–64 years of age. In the oldest age group, the declines of NHW and Hispanic females reached statistical significance [22].

A limitation of the work by Cole et al. [22] and that based on the SEER research data is the lack of confirmed HPV status or type. Chaturvedi et al. [17] did HPV16 assays on tissue from the oropharyngeal squamous cell carcinoma (base of tongue, lingual and palatine tonsil, and oropharynx) cases (1984–2004) of the three SEER program registries (Hawaii, Iowa, and Los Angeles) that collect tissue samples. The prevalence of HPV16 increased with time regardless of the mode of HPV testing, such that the investigators concluded that "Population-level incidence of HPV-positive oropharyngeal cancers increased by 225% from 1988 to 2004 and incidence for HPV-negative cancers declined by 50%."

A complementary perspective can be taken from a recent report by the CDC on HPV-associated cancers in the US for 2004–2008 [16]. For anatomical sites of cancers likely to be caused by HPV, the oropharnyx (defined as base of tongue, tonsil

and "other oropharynx") is projected as the second most frequent cancer site overall in the US and highest for males (5,900 attributable cases). The most frequent cancer is that of the cervix at 11,500 cases attributable to HPV.

The addition of HPV vaccines to the options of cancer prevention modalities merits evaluation for impact on incidence reduction of at least selected HNC sites [25]. Such work should include gender contrasts as well as consider global variation [30, 77].

An aspect to be considered in deliberation of the role of HPV in HNC is that of sexual behaviors. Heck and colleagues [33] assessed data from the INHANCE and found that sexual behaviors were associated with cancers associated with HPV – specifically oropharynx, tonsil and base of tongue.

3.4.3 Nutrition Overview

Diet and nutrition impact HNC patients from a multitude of directions. Prevention and treatment of HNC influence and are influenced by diet and nutrition. Reviews recently published include aspects for prevention [52, 78], risk such as alcohol [8, 21, 39, 52, 78] and malnutrition [78], and during and after therapy [27, 78]. Diet and nutrition is integrated into socioeconomic status assessments of cancer risk [39, 66] and quality of life [67].

The INHANCE consortium recently did an assessment of diets containing a high fruits and vegetables and low red meat intake [18]. This large case-control study (14,520 cases and 22,737 controls) worked with a case definition of oral, pharyngeal, oral cavity or pharynx not otherwise specified, and laryngeal cancers to bring together data from 22 studies in the consortium. Study locations included the US, Western Europe, Germany and Japan. Having a good dietary score (high fruit/vegetable and low red meat) was found to be associated with the risk of cancer in a protective direction. INHANCE also took a look at diet and nutrition in respect to Body Mass Index (body size) and risk of HNC [29]. Their conclusion leads to a recommendation for more research on the associations of BMI and smoking and alcohol use. This study was consistent with other studies of an inverse association between BMI and HNC risk: in that lower BMI is associated with increased risk.

The topic of diet and nutrition is covered in further detail in Chap. 14 [74].

3.5 The Cost of Head and Neck Cancer

Head and Neck Cancers cause significant morbidity and mortality. Previously we described survival statistics for head and neck cancers. In summary, survival over 5-years after diagnosis ranges depending on a number of factors from a high 80+% to a low 25%. Patients with TNM Stage IV disease show the lowest survival, whereas those diagnosed with TNM Stage I have the best chances of surviving this disease.

Equally important with the mortality burden is the effect of HNC on the patients' function and general well-being. Head and neck cancer and the treatments associated with its management have been shown to affect many of our normal every day activities including the ability to swallow and eat, to smell, to speak, to laugh, and to socialize. If patients are treated with surgery, and depending on the extent of the surgical resection that is required, they may be loose parts of their face, they may develop post-operative neck-shoulder dysfunction or trismus, and are often left with a disfiguring appearance that may affect not only their own quality of life and function but also how they are perceived socially. Applying the SF-12 and the UW-QOL scales, Khafif et al. [40] showed that "Appearance", Leisure", "Chewing", "Activity" and Speech were affected by surgical intervention, and these effects tended to be more exaggerated in older patients. However, surgical intervention had a beneficial effect on bodily pain and on the "Sense of Burden", the overall quality of life was preserved [40]. Treatment plans that require chemotherapy and or radiation have many short term side effects such as inability to eat solid foods due to mucositis, skin rashes and burning, osteoradionecrosis, and problems with mucus secretions. Long term residual adverse effects exist such as permanent xerostomia, and all the accompanying maladies, including rampant dental caries.

Researchers at MD Anderson Cancer Center created an inventory of symptoms and assessed the severity of the symptoms and how they interfere with life. According to the authors the most prevalent severe symptoms were problems with mucus, mouth and throat sores, taste problems, dysphagia, xerostomia, pain and fatigue [72]. Other instruments have attempted to assess the effects of HNC cancer treatment on patients' mental health and emotional strengths, and the corresponding survival. Yet others have utilized disability-adjusted life years lost (DALYL, a composite measure that takes into account years of life lost due to premature mortality plus years of healthy life lost due to disability) to document sharp drops of DALYL that are often higher than the burden attributed to kidney cancers or urinary cancers [50]. In the United States, using data from 1997 to 2001 the Centers of Disease Control estimated 131,479 years of potential life lost due to head and neck cancer [15]. Instruments that compare the many dimensions in the burden of illness of patients with head and neck cancer are of paramount importance in the longitudinal evaluation and comparison of various therapeutic protocols.

In addition to their personal, physical, mental, emotional, and social burdens, head and neck cancer is also very costly to manage. HNC patients utilize significant healthcare resources to manage cancer, often for years after initial treatment. A 2004 SEER Medicaid Analysis showed that HNC patients have higher rate of hospitalizations than other patients (82% vs. 55%), higher number of inpatient days (24 days versus 12 for the comparison cohort), require skilled nursing care at a higher rate (22% vs. 13%) as well as having significantly higher rate of home healthcare use (48% vs. 26%) [43]. Medical expenditures seem to be affected by age, race, socioeconomic status, and more importantly stage at diagnosis. Stage at diagnosis is important because it often dictates treatment modality and velocity of care. For example, Zavras et al. showed that costs are directly linked to the stage at diagnosis; patients diagnosed early had lower mortality risks, higher chances of

Table 3.7 Comparison of costs of treatment groups for oropharyngeal squamous cell carcinoma

Treatment Group		Mean cost	Range	Cost ratio
Surgery alone	Private payer	$37,435	$22,486–$48,746	1
	Government payer	$15,664	$13,325–$16,885	1
S + RT	Private payer	$74,484	$72,400–$84,825	1.98
	Government payer	$34,343	$31,565–$40,810	2.19
S + CRT	Private payer	$191,780	$145,450–$217,220	5.12
	Government payer	$53,245	$49,400–$58,325	3.39
CRT	Private payer	$198,285	$168,216–$298,945	5.29
	Government payer	$57,429	$52,900–$59,545	3.66

Moore 2012 [55] Accessed online at http://oto.sagepub.com/content/early/2012/02/14/0194599812437534. Reprinted with permission from SAGE (license 2878270350723)
Abbreviations: *CRT* chemoradiation therapy, *RT* radiation therapy, *S* surgery

single modality treatment (surgery) and lower medical costs whereas advanced stages were associated with significantly higher medical expenditures due to multi-modality treatments [84].

There have been few published studies of the costs of head and neck cancer in the United States. Among the published body, studies seem heterogeneous in their reporting of cost categories as well as among the follow up period covered.

Most recently, Moore et al. [55] presented reimbursement data from two major teaching hospitals including revenues associated with inpatient and outpatient care plus pharmacy charges. Printed with permission of the publisher SAGE, the results are shown in Table 3.7.

In the 3 months of the study (Moore 2012), average hospital reimbursement from government ranged from a low $15,664 for patients in need of surgery alone to $57,429 for those treated with chemoradiation. Reimbursement from private payers was significantly higher, with average reimbursement ranging from $37,437 for "surgery alone" to 198,285 for chemoradiation. Expanding beyond the first 3 months of treatment, and assuming a 30% total increase for medical expenditures over 5 years, we have calculated private payer costs to range from $48,665 for each patient that will be treated with surgery alone; $98,829 for patients that will be treated with surgery plus radiation; $249,314 for patients that will be treated with surgery plus chemoradiation combination; to a high $257,770 for those that will receive chemoradiation alone.

Government expenditures are also affected in the long term. Parthan et al. [63] analyzed linked SEER-Medicare data for those with metastatic cancer and found that mean total costs during follow up were $154,166 per patient, a three-fold rise over the short term expenditures. Outpatient care accounted for 49% ($77,619) of total costs; hospital costs accounted for 35% ($53,204, a figure that compares very well with the work of [55]); physician care accounted for 7% ($10,106); and the rest 7% accounted for nursing care, home health and hospice care. The group that used chemotherapy had average costs that exceeded $215,000, with the greatest cost item being outpatient care ($121,904), followed by hospital care at $62,345 [63].

As mentioned earlier, the dramatic rise in medical expenditures over the long term is correlated with the disease itself through the treatment modalities chosen. Not only are chemotherapy costs higher than surgical costs, but they are associated with a significantly higher incidence of complications that themselves require medical management and frequent hospitalizations. Treatment-related complications among patients with advanced squamous cell carcinoma of the head and neck were found to occur in 86% of patients receiving chemoradiotherapy as compared with a 51% among those treated just with radiation therapy. The economic costs of managing the complications of chemoradiotherapy were $15,825 over 6 months. The economic costs of managing complications of radiation therapy were $6,223 over the same time period [44].

Readers should pay particular attention to the time horizon of the published economic studies of HNC. The published literature on medical expenditures is not standardized and different studies report costs associated with different time horizons, ranging from a 3-months from time of diagnosis to 5 years. Studies that report medical expenditures around the first episode of care are valuable and help realize the majority of the costs, but head and neck cancer patients are in need of multiple interventions long after the first episode of care. Looking at an incident cohort of squamous cell carcinoma patients that required resections in the UK, Kim et al. [41] demonstrated a 26% rise in medical expenditures from Year 1 to Year 5, with average costs rising from BP 19,778 in Year 1 to BP 23,212 in Year 5. As this cohort was comprised of patients that had surgical resections, one may extrapolate significantly higher increases for groups of patients that advanced stage disease is over-represented (requiring multi-modality therapies) [41].

In economic terms, overall costs include a compilation of direct medical expenditures, costs linked to managing a disability over time, costs linked to absenteeism from work and indirect costs associated with productivity losses (decrease in production and income) [54]. There are very few published reports of the effect of HNC on the costs of productivity loss, which back in 2005 was estimated at $2.8 billion annually [15].

3.6 Health Care Professional Practices Regarding Head and Neck Cancer

The locations of HNC have lead to numerous challenges, including that the anatomical sites involved may be considered the prevue of a number of different health care providers, such as the perception of that mouth belongs to the dentist. The differences between dental and medical health care systems may further complicate matters. Many to most dentists are not part of structured health care systems, particularly not in systems that contain hospitals. The study of a range of contributing factors has been conducted, but there is largely a void in documentation of specific health care providers across the continuum of prevention, diagnosis and treatment for HNC. Below is review of evidence concerning health care practitioners' knowledge and education (further discussed in LeHew [46]), their role on patients' delay

to treatment (further discussed in LeHew [46]) and their role in patient referral [FURTHER described in other chapters?]. Application to the broad category of HNC is limited as much of the work is specifically focused on lip, oral or pharyngeal cancers.

3.6.1 Knowledge/Education, Attitudes, and Practices of Healthcare Providers Involved in Prevention and Detection of HNC

Chapter 5, reviews challenges circa community-based programs designed for prevention of HNC [46]. The intent in this section of the epidemiology and HSR chapter is to review the understanding of attributes of health care professionals who have roles in altering the incidence and morality rates of HNC.

Considerable focus has been placed on knowledge and practices of oral health care providers in the USA, particularly dentists [1, 23, 47, 48, 59, 65, 76]. As an example, Morse and colleagues [59] have made particular study in Puerto Rico of these topics and demonstrate that practitioners are deficit in biopsying [58] and detecting potential cancerous lesions [57] such that intervention for oral cancer occurs after development of invasive cancers. This team has subsequently studied practitioners to seek their insight for these shortcomings [59]. The issues identified include deficiency in knowledge about oral cancer and pre-cancer, limited application of oral cancer screening to patients, oral cancer screenings are frequently limited to visual inspections instead of visual and tactile inspections, referrals are delayed by health insurance and other issues, and diagnosis are hindered by bureaucracy and financial disincentives. These findings are consistent with reports from across the US [1, 23, 36, 47, 48, 65, 71, 76, 83] and other countries [34]. A recent review from the United Kingdom captured similar experiences and concluded that there is "a lack of rigour among some general dental practitioners when screening for potentially malignant disorders" and that "patients continue to present to their general medical practitioner when they are concerned about something in their mouth that is not related to their teeth" [12]. The introduction of HPV as a risk factor for oral cancer has created new challenges for health care providers regarding their knowledge and their application to new patient attributes [24].

Some studies have contrasted dentists and primary care physicians with regards to knowledge, attitudes and practices regarding HNC, as mentioned above in the Brockelhurst review [12]. Again this focus has largely been directed at oral cancer. Findings are consistent that dentists perform more oral cancer examinations than physicians [5, 71]; physicians conduct more tobacco counseling [5, 71], and both groups of health care providers are weak on knowledge regarding oral cancer signs, symptoms, locations, and examinations [5, 37, 61].

Assessments of biopsy services find high rates of misdiagnosis of oral lesions. This status is of such great concern that it is recommended that any excised lesion should be submitted for histological diagnosis [42].

3.6.2 Issues of Delay, Referral and Survival

Numerous factors are involved with HNC delays, referrals and survivals. Many of these factors are associated with the anatomical site of the cancer. Concerns also have been raised about differences in these factors regarding etiological agents which may be reflected in the age of the cancer patient.

Delays in obtaining diagnosis and treatment are alarming as there is likelihood of disease progression and untoward outcomes from delay regardless of the reason, whether the delay is driven by practitioner, patient, or health care system. Reviews on delay in oral cancer help provide insight into the challenges and consequences for all HNC – even with the qualification that oral cancers might be anticipated as more accessible for diagnosis. Gomez et al. [31] set out of answer a series of questions falling under two main questions: "Is early diagnosis of oral cancer a feasible objective?" and "Who is to blame for diagnostic delay?" A different take on a question is asked by van der Waal and colleagues [81]: "Early diagnosis in primary oral cancer: is it possible?" Both place major emphasis on the preparation and readiness to respond by the health care provider.

The practices of referral for HNC patients by primary care health care providers are paramount in appropriate management for those patients. Studies have shown that health care practitioners are in need for optimizing these practices both on behalf of early intervention for patients with HNC and for avoidance of overtaxing systems with over-referrals. A series of papers by Brocklehurst and colleagues emphasize the issues [9–11]. A part of the concern has been addressed by Patel et al. [64] in looking at the quality of referral letters and providing an example to emphasize the need for good communication on the available data and the urgency of the referral.

Matched analysis have shown no differences in survival based on patients age when stratified for young versus old at 40 years of age [69] or rates of recurrence-free, disease-specific, or overall survival contrasting African American or Hispanic Americans compared with non-Hispanic white SCCHN patients [19]. However, site specific analyses have found survival differences by age. For example, oral cavity survival differences by stratification at age 45 were seen in Taiwan [35] and for the same research team for oral tongue [49] both seeing better results for the younger patients. Yet an assessment of oral tongue for pediatric (15–20 years old) versus "adult" patients by Morris et al. [56] in New York found equivalent outcomes and the conclusion of similar treatment for pediatric and adult patients for SCC of the oral tongue.

3.7 Conclusions

Variations in the definitions of head and neck cancer contribute to differences in surveillance data and interpretation. Nonetheless, many of the specific sites and the collected sums of head and neck cancers have great impact on the burden of disease and health care systems in the USA and globally. Traditional risk factors of tobacco,

alcohol and diet/nutrition are still contributing much to the HNC counts and rates. However, HPV is adding considerable concern, especially for cancers in the oropharyngeal region for both men and women. In any event, the burden of head and neck cancers merits more understanding of prevention and early detection as to minimize loss of quality of life through costly and invasive treatments and to improve survivorship.

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Chapter 4
Challenges in Community-Based Head and Neck Cancer Prevention Programs

Charles W. LeHew

Contents

Abstract The most promising opportunities for improving both prevention and early detection of cancers of the oral cavity and oropharynx lie in community-based programs to promote routine risk assessment and counseling and regular oral examinations in at-risk populations. The communities in which interventions are needed include both the at-risk populations themselves and also the clinicians who deliver health care to them. The former are generally not well informed about either risks or early detection, and the latter are neither adequately trained nor sufficiently attentive to the need for early detection in their patients. This chapter describes community-based intervention programming in practical terms. It identifies barriers to prevention and early detection, and describes community-based intervention strategies that are designed to overcome those barriers. Many of the challenges are not unique to oral cancers. These include general problems of adherence to practice recommendations

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for prevention and early detection of various diseases. Such problems are associated with lack of awareness, lack of access to adequate care, and conflicting priorities. Some other challenges are somewhat unique to oral cancers: relatively low concern for oral health as opposed to systemic health, limited access to oral health services, multiple signs and symptoms associated with oral cancers (many of which mimic other ailments such as infections), and associations between oral cancer incidence and patient risk profiles that compound access issues and lead to numerous other health care problems or co-morbidities which may either take precedence or simply mask the presence of oral cancers.

Keywords Head and neck neoplasms • Mouth neoplasms • Early detection of cancer • Prevention and control

Abbreviations

HPV	human papillomavirus
US	United States
PLANET	plan, link, network with evidence-based tools
LED	light emitting diode

4.1 Introduction

Cancer control encompasses a broad range of processes directed toward improving cancer prevention, early detection (sometimes called secondary prevention), treatment, rehabilitation, palliation, and survivorship. All these outcomes require attention and effort, and improvements in any of them will be reflected in a reduced cancer burden in a population. Importantly, cancer control applies to the well and the sick, those who are at high risk and those who are not, survivors who are deemed cancer free and those who are experiencing end stages of terminal disease [1]. Cancer control applies to the whole population—any population—though specific control efforts will always be targeted to some specific population, as will be seen below.

This chapter focuses on primary and secondary prevention of head and neck cancers, with special emphasis on squamous cell carcinomas that develop in the oral cavity and oropharynx. A broader treatment is possible, but there are very good reasons for focusing on these cancers. First, they are the most common of all head and neck cancers. Second, the oral cavity and oropharynx are readily accessible for visual and tactile examination by trained clinicians without need of special equipment or facilities other than good light and appropriate hygienic measures. Third, these cancers frequently present early lesions that are either pre-cancerous or localized and highly treatable with minimal morbidity and mortality whereas late-stage disease is associated with poor prognoses. Fourth, these early lesions, when they appear, identify the patient as being

at high risk for disease progression or recurrence and therefore constitute the sorting of higher and lower risk populations that is fundamental to effective cancer screening programs. Finally, and most importantly, despite these features that suggest vigorous cancer control programming for primary and secondary prevention, oral cancers remain largely ignored by the public, clinicians, policy makers, and cancer research funders. Oral cancers do not get the attention they deserve and therefore interventions are needed to redress these failings. Community-based interventions are particularly appropriate to promote awareness and mobilize communities to action [2].

4.2 Community Collaborative Interventions in Cancer Control

Most oral cancers are attributable to environmental exposures including particularly tobacco, alcohol, poor diet, human papillomavirus (HPV), and, particularly in Southeast Asia, products derived from areca nut [3]. Other exposures have also been implicated or are suspected [3]. These exposures are not inevitable or unavoidable. Rather, their frequency and commonality are largely dependent upon personal choices that are subject to social influences.

Similarly, early detection depends in large part upon choices made by at-risk populations and the health care providers who deliver clinical services in those populations. These choices can also be conditioned by normative expectations.

Because of the normative implications for both exposures and clinical services, community-based interventions can be effective in both reducing risk and promoting early detection through clinical examinations. Communities set expectations and sanction behavior [4]. Communities can thereby contribute to reducing cancer exposures and to promoting both preventive measures and competent examinations.

What do we mean by "community?" Community is a broad and flexible concept. Community can be many things. At minimum, community implies multiple participants and some capacity for collective action based on perceived common interests. Communities can be as narrow as a group of neighbors or as broad as the world's population. They can be circumscribed by geographical space or social space. Communities of interest in cancer control constitute identifiable populations with shared interest in the specific cancer burdens of a population or populations. They include, but are not limited to governmental jurisdictions at all levels, health care institutions, professional associations, educational institutions, social service organizations—simply any collective group of persons or organizations with a common interest in reducing the cancer burden experienced by them and the populations of which they are a part.

4.2.1 Community/Academic Collaboration

Communities can gain several advantages by engaging with academic partners in their cancer control efforts. Academic researchers can contribute expertise in designing,

implementing, and evaluating interventions. Academic researchers can help identify effective, proven interventions and to adapt them to specific contexts. Academic researchers can suggest theories of individual, group, and formal organizational behavior which community collaborators can adapt to their local context and at-risk populations. In addition, academic researchers often also contribute by generating research grant funding to enable interventions.

Communities in their turn make important contributions that academic researchers need for intervention studies and advancement of social theories. These include access to populations at risk, understanding of the community, including its normative structures and associated risk behaviors, awareness of community assets and capacities, and credibility with community members.

It is important to recognize that the experiences of community/academic partnerships have not always been perceived as sufficiently beneficial to the communities. Asymmetrical power relationships between academic institutions and community partners are rife with potential problems [5]. Moreover, research funding is always temporally limited and interventions may prove unsustainable without the temporary, external funding academic researchers bring to the table [6, 7].

Nevertheless, well managed community/academic partnerships can contribute lasting resources to communities. These contributions may include community empowerment through knowledge and skills acquired from the partnerships. Such partnerships work best when both sides are sensitive to unequal power distribution and strive to be clear and sensitive about mutual expectations and the constraints under which all parties operate [5].

4.2.2 Sectors of Community and Channels of Influence

Within any community, relationships among its members are not symmetrical. The units that make up a community are not homogeneous. Although, by definition, all the units within the community are connected to each other, they are not equally connected. Some people and groups of people will have more connections than others. Some will be more influential than others. It is beyond the scope of this chapter to deal with these asymmetries completely, but it is useful to consider that these asymmetries can be used to advantage in cancer control activities.

Consider, for example, that communities may be divided into sectors which relate to fundamental functions of the social system such as religion, education, and commerce [4]. Such sectors of a social system can have powerful influence over community norms, sanctioning some behaviors and discouraging others. Successful interventions will open channels into these sectors and leverage their influence to promote healthy behaviors and risk avoidance.

Channels for penetration of systems by outsiders are provided by influential members of the targeted system who also have membership in other systems such as academia. In organizational theory these individuals may be called boundary spanners [8]. In informal systems they may be called cosmopolites [9]. In any

case, because these people are part of both groups, they can serve as conduits for transmitting influence from one system to another.

System norms are set within sectors as a result of collective actions. Modify system norms and behavior change follows. Because of these powerful mechanisms that sanction community norms, community-based interventions proceed through open channels to communicate normative messages within sectors [4].

4.3 Intervention Design

To design community-based interventions, then, it is necessary to identify the target population, the behaviors within the population that are to be modified, the normative regime that sanctions those norms, sectors in which those at risk in the population are embedded or at least most closely a part, and channels into those sectors. Because community members are those who best understand how their communities function, their assistance in designing interventions is invaluable. Community members can be recruited for this purpose by working with cosmopolites who are connected to both the community and the intervening agents.

Theories of individual behaviors should also be employed to guide design. Several theories of help-seeking and of behavior change can be used to guide thinking about how and why individuals make and act on choices. Similarly, theories can help identify the circumstances under which health care providers may adopt practices consistent with intervention goals.

Surveillance data also can be used to define high risk populations. In the U.S., African American men, followed by white men, are at greatest risk. For the period 2004–2008 the median age at diagnosis was 62 years [10] suggesting that older populations might be targeted. However, trends clearly show that younger people, whites, and women are at increasing relative risk which suggests that careful monitoring of surveillance data is necessary to ensure that programming continues to be appropriately targeted over time (see A. Zavras, Chap. 3, this volume).

Interventions should be theory-driven and, where possible, they should utilize proven strategies. Theoretically driven interventions enable purposeful selection of variables to be manipulated to obtain expected results. Theoretical constructs facilitate measurement of inputs and results for evaluative assessment. Obtained results can then be fed back and used to assess and improve the theories themselves, furthering both science and intervention capacity [11].

Theory based and previously proven interventions may not be directly designed for oral cancer interventions. However, proven, theory-driven methods for improving public health knowledge, motivating behavior change, and improving provider capacity to deliver services are readily available. An excellent resource is the Cancer Control P.L.A.N.E.T web site: http://cancercontrolplanet.cancer.gov. (Accessed 05/21/2012.) Intervention strategies can be obtained and modified by collaborating partners to ensure their feasibility and practicality in specific contexts. A challenge in implementing established intervention designs, which are often quite complex and

elaborate, is ensuring that essential, core elements are retained when interventions are modified for specific contexts [12].

4.4 Challenges in At-Risk Populations

As indicated above, several different population groups may be reasonable targets for oral cancer control programming. Generally, populations at greatest risk should be targeted because they offer the greatest opportunities for reducing the oral cancer burden if effective interventions can be directed toward them. Several risk factors for oral cancers are well established, and others are suspected but as yet not well demonstrated. The behaviors associated with many of these risk factors can be targeted and variability in these behaviors across different populations may suggest different strategies that are contextually appropriate.

Cancer control activities directed at risk reduction and early detection in high-risk populations can use assessments of risk exposure to identify target populations. Importantly, oral-cancer risk behaviors are often most common in rural and poor communities whose populations may also lack access to health care and have limited health literacy. Lack of access to health care may in fact be viewed as an additional risk factor for late-stage diagnosis as well as an impediment to effective interventions through clinical outreach. Lack of health literacy presents particular challenges for efforts to educate populations at risk which may find it difficult to understand and act on cancer control messages. Thus, the populations with the greatest need are frequently also the populations most difficult to reach with effective programming.

Nevertheless, even in the most resource-poor environments there are still resources that can be tapped for cancer control. There is always social capital, however limited, and that can be a powerful tool for addressing cancer control challenges. The key is to find the boundary spanners and cosmopolites that can provide channels into those resource-poor communities, and work through them to identify resources that can be brought to bear [13, 14].

Reaching the population is insufficient in itself. They must be reached with effective interventions. Additional challenges come from value structures that may differ greatly from those of the interveners. This can be overcome somewhat by means of influential others, but serious challenges remain. Greatest among these may simply be that the healthy behaviors that are to be promoted may not be valued by the target population. Health itself is not inherently or universally valued; and it is often not valued more than the risk behaviors, particularly ones associated with pleasure such as tobacco, alcohol, drug use, and sexual activity. A great deal of persuasion may be required to achieve risk reduction.

Again, the key is to gain allies from within the community. The best community partners are those who are regarded within the community as influential and those who are most ready or willing to adopt changes. Working through influential change agents and effecting change in those most willing to adapt are basic strategies for changing the normative environment in favor of healthier behaviors [9].

Several alternative theories of health behavior and behavior change can be used to guide strategies [15]. Helping community partners think theoretically about their populations is an important contribution that academic researchers can bring to the table. It is beyond the scope of this chapter to detail these alternative theories, and all may be useful in their own way. Community partners can help identify which theoretical orientations may be more likely to work well in their community.

Several factors associated with developing oral cancers appear also to pose barriers to early detection. The literature suggests that tobacco use [16, 17], alcohol use [17–19], age [20–22], and male gender [18, 23] may be associated to some degree with delayed or late diagnoses. However, these associations are not straightforward and the literature has produced many null findings as well. It appears that the relationships between risk and stage or delay may be highly complex interactions implicating access, quality of care, co-morbidities, and other complicating factors.

These associations do, however, suggest strategies for improving early detection by focusing not only on high risk groups, but by working through programs and organizations that already target the priority populations and the risk behaviors. Tobacco control programs have proven to be strong natural allies of oral-cancer prevention programs because there is so much overlap in their missions. Investments in tobacco programming can be leveraged to promote early detection as well. Similarly, alcohol treatment programs, drug abuse programs, programs for the elderly, for youth, for men, and for persons with sexually transmitted diseases have all proven to be highly adaptable to promotion of oral cancer awareness and early detection strategies. These programs offer direct channels to some of the highest risk populations and established linkages in the at-risk community are well used to channel cancer control messages.

4.5 Challenges in Healthcare Provider Communities

In addition to at-risk populations, the health care providers who serve those populations also should be targeted with interventions to promote prevention and early detection in their patients. It is well established that the clinician community does not do an adequate job of either assessing and counseling about risk or detecting early stage disease [24–29]. In addition, failure to diagnose the extant of disease remains a serious problem [27, 30].

An initial problem to be addressed is simply which clinicians are to be held responsible for prevention and early detection. Although some may argue about whether medical or dental professionals have greater responsibility, it can also be argued that all clinicians should play an appropriate role. It is true that dentists, for example, are far more familiar with the oral cavity than medical physicians; and therefore some argue that they have greater responsibility for early detection of oral cancers [31]. This debate is at best misguided. First, it has to be recognized that access to dental care is not universal. Indeed, there is also evidence that some of the highest risk populations are particularly unlikely to have regular oral health care [32–35]. If medical providers

take no responsibility for early detection, then much of the at-risk population will have little or no access to that care. This is not to suggest that dentists and dental hygienists (or even dental assistants) should not look for signs and symptoms during routine oral examinations and provide risk counseling. They should. However, medical providers can also learn to examine the oral cavity for signs of cancer. They should as well, but they are not typically trained in these techniques and so interventions are needed to train them and encourage examinations [36].

Notably, the questionable distinction between oral diseases and responsibility for them can be much broader. Oral abnormalities frequently occur as a consequence of systemic disease, and oral abnormalities can become systemic problems. There is a general need for all clinicians, medical and dental, to take broader responsibility for human health, and that can be advanced by programming directed at improving oral cancer prevention and early detection.

Even if one were to take the position that the oral cavity is primarily dentists' responsibility, research clearly shows that dentists are not as well prepared to perform these examinations as they should be. Study after study concludes that dentists are not well acquainted with oral cancer risk factors, signs and symptoms, and examination methods. Nor do they perform examinations regularly or appropriately [24–29].

Similarly, all health care providers, oral or medical, can take much more responsibility for risk reduction in their patients. There are great challenges to get providers to do more to counsel their patients about tobacco. They simply do not do it regularly [24–29]. Even greater reluctance pertains to alcohol use, drug use, and sexual practices [37–40]. There is much need for interventions that promote risk counseling.

Another challenge to promoting oral cancer early detection is that there is no generally accepted set of examination techniques. Different sources recommend different procedures. Additionally, there are no clinical practice guidelines that recommend regular screening. This is another impediment to promoting early detection. The research basis on which to establish such recommendations does not exist. There simply are not enough large, high quality, randomized trials showing reductions in mortality to persuade standard setters to set those standards [41–43]. Much more work needs to be done, to establish the value of early detection examinations. Improvement in diagnostic techniques themselves is also needed [44], as are standard protocols that can be promulgated.

Nevertheless, it is well established that late stage disease results in higher morbidity and mortality than early stage disease. The evidence is sufficient to warrant opportunistic screening, even if population-based screening programs cannot be justified at this time.

Training cannot be a one-time event either. Research suggests that the longer the time since a clinician's most recent training, the less the clinician knows and the less vigilant the clinician is [29]. Moreover, new innovations, such as diagnostic adjuncts, emerge from time to time and clinicians should be well instructed in how to use them and for what.

Finally, surveillance systems observe trends in incidence and death rates and in risk distributions in different populations. Clinicians need to be abreast of these changes in order properly to identify, counsel, and examine high-risk

patients. For these reasons, training programs should be delivered to provider populations regularly to ensure that they are kept knowledgeable and vigilant.

Recent trends in HPV-positive oral cancers in the West and changing risk profiles in emerging economies are examples of changes of which clinicians need to be aware. HPV-positive tumors appear to be on the rise in western countries [45–50] with comparatively higher incidence rates of oropharyngeal and base of tongue cancers in Whites versus Blacks [51] and in younger people versus older people [49]. There is also evidence that oral-cancer survival rates have been changing in association with the spread of HPV and HPV-positive cancers [52–54]. These changes have important implications for prevention, early detection, and treatment. Similarly, the emerging economies in the East and the associated increase in the size of the middle class in these countries may be associated with changes in national risk profiles. Surveillance systems do reflect at least some of these trends (see A. Zavras, Chap. 3, this volume), though good cancer surveillance is not as wide spread as it should be.

The distribution of providers in populations also has important implications for early detection. Access to care is highly limited geographically in much of the U.S. and elsewhere. Where high risk populations don't have regular access to routine health care, the need for alternative providers to be trained and then made accessible through screening programs is heightened. Communities can find ways to recruit providers to perform screening in these populations thereby reducing unequal access, at least to these important services.

4.6 Practical Matters

So, what does a comprehensive, community-based oral cancer control program look like? What are the essential elements?

First of all, partners are required. Partners can be any individual, group or formal organization that can provide useful resources, and all participants in a partnership can benefit from collaboration [55, 56]. A partnership can be formed by any number of partners. Typically, one or two key partners may initiate a partnership and then recruit additional partners with their specific resource bases as needs and opportunities are identified. Partnerships may grow rapidly for several months as new partners are recruited, though they tend to become more stable as needs are met and the partners develop routines among themselves with continuing, mutual expectations.

Often one organization will serve as a lead agency. The lead agency may perform fiscal management for the larger partnership. Well established community organizations are most appropriate for these leadership and ministerial roles. An individual or committee may then act as organizers and change agents, reaching out to potential partners, explaining what the partnership is trying to do, how it functions, and what it has to offer in exchange for contributions from the prospective partner(s).

The most important resource community-based partners provide is access to at-risk populations which includes not only linkages to the populations, but also

understanding of and credibility with those populations. In addition, clinical practices are badly needed both for their expertise and for their capacity to deliver services. The best scenario is to link community credibility and access to expertise in care delivery so that populations can be reached with effective messages and the services they need can be provided.

Public awareness of oral cancer is limited. Many people simply do not know that it is possible to have cancer in the mouth. An essential starting point, then, is to build awareness in the community. The public needs to be educated so they:

- are aware that oral cancer exists;
- know how and why it develops;
- know whether their behaviors put them at greater risk;
- know how to reduce their risk;
- know how to perform self-examinations;
- know how to obtain a professional examination;
- demand examinations from their health care providers;
- know what to do if a lesion is detected.

Although population-based screening programs are not recommended, screening programs can have several benefits beyond the narrow requirements for attaining endorsement as practice guidelines. Screening programs may be the only access many people have to head and neck examinations by well trained providers. They are often welcome additions to health fairs and community events. As such, they have the further benefit of facilitating public health education and oral cancer awareness programs. Screening events in public settings require limited resources, but some things are essential. These include:

- a venue where at-risk populations can be reached;
- a chair in which the patient can sit during the exam;
- good, white light (headlamps are especially desirable, but a hand-held LED light can serve well);
- gauze, gloves, and hand sanitizer;
- a trained clinician;
- intake staff;
- and referral forms, which are absolutely necessary.

Other things that are nice to have, though perhaps unnecessary, include:

- promotional materials;
- educational materials;
- privacy screens;
- seating in a waiting area;
- counseling services for risk reduction and to facilitate follow-up care.

A good resource for anyone planning an event is the National Institute for Dental and Craniofacial Research. Many materials can be obtained free by visiting their website: https://www.nidcr.nih.gov/OrderPublications/#6. (Accessed 05/18/2012).

The capacity of the health care system to detect and manage oral cancers also needs improvement. Health care providers are not well trained in detecting and managing oral lesions that might be cancers or pre-cancers; and their use of marketed diagnostic adjuncts may well be misguided. In addition, they are not compensated under most insurance programs for performing the examinations and, so, may lack motivation. Finally, providers' performance of risk counseling remains inadequate and needs improvement.

Providers need training in several areas including:

- the epidemiology of head and neck cancers (which is not static over time);
- proper performance of head and neck examinations;
- proper referral and follow-up when lesions are detected;
- risk assessment and patient counseling;
- proper use of diagnostic adjuncts.

4.7 Summary and Conclusion

The recommended strategy is to identify at-risk populations, assess risk profiles, and select or develop interventions to promote risk reduction and early detection. Social marketing to inform and motivate the public, and provider training programs to improve system capacity for prevention and early detection, are two good approaches.

These things are best accomplished through collaborations between community partners and academic researchers. Each can bring much needed expertise and other resources to the table. These partnerships can be initiated with a small number of community partners and then be developed to broaden the interventions' reach into the community over time.

Collaboration will give interventions credibility with the targeted populations, and will also make them better able to predict how the community will respond to alternative approaches. The partnerships should develop, implement and then assess interventions collaboratively, drawing on community partners' expertise to interpret the data and adjust the interventions as needed.

It is best to work through existing programs that already address the needs of the targeted populations. Much of the infrastructure for well-tailored and well-targeted interventions may already be in place even in the smallest, poorest communities. Any organization or group that has access to and an understanding of the community and targeted populations can be a valuable ally.

If the program will include public screening events, they will thereby gain additional ability to reach at-risk populations and to reinforce the health education messages by making the examinations available. However, if lesions are detected, then patients will need additional support. At the very least, lists of oral surgeons or otolaryngologists need to be made available. Direct referrals to pre-determined diagnosticians are better. In addition, because many patients may lack insurance, referrals to providers with sliding scales or even capacity to offer no-cost examinations are appropriate.

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Chapter 5
Head and Neck Anatomy

Maaly Bassiony

Contents

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Abstract This chapter presents a summarized, quick review of the anatomical structures associated with head and neck cancer. Basic knowledge of anatomy is an essential key for diagnosis, treatment and prognosis of this disease. This chapter will not cover all the anatomical details. Instead it will discuss the head and neck anatomy from the regional point of view focusing on the regions of head and neck where cancer develops. The gross anatomy of these regions will be described with some additional microscopic pictures of some structures.

Keywords Anterior: front • Posterior: back • Cranial or Superior: headward • Caudal or Inferior: downward • Medial: close to midline • Lateral: away from midline • Proximal: position relative to the body (close) • Distal: position relative to the body (away) • External: Superficial • Internal: Deep

5.1 Nose and Paranasal Sinuses

5.1.1 Nose

The nose is the first part of the respiratory system. It has an external part covered by skin and an internal part formed by the nasal fossa (cavity).

5.1.1.1 External Nose

The external nose is triangular in shape and projects forward in the face between the eyes. The skeleton of the nose is formed by a bony structure and a cartilaginous apex. The skin over the nose is thin and movable while the skin covering the cartilaginous part is firmly attached to it. The nose has two inferior openings called nares that lead into the internal nose. The two nares are separated by a midline columna.

The lateral aspect of the nares is formed by the alar of the nose.

5.1.1.2 Nasal Skeleton

The skeleton of the nose is both bony and cartilaginous. The nasal bones articulate with the maxillae, frontal, and ethmoid bones. The cartilaginous skeleton of the external nose is composed of five large, principal cartilages and a variable number of smaller cartilages. The principal cartilages are the median nasal septum and the paired lateral nasal and greater alar cartilages. The smaller ones are the vomeronasal, lesser alar and accessory cartilages (Fig. 5.1).

The nasal cavity is divided into a right and left compartment by the nasal septum which is composed of hyaline cartilage and quadrangular in shape. It articulates with the nasal bone and the lateral and greater alar cartilages superioanteriorly; the ethmoid bone posteriorly; the vomer, anterior nasal spine, and vomeronasal cartilage inferiorly.

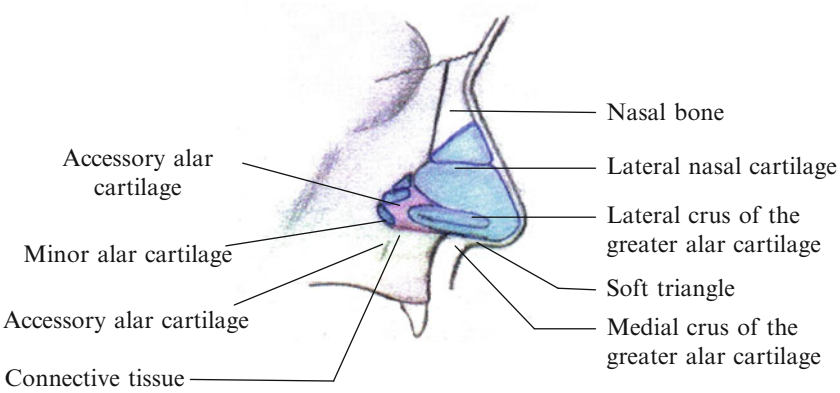

Fig. 5.1 Lateral view of the bony and cartilaginous structures of the nose

5.1.1.3 Vascular Supply and Innervation

The blood supply of external nose is via branches from facial, ophthalmic and infraorbital arteries.

The skin over the nose is innervated by the infratrochlear and external nasal branches of the nasociliary nerve and the infraorbital nerve through its nasal branch.

5.1.1.4 Nasal Cavity

The nasal cavity lies between the oral cavity and the base of the skull (Fig. 5.2). It is divided into right and left halves by the median nasal septum. The anterior aperture of each half is called nares. Each nasal cavity is related to four paranasal sinuses. The nasal cavity has a medial & lateral walls and floor and roof. The medial wall of the nasal cavity is formed by the median nasal septum, the vomer and the perpendicular plate of the ethmoid. The entire median nasal septum is covered by mucoperiosteum. The vomernasal organ (the Jacobson organ) which is olfactory in nature is related to the anteroinferior aspect of the septum.

5.1.1.5 Lateral Wall of the Nose

The lateral wall of the nasal cavity has three bony projections called superior, middle and inferior nasal turbinates or conchae (Fig. 5.2). These bones are entirely covered by mucoperiosteum. Under each projecting concha lies a corresponding groove called meatus. Superior to the superior meatus is the opening of the sphenoidal sinus. A region of another sinus, the posterior ethmoidal air cells, opens below the superior concha into the anterior region of the superior meatus.

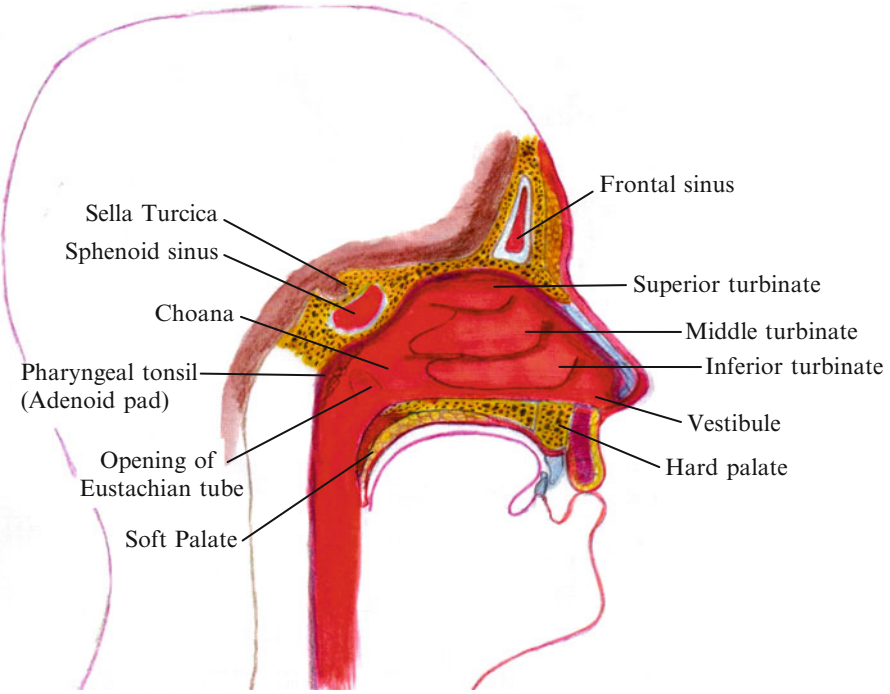

Fig. 5.2 An illustration of a sagittal section of head and neck showing the lateral wall of the nose

The middle nasal concha overlies and covers the lateral wall of the middle meatus. A rounded projection is formed on this wall by the middle ethmoidal air cells of the ethmoidal air sinus which is known as ethmoidal bulla.

The inferior nasal concha is often the largest concha. The nasolacrimal duct opens into the anterosuperior aspect of the inferior meatus [1, 2].

5.1.1.6 Floor and Roof

The floor of the nasal cavity is formed by the horizontal process of the palatine bone and the palatine process of the maxilla. The roof of the nasal fossa is concave and its bony vault is composed of the cribriform plate of the ethmoid bone as well as parts of the sphenoid, vomer, frontal, and nasal bones.

There are two types of mucous membrane lining the nasal cavity: a rich, highly vascularized respiratory mucosa lining most of the nasal walls to moisten and warm the inhaled air, and a yellowish-brown olfactory mucosa, responsible for olfaction, located superiorly.

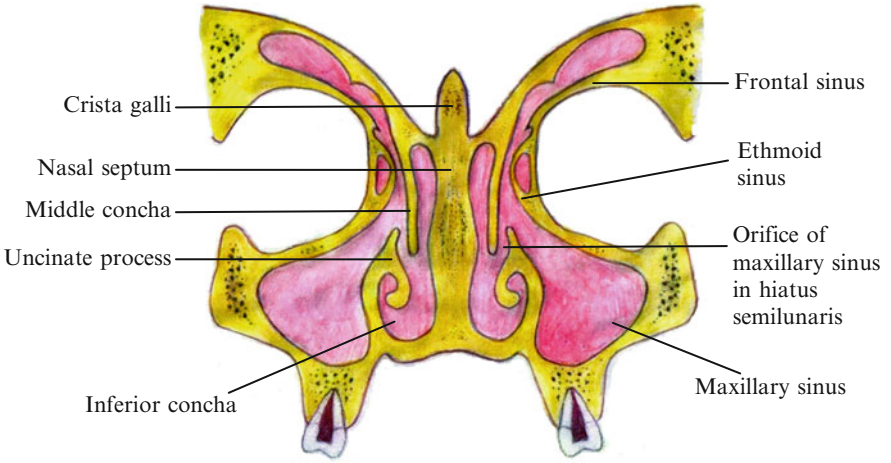

Fig. 5.3 An illustration showing the paranasal sinuses

5.1.2 Paranasal Sinuses

Paranasal sinuses are vacant cavities lined with respiratory mucosa (ciliated epithelia) within the maxillae, frontal, ethmoid, and sphenoid bones. These sinuses are in communication with the nasal fossa (cavity) via small ostia (openings). There is four paranasal sinuses (Fig. 5.3). They are bilateral except the sphenoidal sinus which is located in the midline. Instead, it is divided into two halves by an interposed plate of bone. The function of these sinuses is not exactly known, however it has been suggested that they have a role in sound resonance during speech and lightening the weight of the skull. The mucous membrane lining these sinuses is continuous with that of the nasal fossae via the various ostia of the sinuses into the nasal cavity [3].

5.1.2.1 Maxillary Sinus

Maxillary sinus is the largest of the paranasal sinuses (Fig. 5.3). The average dimensions of the adult sinus are 2.5–3.5 cm wide, 3.6–4.5 cm high, and 3.8–4.5 cm deep. It has an estimated volume of approximately12–15 cm^3. It lies in the body of the maxilla. It is pyramidal in shape where its base forms part of the lateral wall of the nasal cavity and its apex extends into the zygomatic process of the maxilla. Its roof represents the floor of the orbit. The floor of the sinus is formed by the alveolar process and part of the palatine process of the maxilla.

The maxillary sinus is intimately related to the maxillary first and second molar teeth, whose roots not only form considerable bulges but also may perforate the osseous floor of the sinus (but do not perforate the lining mucosal membrane known as Schneiderian Membrane). Moreover, the sinus may enlarge in size after extraction of maxillary teeth, a phenomenon known as pneumatization [4].

5.1.2.2 Vascular Supply and Innervation

The blood supply to the maxillary sinus is primarily derived from the posterior superior alveolar artery and the infraorbital artery; both are branches of the maxillary artery. The greater palatine artery also supplies the inferior portion of the sinus.

Nerve supply to the sinus is derived from the superior alveolar branch of the maxillary division (V2) of the trigeminal nerve.

5.2 Oral Cavity

The oral cavity (mouth) is the first part of the digestive system (Fig. 5.4). It is divided into two parts: the oral vestibule and the oral cavity proper.

The Vestibule is a space, enclosed between the lips and cheeks externally and the gums and teeth internally. The orifice of the parotid duct opens in the oral vestibule facing the first upper molar tooth.

The oral cavity proper is enclosed behind the alveolar ridge and teeth and communicates posteriorly with the oropharynx. The roof of the oral cavity proper is made by the hard and soft palates. The tongue lies on the floor of the mouth. Both the submandibular and sublingual salivary glands ducts open in the floor of the mouth [5].

5.2.1 Lips

The mouth opening is surrounded by two fleshy folds called lips (labia oris) (Fig. 5.4). It consists of outer skin part called the vermillion border (the red portion of the lips, whose coloration is referred to a rich vascular bed visible through the thin epithelium) and inner part covered by muscous membranes. The orbicularis oris muscle is enclosed between the outer skin layer and the inner mucus membrane layer. Also connective tissue, blood vessels, areolar, adipose (fat) connective tissue, and many minor mucous glands are enclosed. The inner surface of each lip is attached at the middle line to the gingivae by a fold of mucous membrane called the labial frenum. On the corner of the mouth, thin folds known as the labial commissures connecting the upper and lower lips together.

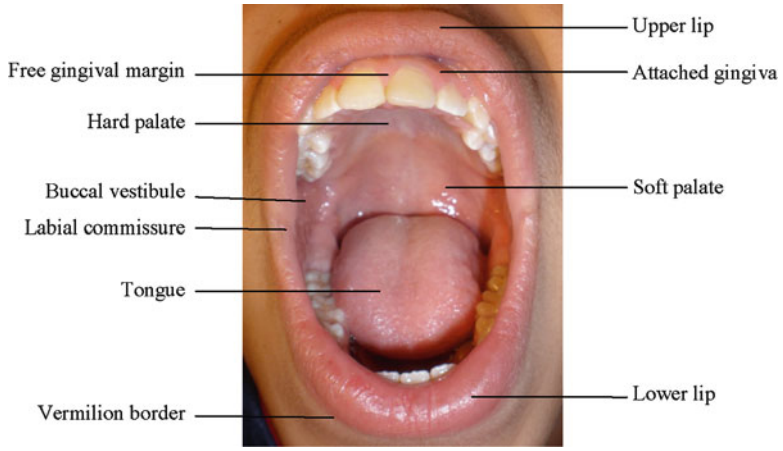

Fig. 5.4 A photograph showing the gross anatomical structures of the oral cavity

5.2.2 Tongue

The tongue is a highly specialized muscular organ lies in the floor of the mouth (Fig. 5.4) and responsible for speech, taste and deglutition.

The tongue can be divided into anterior, middle, and posterior thirds. Also it can be divided into the body and the base (Fig. 5.5). The body of the tongue lies in the oral cavity and moves relatively free in the oral cavity. The base of the tongue is fixed to the hyoid bone. The base extends into the pharynx and the oral cavity. The tongue has two surfaces dorsal and ventral surfaces. The dorsum (upper surface) is divided by a shallow groove in the midline known as the median sulcus. Also another V-shaped shallow groove separates the anterior two thirds (body) from the posterior third (base) called sulcus terminalis [2].

Anterior to the sulcus terminalis, a row of 8–10 circular mushroom shaped circumvallate papillae (vallate papillae) are located. These structures possess taste buds and receive the ducts of the serous glands of Von Ebner (accessory minor salivary glands). The remaining mucosal surface of the dorsum of the anterior two thirds of the tongue is covered with specialized projections, known as lingual papillae. The filiform papillae have a rough surface and they have no taste buds, whereas the fungiform paplillae have a few taste buds on their dorsal surface.

On the lateral sides of the anterior two thirds of the tongue, vertical grooves known as the foliate papillae are located; their taste buds degenerate after the first 2 years of years of life. A shallow depression representing the remnant of the developmental thyroglossal duct located in the midline, just posterior to the apex of the sulcus, is called the foramen cecum. The lingual tonsils; an irregularly circular shaped structures on the dorsal surface of the posterior one third of the tongue are located on the lateral aspect. The mucosa of the ventral surface of the tongue is

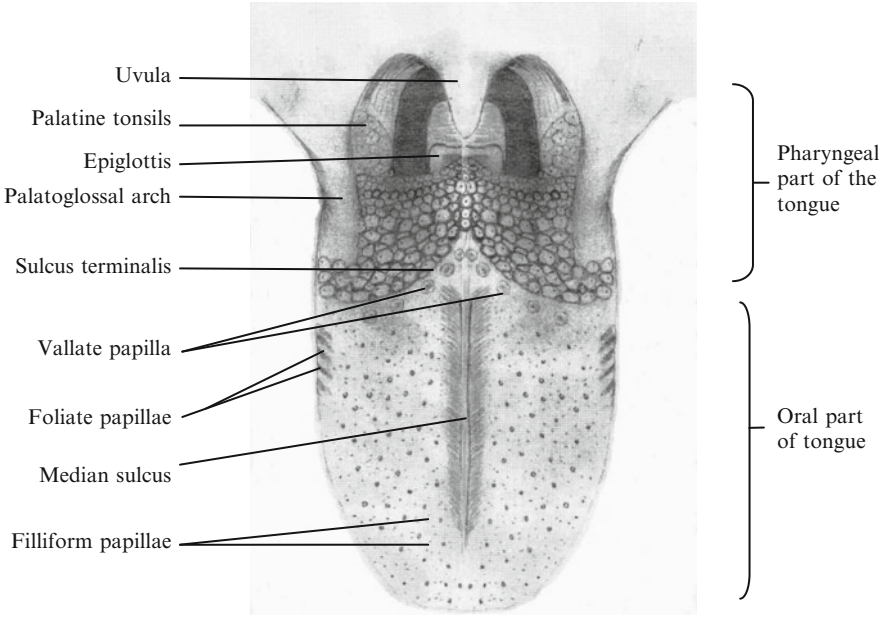

Fig. 5.5 An illustration showing the dorsal surface of the tongue

smooth and has no papillae. The anterior two thirds of the tongue are attached to the floor of the mouth by the lingual franum (Fig. 5.5).

5.2.2.1 Musculature of the Tongue

Muscles of the tongue are divided into two groups, the extrinsic and the intrinsic group. Each group consists of four muscles each. The extrinsic muscles are the genioglossus, hyoglossus, palatoglossus and styloglossus muscles. The genioglossus and hyoglossus muscles attach the tongue to the mandible and hyoid bone, while the styloglossus and palatoglossuss connect the tongue to the styloid process and the palate. The extrinsic muscles are responsible for moving the tongue upward, downward, retraction and protrusion of the tongue. The intrinsic muscles are responsible for changing the shape of the tongue. They are vitally important to speech and swallowing (Fig. 5.6).

5.2.2.2 Innervation of the Tongue

Motor innervation: The hypoglossal nerve is exclusively responsible for the motor innervations of the extrinsic and intrinsic muscles except one of the extrinsic muscles the palatoglossus, which is innervated by the Vagus nerve.

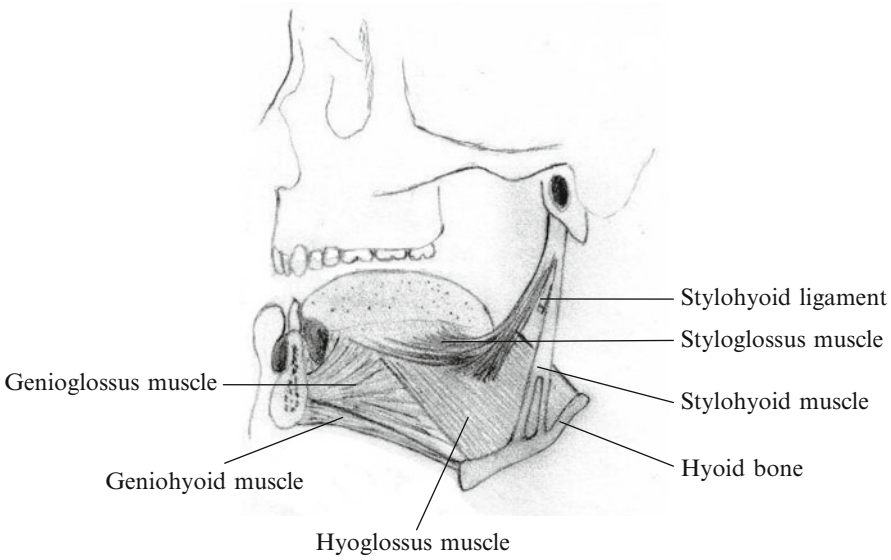

Fig. 5.6 An illustration showing the muscles of the tongue except palatoglosus muscle

Sensory innervation: The sensory supply of the tongue is divided between general sensation and special taste sensation

General sensation of the tongue is mediated by the lingual nerve which is branch of mandibular nerve (V3) of the trigeminal nerve.

Taste sensation of the anterior 2/3rds of tongue is via chorda tympani branch of facial nerve (carried to the tongue by the lingual nerve).

Posterior 1/3rd of tongue: general sensation and taste is via glossopharyngeal nerve.

5.2.2.3 Vascular Supply

Lingual artery is the primary blood supply of the tongue which is a branch of the external carotid artery and lingual veins which drain into the internal jugular vein. The floor of the mouth also receives its blood supply from the lingual artery. Ligation of lingual artery could stop severe bleeding from the tongue. The tonsillar branch of the facial artery and the ascending pharyngeal artery are additional blood supply to the tongue.

Lymphatic drainage of the tongue is complex because the tongue has a rich lymphatic plexus of vessels that is drained by three vessel groups: the marginal, dorsal, and central vessels. In addition, drainage from the two sides is intermingled to a large extent and the base of the tongue is drained by lymph nodes situated more

cranially than those that receive lymph from the tip of the tongue. Vessels from the tip of the tongue pass to the submental nodes along with those of the region of the lingual frenum.

The lateral aspect of the anterior two thirds of the tongue is also drained by marginal vessels, into the jugulodigastric lymph nodes. The central vessels drain the medial region of the anterior two thirds of the tongue, delivering the lymph to the jugulo-omohyoid lymph nodes. In addition, dorsal vessels drain the region of the sulcus terminalis and the posterior one third of the tongue, delivering lymph to the marginal lymph vessels that are drained by the jugulo-omohyoid lymph nodes [2, 5].

5.2.3 Oral Mucosa

The oral mucosa continues with the skin at the vermilion border of the lip and the pharyngeal mucosa at the oropharynx. It is divided into three types based on its function: lining, masticatory, and specialized mucosa.

5.2.3.1 Lining Mucosa

Lining mucosa covers the anatomical structures of the oral cavity (Fig. 5.4) except the dorsal surface of the tongue and the gingivae. It is red in color formed by a non-keratinized stratified squamous epithelium. Lining mucosa is demarcated from the masticatory gingival mucosa, which covers the upper part of the alveolar bone and the necks of the teeth, by a well-defined junction, the mucogingival junction. The alveolar mucosa appears dark red, the gingival appears pale pink.

5.2.3.2 Masticatory Mucosa and the Gingivae

Masticatory mucosa and the gingivae are frequently exposed to stress and fraction during mastication so it is firmly attached to the underlying periosteum and bone and to the necks of the teeth forming a mucoperiosteum in the gingivae and palatine raphe. This type of mucosa is keratinized or parakeratinized. Gingivae, palate and dorsal surface of the tongue are covered by this type of mucosa.

The gingivae are divided into the attached and the free gingivae. Attached gingivae are firmly attached to the underlying periosteum of the alveoloar process, whereas free gingivae, which constitute about 1 mm margin of the gingivae are unattached around the cervical lines teeth. The attached gingivae are pink in color. In the palatal side the attached gingivae continue with the palatal mucosa. On the lingual side the mucogingival line demarcates the attached gingivae on the lingual surface of the lower jaw from the alveolar mucosa towards the floor of the mouth.

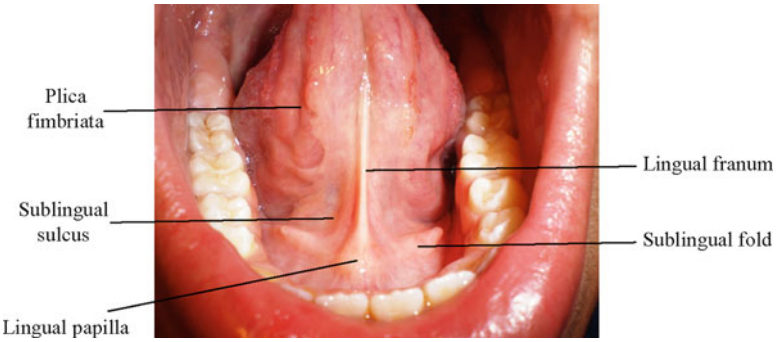

Fig. 5.7 A photograph showing the gross anatomical structures of the floor of the mouth

There is no submucosal layer under the gingivae and the palatine raphe. In the posterior outer part of the hard palate, the submucosa is thick and contains mucous salivary glands and the greater palatine nerves and vessels.

The gingivae of maxillary teeth are innervated by maxillary nerve via its greater palatine, nasopalatine and anterior, middle and posterior superior alveolar branches. The mandibular nerve innervates the gingivae in the lower teeth by its inferior alveolar, lingual and buccal branches.

5.2.3.3 Specialized Oral Mucosa

The specialized mucosa covers the anterior two-thirds of the dorsum of tongue (described in tongue anatomy).

5.2.4 Floor of the Mouth

The floor of the mouth represents the area underneath the tongue (Fig. 5.7). It is covered by lining mucosa which is non keratinized stratified squamous epithelia. It covers the underlying mylohyiod muscular diaphragm. The lingual franum is a fold of tissue that connects the tongue to the floor of the mouth and sometimes extends to reach the alveolar process. In the floor of the mouth opens the orifices of the submandibular and sublingual salivary glands underneath the center of the tongue. The sublingual duct (Bartholin's duct) from the sublingual gland joins the submandibular duct (Wharton's duct) just before interring the floor of the mouth. The Wharton duct empties at the sublingual caruncula, an enlarged papilla adjacent to the lingual frenum. A small group of minor accessory salivary glands (incisor's glands), may also be seen on the floor of the oral cavity on either side of the lingual frenulum in the anterior part of the floor of the mouth.

5.2.5 *Palate*

Palate or (palatum) constructs the roof of the mouth and the floor of the nasal cavity. It consists of two parts the hard palate anteriorly and the soft palate posteriorly (Fig. 5.4).

5.2.5.1 Hard Palate

The hard palate is bounded by the alveolar process & maxillary teeth in front and continues posteriorly with the soft palate. A dense periosteum covered by thick mucosa (keratinzed stratified squamous epithelium) is strongly adherent to the underlying periosteal membrane. At the borders of the hard palate, submucosa is present. It contains the neurovascular bundle and numerous minor salivary glands. In the midline of the anterior region a small ridge caller the palatine raphe has no submucosa.

Blood Supply and Lymphatics

Greater palatine artery and veins accompany the artery branches and drain in the ptrygoid plexus.

Nerve Supply

The hard palate is innervated by the greater palatine nerve and nasopaltine nerve.

5.2.5.2 Soft Palate

The soft palate is a soft tissue fold, attached to the posterior border of the hard palate and lateral wall of the pharynx. It suspends between the oral and nasal parts of the pharynx. It contains little muscular tissue and more aponeurosis which is thin fibrous tissues composed of tendons of tensor veli palatini muscle, vessels, nerves, lymphoid tissue and mucous glands. In the middle of its posterior border hangs the palatine uvula [2, 5].

5.2.6 *The Teeth*

There are two sets of teeth which appear in the mouth at different times of life. Those of the first set appear in childhood, and are called the deciduous or milk teeth. Those of the second set, which also appear at an early period, may continue until old age, and are

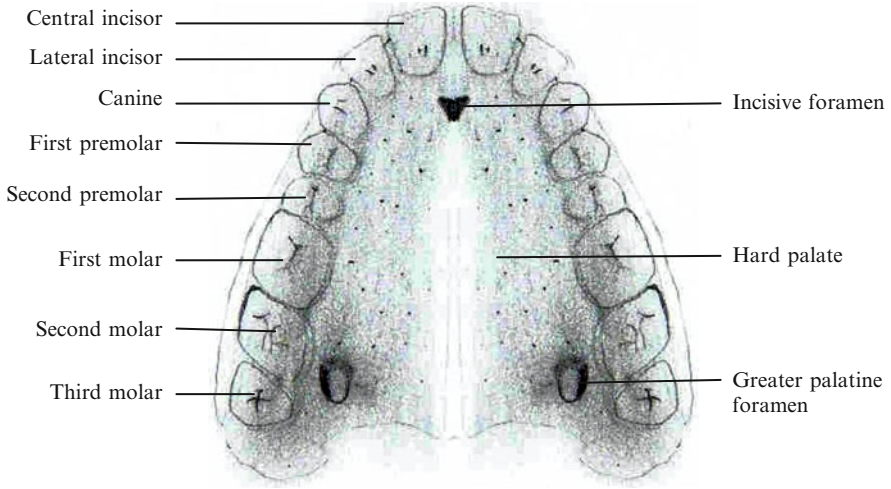

Fig. 5.8 An illustration showing permanent maxillary teeth

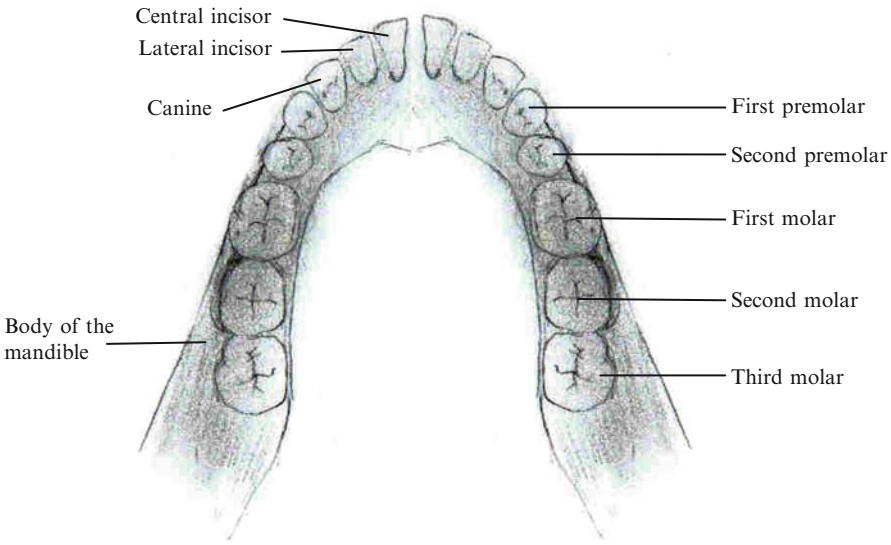

Fig. 5.9 An illustration showing permanent mandibular teeth

named permanent teeth (Figs. 5.8 and 5.9). The deciduous teeth are 20 in number: four incisors, two canines, and four molars, in each jaw. The permanent teeth are 32 in number: four incisors, two canines, four premolars, and six molars, in each jaw.

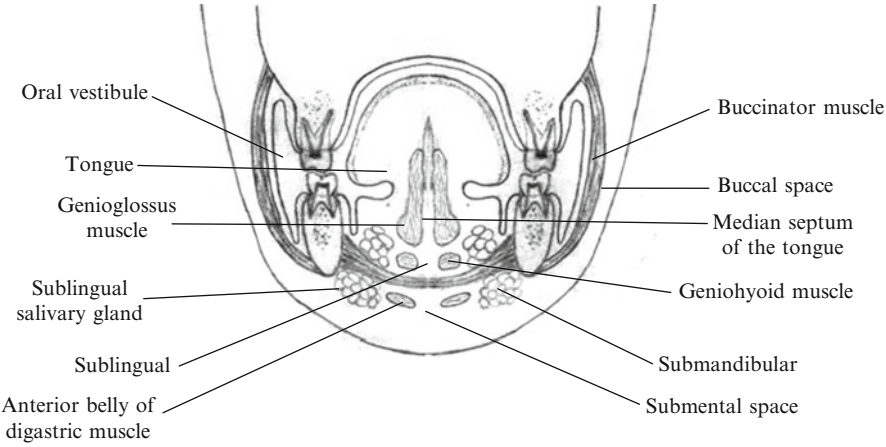

Fig. 5.10 Coronal view of the head showing the buccal vestibule, buccinator muscle and fascial spaces in relation to oral cavity

5.2.7 Cheeks

Cheeks are covered from the outer surface by skin and lined by oral mucosa from inside (Fig. 5.10). Within the cheeks there are different types of tissues. Muscular tissue is represented by the buccenator muscle, variable amount of adipose tissue known as the buccal pad of fat, also fibrous connective tissue, blood vessels, nerves and large numbers of minor salivary glands are enclosed. Few structural landmarks are visible. The parotid papilla (the orifice if the parotid duct) delivering saliva from the parotid gland into the oral vestibule is seen opposite the maxillary second molar tooth. A hyperkeratinized line (the linea alba) may be seen at a position related to the occlusal plane of the teeth. In the retromolar region, a fold of mucosa which contains the pterygomandibular raphe extends from the upper to the lower alveolus. The entrance to the pterygomandibular space (which contains the lingual and inferior alveolar nerves) lies lateral to this fold and medial to the ridge produced by the anterior border of the ramus of the mandible [2].

5.3 Neck

5.3.1 Superficial Structures of the Neck

The skin of the neck envelops the superficial fascia which is an areolar connective tissue surrounding the neck where the platysma muscle is contained which is very thin sheet of muscle originating in fascia and inserting over the mandible and skin of the face (Fig. 5.11).

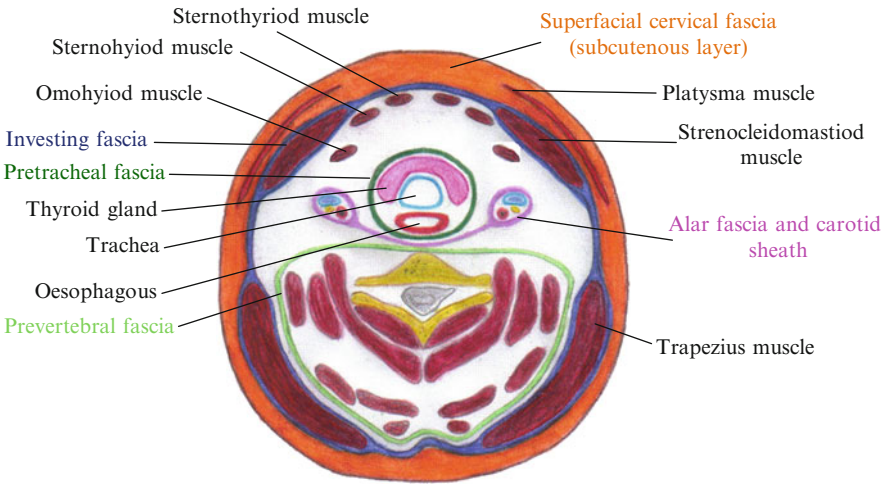

Fig. 5.11 An illustration of a transverse section of the neck showing the fascial layers of the neck

5.3.1.1 Vascular Supply and Lymphatic Drainage

The vascular supply of the cutaneous tissue in the neck is derived mainly from facial, occipital, posterior auricular and subclavian arteries. The anterior skin of the neck is supplied by the superior thyroid artery and the transverse cervical branches of the subclavian artery. The posterior skin gets the blood supply through branches from the occipital artery and the deep cervical and transverse cervical branches of the subclavian artery; superiorly, by the occipital artery branches, submandibular & submental branches of the facial artery and inferiorly, by transverse cervical and suprascapular branches of the subclavian artery. Venous drainage of the superficial neck drains into the external jugular vein which drains into the subclavian vein at the base of the neck [6].

5.3.1.2 Innervation

The cutaneous tissue in the neck is innervated by branches of cervical spinal nerves.

5.3.2 Deep Fascia

The deep fascia of the neck is arranged into three layers: investing fascia, prevertebral fascia, and pretracheal facsia.

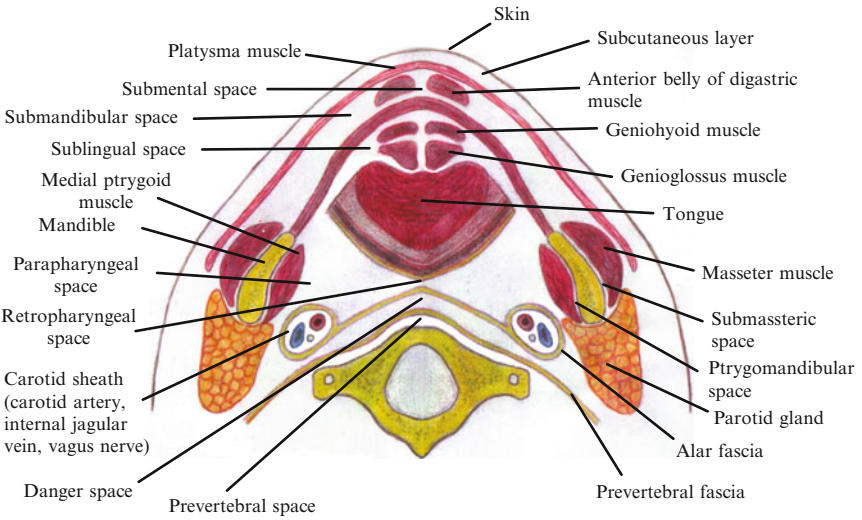

Fig. 5.12 An illustration showing prevertebtal, alar fascia and fascial spaces of the neck

5.3.2.1 Investing Fascia

The investing fascia (the superficial layer of the deep fascia) (Fig. 5.11) divides to envelop the sternocleidomastoid and trapezius muscles as it encircles the neck.

5.3.2.2 Prevertebral Fascia

Prevertebral Fascia surrounds the muscle masses encompassing the cervical vertebrae along all seven cervical vertebrae; it contains loose connective tissue forming the "danger space" which can lead to spread of infection (Fig. 5.12).

Laterally, it covers the deep muscles of the neck and all of the cutaneous nerves. This fascia attaches to the transverse processes of the cervical vertebrae and continue deep to the trapezius muscle as a thin film of fascia. All cranial nerves are enclosed within this fascia except the accessory nerve which lye superficial to the prevertebral fascia. Inferiorly, this fascia continues into the thorax, along with the muscles of the neck as these muscles insert on the bones surrounding the superior thoracic cavity.

5.3.2.3 Pretracheal Fascia

Pretracheal Fascia runs around the thyroid gland, larynx, trachea and esophagus. The superior attachment of the pretracheal fascia is the body and lesser and greater cornua of the hyoid bone, the stylohyoid ligament, medial pterygoid plate of the sphenoid

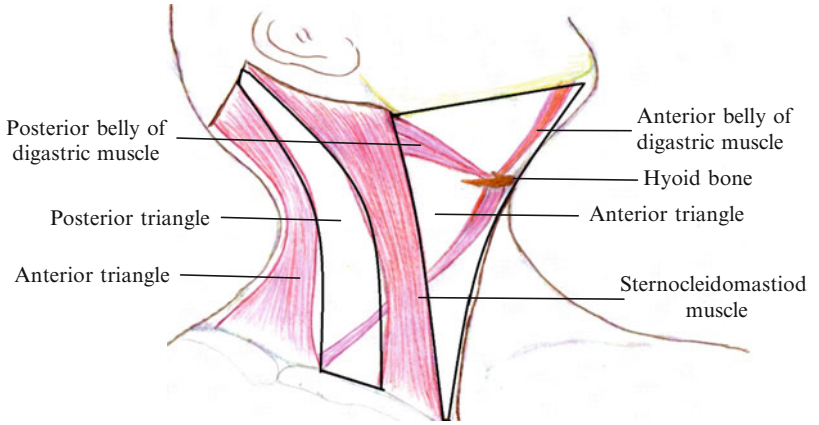

Fig. 5.13 An illustration of the side of the neck showing the triangles of the neck

bone, and the pharyngeal tubercle of the occipital bone, where the pretracheal fascia is met by its counterpart from the opposite side. Inferiorly, it is bounded by the oblique line of the thyroid cartilage, and it then merges with the fasciae of the aorta and pericardium.

5.3.2.4 Carotid Sheath

Carotid Sheath is a strong connective tissue formed by contributions of the three layers of the deep cervical fascia. It contains the common carotid artery, the internal carotid artery, the internal jugular vein, and the Vagus nerve, which are the major neurovascular bundle of the neck (Fig. 5.12).

Compartments exist within this cylindrical connective tissue sheath that separate constituent parts of the neurovascular bundle. The sheath is attached superiorly to the jugular foramen, whereas inferiorly it is continuous with the fasciae of the great vessels and heart [7].

5.3.3 Triangles of the Neck

The space lying between the anterior border of the trapezius muscle and the midline of the neck is divided into two major triangles (Fig. 5.13). The sternocleidomastoid muscle divides it into two major triangles as it passes obliquely across this space. The anterior cervical triangle lies anterior to the sternocleidomastoid muscle. The posterior cervical triangle lies posterior to the sternoclidomastoid muscle. Then these two major triangles are further subdivided into subtriangles by various anatomical landmarks. These subtriangles are the digastrics (submandibular) triangle, submental triange, carotid triangle and muscular triangle [2].

5.3.3.1 The Anterior Triangle

Boundaries:
Anteriorly: it is bounded by the anterior midline of the neck.
Posteriorly: the anterior border of the sternocleidomastoid.
Superiorly: the inferior border of the mandible.

The Digastrics Triangle

It contains the submandibular salivary gland, the facial vein, facial artery, the submandibular lymph nodes, and the lower part of the parotid gland.

Boundaries:
Superiorly: inferior border of the mandible.
Medially: superior border of anterior belly of digastrics.
Laterally: superior border of posterior belly of digastrics.

The Submental Triangle

Boundaries:
This triangle is surrounded by the anterior bellies of digastrics muscles.
It contains lymph nodes and small veins that unite to form the anterior jugular vein.

The Carotid Triangle

It contains the common carotid artery and its division into external and internal carotid arteries.

Boundaries:
Superiorly: it is bounded by the Inferior border of the posterior belly of the digastrics.
Medially: by the Superior border of superior belly of omohyoid, laterally by the anterior border of sternocleidomastoid.

The Muscular Triangle

This triangle contains the omohyoid, sternohyoid, sternothyroid and thyrohyoid muscles.

Boundaries:
Anteriorly: it is bounded by the midline from inferior border of body of hyoid to the jugular notch.
Posteriorly: anterior border of sternocleidomastoid muscle.

5.3.3.2 The Posterior Triangle

Boundaries:
Anteriorly: the sternoclidomastoid muscle;
Posteriorly: the anterior edge of the trapezius muscle.
Inferiorly: the clavicle. It is divided into two subtriangles; the occipital triangle and supraclavicular triangle.

The Occipital Triangle

It contains semispinalis capitis, splenius capitis, levator of scapulae, posterior scalene and middle scalene muscles. Also it contains spinal accessory, great auricular, lesser occipital and transverse cervical nerves, Branches from the external jugular artery, lymph nodes and fat are also present.

Boundaries:
Anteriorly: posterior border of the sternoclidomastoid muscle.
Posteriorly: anterior border of the trapezius muscle.
Inferiorly: inferior belly of omohyoid muscle.

The Subclavian Triangle

It contains the brachial plexus, the transverse cervical and suprascapular arteries and veins, the subclavian artery, termination of the jugular vein, the pherenic nerve, the thoracic duct, fat, and lymph nodes.

Boundaries**:**
Anteriorly: posterior border of the sternoclidomastoid muscle.
Superiorly: inferior belly of omohyoid muscle.
Inferiorly: upper border of the clavicle.

5.3.4 Lymph Nodes of the Neck

The mechanism of drainage of lymph nodes runs in a systematic way. The primary node drains into a secondary node then to a tertiary node, so each one act as a barrier to the spread to the second level. Lymph nodes of the neck are organized in groups based on their anatomic location (Fig. 5.14).

These groups are the anterior cervical, submental, submandibular, superficial cervical and deep cervical lymph nodes [2, 8]

Anterior cervical group are subdivided in two groups, superficial and deep, in front of the viscera of the neck.

- **The superficial group** is located in an irregular chain along the course of the anterior jugular vein.

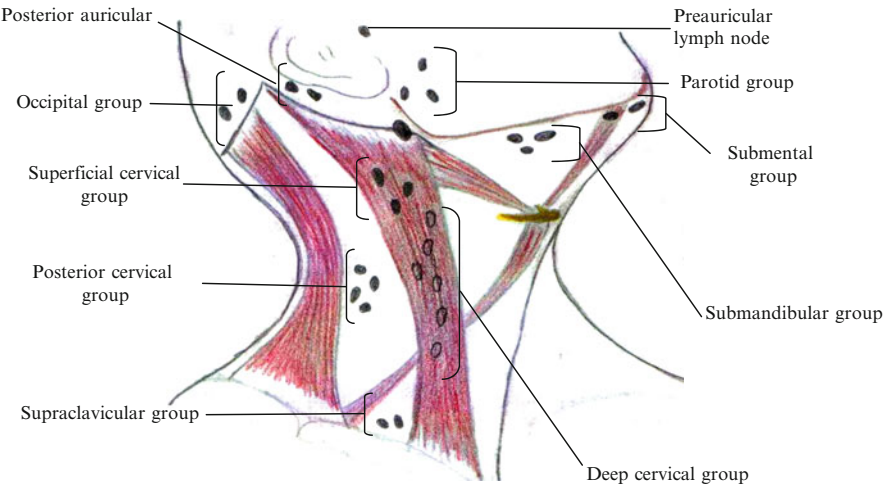

Fig. 5.14 An illustration of the lateral view of the neck showing lymph nodes groups

- **The deep group** is further classified into four small chains: the paratracheal lymph nodes; the infrahyoid group lying superficial to the thyrohyoid membrane; the pretracheal group between the investing layer of the deep cervical fascia and the trachea; and the prelaryngeal nodes, which are located on the cricothyroid ligament.

Submental lymph nodes are located between the anterior bellies of the right and left digastric muscles (submental triangle). Submental lymph nodes receive lymph from the mucosa over the floor of the mouth, the tip of the tongue, and the central portion of the lower lip then into the jugulo-omohyoid lymph node of the inferior deep cervical chain.

Submandibular lymph nodes are located in the submandibular (digastric) triangle in close proximity to the submandibular gland. This chain is composed of 3–6 lymph nodes. Submandibular lymph nodes receive lymph from the nose, cheek, and lip. The lateral aspect of the cheek and the skin over the bridge of the nose are partially drained also by the parotid lymph nodes.

Superficial cervical lymph nodes lie superficial to the sternocleidomastoid muscle adjoining the external jugular vein.

Deep cervical lymph nodes are organized to form a chain along the carotid sheath. This group collects all drainage of the lymph from the head and neck. Their efferent vessels form the jugular trunk, then to the right lymphatic duct in the right side (or to the thoracic duct on the left side).

These deep cervical lymph nodes run parallel along the carotid sheath. The deep cervical lymph nodes are divided into two subgroups; the superior and inferior deep cervical lymph nodes.

- *Superior deep cervical lymph nodes*: run along the upper part of the internal jugular vein extending from the mastoid process to the superior border of the subclavian triangle. The most superior node of this group is the large jugulodigastric

(tonsillar) lymph node, located between the posterior belly of the digastric muscle and the internal jugular vein.

- *Inferior deep cervical lymph nodes*: lie deep to the sternoclidomastoid muscle and partially related to the internal jugular vein. It is concerned with lymphatic drainage of the tongue. Accompanying the deep chain in the posterior cervical triangle are the accessory lymph nodes (2–6) lying alongside the accessory nerve, and the transverse cervical lymph nodes (1–10 in number) accompanying the transverse cervical vessels.

Retropharyngeal nodes lie between the prevertebral and the pharyngeal fascia forming median and lateral groups. The nodes receive drainage from the nasopharynx, pharyngeotympanic tube then they drain into deep cervical lymph nodes.

Paratracheal nodes are arranged along the trachea and oesophagous along the recurrent laryngeal nerves. They drain into the deep cervical nodes.

Infrahoid, prelaryngeal, pretacheal nodes This group lies underneath the deep cervical fascia. They receive afferents from the anterior cervical lymph nodes then drain into the deep cervical lymph nodes.

Lingual nodes are small irregular nodes located on the external surface of hyoglossus muscles and also between the genioglossi. They also drain into the upper deep cervical nodes.

Superficial tissues of the neck are drained by the deep cervical lymph nodes either directly or indirectly. Lymph collected from the posterior cervical triangle may first enter the superficial cervical and occipital nodes, from which the lymph flows to the deep cervical lymph nodes. Lymph collected from the anterior cervical triangle, above the hyoid bone, is drained into the submental and submandibular lymph nodes, whereas lymph collected from the region inferior to the hyoid bone drains into the anterior cervical lymph nodes that drain to the inferior deep cervical lymph nodes.

Lymph of the nasal cavity, paranasal sinuses, and nasopharynx drains into the retropharyngeal lymph nodes or directly into the inferior deep cervical lymph chain. The thyroid gland is drained by the pretracheal, prelaryngeal, and paratracheal lymph nodes, then into the deep cervical lymph nodes.

Some of the lymph from thyroid gland passes directly into the deep cervical lymph nodes. The tracheal, esophageal, and laryngeal lymph may be drained directly or indirectly via the prelaryngeal or paratracheal lymph nodes, into the deep cervical chain. Tonsillar lymph nodes drain into the jugulodigastric lymph node of the superior deep cervical chain.

5.4 Larynx

The larynx is a unique organ performing three functions; passage for air, sphincter, and phonation. The larynx is continuous with the pharynx superiorly and with the trachea inferiorly. It moves during swallowing. It lies at the level of the third (C3) to six (C6) cervical vertebrae. The larynx skeleton is formed by a group of cartilages (Fig. 5.15)

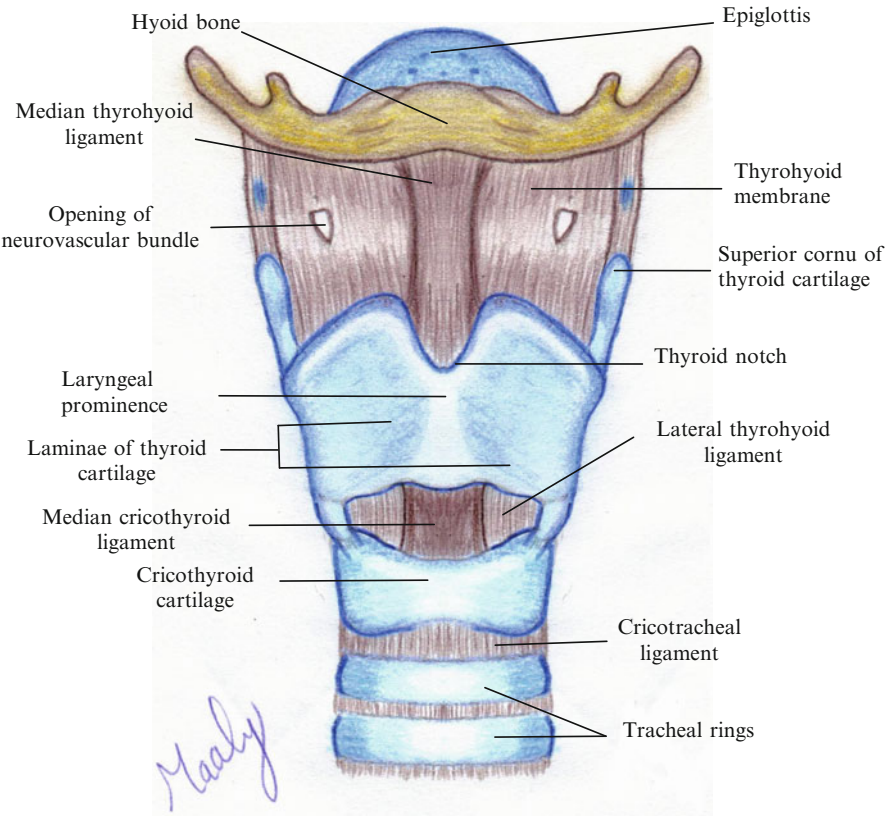

Fig. 5.15 An illustration showing the anterior view of the larynx

that are connected by ligaments and fibrous membranes and moves by a number of muscles. The larynx lies anteriorly in the midline of the neck and is covered by skin, the infrahyoid group of muscles, and associated fascia and hyoid bone [9].

The larynx is lined by a mucous membrane which is continuous with those of the pharynx and trachea. This membrane is modified in places to form two pairs of folds, (false vocal folds and true vocal folds), the latter overlying the vocalis muscles and being responsible for the formation of sound (Fig. 5.16).

The cavity of the larynx consists of three compartments: the vestibule, the ventricle, and the infraglottic cavity [10].

- The vestibule extends from the superior laryngeal aperture (aditus) to the rima glottidis (the space between the two true vocal folds and the two arytenoid cartilages).
- The ventricle is a space lying directly between the ventricular and vocal cords, being lateral outpocketings of the vestibule.
- The infraglottic cavity is the space between the rima glottidis and the beginning of the tracheal cavity.

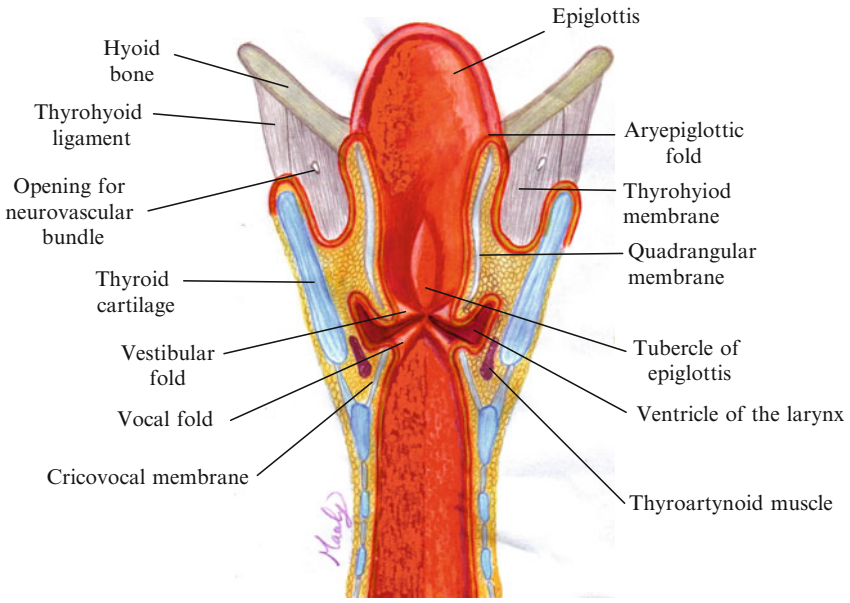

Fig. 5.16 An illustration showing the posterior view of the larynx

5.4.1 Laryngeal Cartilages

The skeleton of the larynx consists of nine cartilages. The unpaired are the thyroid, cricoids and epiclottic cartilages. The paired are arytenoid, cuneiform, and corniculate cartilages.

Thyroid Cartilage is composed of two quadrilateral plates, the right and left laminae, which fuse to form the laryngeal prominence (Adam's apple) of the neck. The angle of fusion is more acute in the male than in the female. The medial surface of the thyroid lamina is smooth and unremarkable.

Cricoid Cartilage is a ring-shaped structure whose width is greater posteriorly than anteriorly. It comprises the anteroinferior and lateroinferior walls as well as most of the posterior wall of the larynx. It consists of a quadrilateral, dorsal lamina and a ventral, narrow arch. At each junction of the lamina and the arch are the facets for articulation of the cricoid with the inferior cornua of the thyroid cartilage.

The internal surface of the cricoid cartilage is smooth. The superior margin of the lamina on either side of the midline bears two elliptical depressions for articulation with the arytenoid cartilages.

Epiglottic Cartilage is an unpaired, leaf like elastic cartilage, is attached by the thyroepiglottic ligament to the internal aspect of the laryngeal prominence, just inferior to the superior thyroid notch. This ligament attaches to the slender petiole, the narrow, inferior, stalk like extension of the epiglottic cartilage.

The broad, leaf-shaped, superior portion of the epiglottic cartilage extends cranialy but in a posterior direction behind the tongue and hyoid bone, projecting above and anterior to the superior laryngeal aperture. Laterally, the aryepiglottic folds attach the epiglottis to the arytenoid cartilages.

The epiglottis is invested by a mucous membrane that is continuous with the mucosa of the root of the tongue and the lateral pharyngeal walls. The mucosa forms three folds between the tongue and the epiglottis: the single median glossoepiglottic fold and the two lateral glossoepiglottic folds. The depressions between these folds, on either side of the median glossoepiglottic fold, are known as the epiglottic valleculae.

Arytenoid Cartilage The paired arytenoid cartilages are pyramidal structures located on the superior border of the lamina of the cricoid cartilage. The arytenoid cartilage has a concave base that articulates with the arytenoid articular surface of the cricoid lamina, a dorsomedially inclined apex to which the corniculate cartilage attaches, and three surfaces that provide attachments for muscles and ligaments. The base has two free processes: the lateral angle, which is the muscular process, the point of insertion for the posterior and lateral cricoarytenoid muscles, and the anterior angle, or vocal process, to which the vocal cord attaches.

The posterior surface serves for the attachments of the transverse arytenoid muscles. The ventrolateral surface presents a superiorly positioned triangular fovea containing mucous glands and providing attachment to the vestibular ligament. Positioned inferiorly is an oblong fovea that is the site of attachment for the vocalis and the lateral cricoarytenoid muscles. The medial surface is smooth and invested by a mucous membrane.

Corniculate and Cuneiform Cartilages are tiny pieces of elastic cartilage. The Corniculate cartilage articulates with the arytenoid apex, whereas the Cuneiform cartilage is attached to the aryepiglottic fold just anterior to the corniculate cartilage.

5.4.2 Membranes, Ligaments, and Muscles

Membranes and ligaments are associated with the muscles that move the cartilages of the larynx. Tensions and movements of the vocal cords change the amount of air passage through the larynx leading to audible sounds.

Under the lining mucosa of the larynx a thick, intrinsic membrane of elastic lamina whose cranial portion is referred to as the quadrangular membrane and whose caudal portion is the elastic cone.

The inferior free edge of the quadrangular membrane helps the formation of the ventricular vocal cords. The elastic cone has a well-defined anterior portion, known as the median cricothyroid ligament, and two thickened lateral portions, the vocal ligaments, whose free edges assist in formation of the vocal cords. Two extrinsic membranes are vitally important; the thyrohyoid and cricothyroid membranes. The thyrohyoid is a thick, fibroelastic membrane suspended between the body and greater cornua of the hyoid bone superiorly and the cranial aspect of the thyroid

cartilage inferiorly. It becomes thicker in its median portion, whereas the lateral portions are called lateral thyrohyoid ligaments. The median cricothyroid ligament is a narrow band of fibroelastic tissue connecting the superior rim of the cricoid cartilage with the inferior rim of the thyroid cartilage. The cricotracheal ligament originates from the inferior rim of the cricoid cartilage and attaches to the superior rim of the first tracheal cartilage [9].

5.4.2.1 Muscles of the Larynx

The muscles of the larynx are classified into extrinsic and intrinsic groups. The extrinsic muscles have been described. There are six bilateral pairs of intrinsic muscles.

The intrinsic muscles of the larynx are the cricothyroid, lateral cricoarytenoid, posterior cricoarytenoid, arytenoid, and thyroarytenoid, and the vocalis. These muscles play a role in the movements of vocal cords and sound production [9, 10].

5.4.2.2 Vascular and Nerve Supply

The blood supply to the larynx is provided by branches from superior thyroid artery and a branch of the thyrocervical trunk.

Venous drainage is by the superior and inferior laryngeal veins.

5.4.2.3 Sensory and Motor Innervations

Sensory and motor innervation to the larynx is provided by several branches originating from major branches of the Vagus nerve in the neck.

Motor innervation of the larynx: all intrinsic muscles of the larynx except the cricothyroid are innervated by the recurrent laryngeal branch of the Vagus nerve. The cricothyroid muscle is served by the external laryngeal branch of the superior laryngeal nerve also a branch of the Vagus nerve.

5.5 Pharynx

The pharynx is 12–14 cm long musculomembranous tube. It extends from the cranial base to the lower border of the cricoid cartilage at the level of the 6th cervical vertebra (C6). Its shape resembles an inverted cone. It is widest at its top and narrowest at its esophageal junction. It is divided into three parts the nasopharynx, oropharynx and Laryngeopharynx [11] (Fig. 5.17).

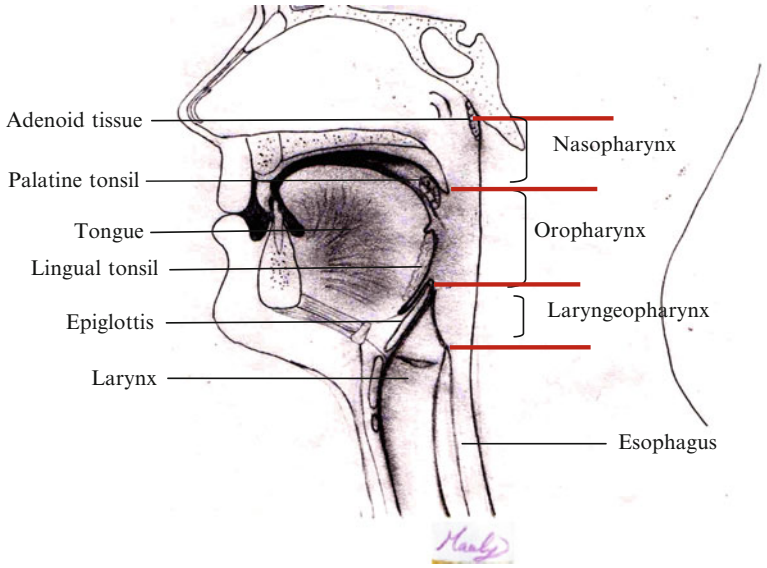

Fig. 5.17 An illustration of a midsagittal section of the neck showing the lateral view of the pharynx

5.5.1 Nasopharynx

It is the most superior and widest portion of the pharynx continuing the posterior of the nasal cavity. It also communicates with the oropharynx by the pharyngeal isthmus (a space between the posterior wall of the pharynx and the free border of the soft palate). It also communicates with the auditory tube. The posterior wall contains the pharyngeal tonsil.

During respiration, the soft palate is relaxed. During deglutition, the soft palate is elevated and contacts the posterior wall of the pharynx, blocking the communication between the nasal and oral cavities.

The lateral wall of the nasopharynx presents an opening of the auditory canal, the ostium of the auditory tube is located inferoposterior to the inferior nasal concha projecting and forming an elevation called the torus tubarium. Behind the torus is the pharyngeal recess, a mucosa-lined space extending to the base of the skull. Two folds extend from the torus: the smaller salpingopalatal fold covers the levator veli palatini muscle, extending from below the ostium of the internal auditory tube to the root of the soft palate. The pharyngeal tonsils(mass of lymphatic tissue) are located on the posterior wall of the nasopharynx.

5.5.2 Oropharynx

The oropharynx extends from the soft palate to the epiglottis and contains the palatine tonsils. It leads into the laryngeal pharynx. It extends from the soft palate to the level of the epiglottis.

Boundaries:

Anteriorly: it begins at the oral cavity through the oropharyngeal isthmus. The palatine tonsils are located on the lateral wall of the oropharynx between palatoglossal and palatopharyngeal arches.

5.5.3 Laryngeopharynx

The laryngeopharynx begins at the epiglottis and becomes continuous with the esophagus at the level of the inferior border of the cricoid cartilage. It is the most inferior art of the pharynx.

Boundaries:

Anteriorly: it begins at the larynx where its opening is guarded by the epiglottis (a movable, flaplike structure). The epiglottis is connected to the midline and side of the pharyngeal root of the tongue by the median and lateral glossoepiglottic folds.

5.5.4 Pharyngeal Wall

The pharyngeal wall consists of three layers; the inner-most mucous layer, the middle fibrous and muscular layer, and the outer fibrous layer.

The pharyngobasilar fascia lies deep to the mucosa. The cranial portion of the pharyngobasilar fascia has no muscular covering. It is attached to the base of the skull at various points: at the basilar portion of the occipital bone, anterior to the pharyngeal tubercle; at the petrous temporal bone; and at the medial pterygoid plate. Anteriorly, it is attached to structures in the neck, thyroid cartilage, hyoid bone, stylohyoid ligament, and pterygomandibular raphe. Also, this fascia is attached posteriorly to a strong, longitudinally oriented fibrous band of connective tissue known as the pharyngeal raphe, which extends from the pharyngeal tubercle of the occipital bone to the lower border of the pharynx.

Boundaries:

Laterally: it is fixed to the medial pterygoid plate, pterygomandibular raphe, alveolar process of the mandible, lateral aspect of the tongue, hyoid bone, thyroid and cricoid cartilages.

Posteriorly: the pharynx approximates the first six cervical vertebrae and is separated from them by the prevertebral fascia.

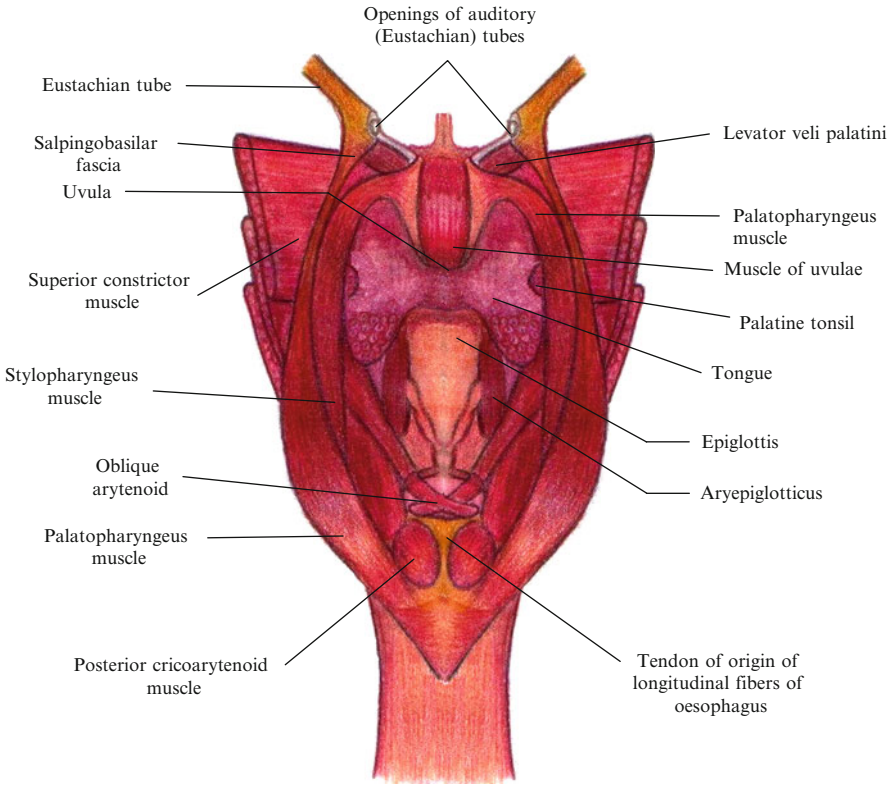

Fig. 5.18 An illustration showing the posterior view of the pharynx and pharyngeal muscles

Anteriorly: the pharynx has no complete wall but it is continues with the nasal, oral, and laryngeal cavities [12].

5.5.5 Muscles of the Pharynx

The muscles of the pharynx are divided into three constrictors and three elevators (Fig. 5.18).

The constrictor muscles of the pharynx insert into the pharyngeal raphe. The muscular layer of the pharynx is positioned between the pharyngobasilar fascia and the thin outermost layer of the pharynx the buccopharyngeal fascia. Superiorly, in the region devoid of the superior constrictor, this fascia fuses with the pharyngobasilar fascia.

Nerves and vessels adjoin the course of the pharynx in the buccopharyngeal fascia.

Additional accessory muscles originating from other areas beside the constrictor muscles are attached to the pharynx and insert into the pharynx.

The musculature of the pharynx is composed of the superior, middle, and inferior pharyngeal constrictors as well as the stylopharyngeus, salpingopharyngeus, and palatopharyngeus muscles. The constrictor muscles to a certain extent overlap each other and may look like as three sleeves partially telescoped inside one another from superior to inferior.

5.5.5.1 Superior Pharyngeal Constrictor

The superior pharyngeal constrictor is a thin, quadrilateral muscle whose fibers originate from the pterygoid hamulus and the medial pterygoid plate, the pterygomandibular raphe, the posterior quarter of the mylohyoid line, the alveolar process of the mandible, and the lateral aspect of the root of the tongue.

The muscle fibers turn posteriorly to insert into the pharyngeal raphe and pharyngeal tubercle. It arises from the palatal aponeurosis and merges with the fibers of the main muscle mass of the superior constrictor. This muscle slip, the palatopharyngeal sphincter, creates a ridge, the bar of Passavant, on the posterior pharyngeal wall, which is contacted by the elevated soft palate during deglutition to separate the nasopharynx from the oropharynx.

Nerve supply:

The superior constrictor muscle is innervated by the Vagus nerve through its branches that accompany the pharyngeal plexus. This motor innervation is responsible for the constriction of the pharynx.

5.5.5.2 Middle Pharyngeal Constrictor

The middle pharyngeal constrictor muscle originates on the lesser and greater cornua of the hyoid bone and the stylohyoid ligament. It looks like a fan – shaped muscular sheet. The cranial fibers pass superficial to the superior constrictor muscle covering part of it. The inferior fibers pass deep to the inferior constrictor muscle. The middle constrictor inserts into the median pharyngeal raphe.

Nerve supply:

The middle pharyngeal constrictor muscle is innervated by the Vagus nerve through its branches that accompany the pharyngeal plexus. This motor innervation is responsible for the constriction of the pharynx.

5.5.5.3 Inferior Pharyngeal Constrictor

The inferior pharyngeal constrictor, the lower-most of the three constrictors, covers the lower part of the middle constrictor. It originates from the lateral aspect of the cricoid cartilage, from the oblique line of the thyroid cartilage and the area behind it, to be inserted into the median pharyngeal raphe. The caudal-most fibers of the inferior constrictor continue with the superior-most, circular inner muscle fibers of the esophagus.

Nerve supply:

The inferior constrictor muscle receives its motor nerve supply from the Vagus nerve through its branches that accompany the pharyngeal plexus and from the external and recurrent laryngeal branches of the Vagus nerve. Functionally, the inferior constrictor has two parts: the superior thyropharyngeal and the inferior cricopharyngeal. The former constricts the pharynx, and the latter acts as a pharyngoesophageal sphincter, preventing reflux of esophageal contents back into the pharynx.

5.5.5.4 Stylopharyngeus

The stylopharyngeus muscles a long, thin, cylinder shaped muscle, arises from the styloid process of the temporal bone and passes inferomedially between the middle and superior pharyngeal constrictor muscles to insert in common with the palatopharyngeus muscle on the dorsal aspect of the thyroid cartilage.

The stylopharyngeus is the only muscle to receive its motor innervation from the glossopharyngeal nerve. It acts to elevate the larynx and pharynx.

5.5.5.5 Salpingopharyngeus

The salpingopharyngeus muscle is a thin, fusiform muscle arising from the inferior aspect of the cartilaginous auditory tube at its terminal end in the nasopharynx. It passes inferiorly, deep to the pharyngeal mucosa, to insert into the muscular wall of the pharynx by interdigitating with the fibers of the palatopharyngeus muscle.

The salpingopharyngeus is innervated by the Vagus nerve via its contributions to branches of the pharyngeal plexus. It functions in elevating the pharynx and may assist in opening the auditory tube during deglutition.

5.5.6 Vascular and Sensory Nerve Supply of the Pharynx

5.5.6.1 Vascular Supply

The pharynx receives its blood supply from the pharyngeal branches of the external carotid artery, the maxillary artery, and branches of the facial artery. The lower portion of the pharynx is supplied by the superior and inferior thyroid arteries.

Arterial supply of the cranial portion of the pharynx is derived chiefly from the ascending pharyngeal branch of the external carotid artery, the pharyngeal branches of the maxillary artery, and the ascending palatine and tonsillar branches of the facial artery.

The superior thyroid and, to a lesser extent, the inferior thyroid arteries supply the caudal portion of the pharynx.

Venous drainage is via a plexus of veins, the pharyngeal plexus, located between the prevertebral fascia and the constrictor muscles. This plexus is drained by the pterygoid plexus of veins and the internal jugular and facial veins [2, 11].

5.5.6.2 Sensory Nerve Supply

The nasopharynx and oropharynx receive their sensory supply via branches of the maxillary division of the trigeminal nerve and glossopharyngeal nerve. The sensory supply to the remainder of the pharynx is supplied by the glossopharyngeal and Vagus nerves.

Additional innervation is provided by the facial nerve via its greater petrosal branch.

5.6 Salivary Glands

Salivary glands are exocrine glands. They can be classified into two groups: major and minor salivary glands. The major salivary glands are the parotid, the submandibular and the sublingual salivary glands (Fig. 5.19). Minor salivary glands are distributed in the oral cavity and oropharynx.

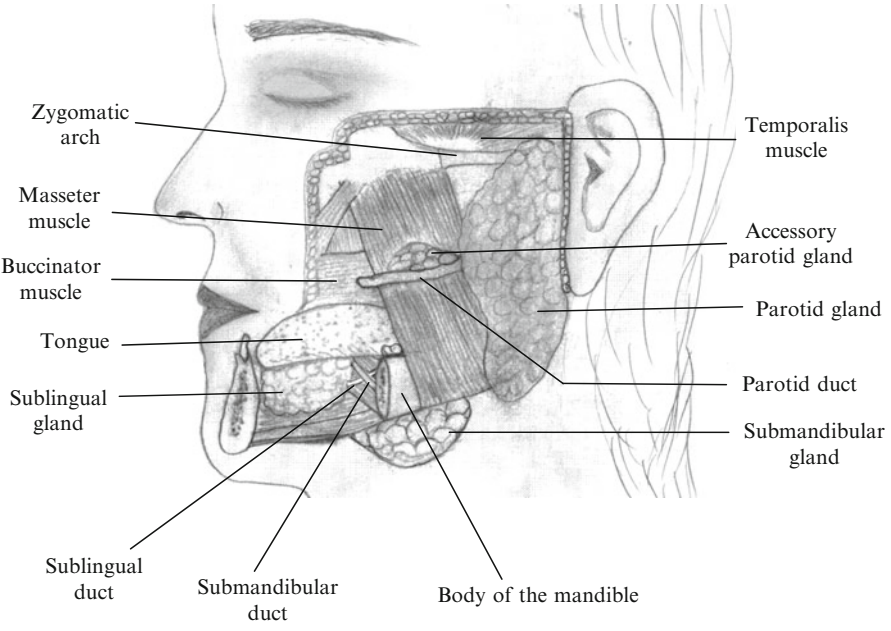

Fig. 5.19 An illustration of the lateral view of the head showing parotid, submandibular and sublingual glands

5.6.1 Major Salivary Glands

5.6.1.1 Parotid Gland

The parotid gland is the largest of the three major salivary glands. It is encapsulated within a fibrous capsule formed by the deep cervical fascia. Part of the gland lies superficial to the lateral surface of the masseter muscle; whereas most of it is impeded within the parotid bed between some muscle masses in the deep face [13].

Boundaries:

Inferiorly: it is related to the region between the mastoid process, the sternocleidomastoid muscle, and the angle of the mandible extending over the posterior aspect of the masseter muscle.

Medially: the gland extends deeply into the parotid bed to the styloid process where a wedge-shaped portion of the gland is embedded between the medial and lateral pterygoid muscles.

The parotid duct (Stenson'duct) exits the anterior aspect of the superficial portion of the gland, which passes anteriorly, superficial to the masseter muscle, then submerges medially into the buccal fat pad piercing the buccinator muscle to reach the vestibule of the oral cavity carrying the parotid salivary secretions (saliva) at the opening of the parotid papilla located opposite the second maxillary molar tooth.

Relationships

Superficially: structures associated with the superficial aspect of the gland are branches of the great auricular nerve originating from the cervical plexus and small lymph nodes draining the superficial area.

Deeply: structures associated with the deep aspect of the gland are the external and internal carotid arteries, the internal jugular vein, the Vagus and glossopharyngeal nerves.

Several structures pass through the gland:

- The external carotid artery enters the substance of the gland where many of its branches arise, including the posterior auricular, maxillary, and superficial temporal arteries. The retromandibular vein as well as the veins uniting to form it, also passes through the gland.
- The facial nerve (cranial nerve VII) emerges through the stylomastoid foramen and enters the substance of the gland where it forms a plexus before exiting the gland to innervate the muscles of facial expression.
- The auriculotemporal nerve, a branch of the mandibular division of the trigeminal nerve (cranial nerve V), enters the substance of the gland from its deep and

emerges from the gland just inferior to the root of the zygomatic arch. While within the gland, it communicates with the facial nerve and distributes fibers to the gland.
- The posterior auricular artery exits from the posterior aspect of the gland.
- The superficial temporal artery and vein, auriculotemporal nerve, and temporal branches of the facial nerve exit from the superior aspect of the gland.
- Inferiorly, the retromandibular vein exits the parotid gland just before joining the posterior auricular vein to form the external jugular vein.
- From anterior aspect of the gland, the terminal branches of the facial nerve emerge gathered into five major branches: the temporal, zygomatic, buccal, mandibular, and cervical branches.

Vascular Supply and Lymphatic Drainage

The posterior auricular artery is the major vascular supply to the parotid gland. It arises from the external carotid artery within the substance of the parotid gland. Additional small glandular branches arising from the superficial temporal and transverse facial arteries also supply the gland.

Venous drainage is via the tributaries passing through the gland, and these vessels empty into the external jugular vein.

Lymph nodes are located within the gland and drain into the cervical lymph nodes.

Lymph collected through lymph nodes located superficially and within the substance of the gland is delivered to the superficial and deep cervical lymph nodes.

Innervation

The parotid gland receives sensory and autonomic innervation.

- General sensation to the parotid gland is provided by the great auricular nerve of the cervical plexus.
- The sympathetic component of the autonomic nervous system reaches the gland via postganglionic sympathetic fibers derived from the carotid plexus.
- The parasympathetic innervation (secretomotor innervations) is provided by the auriculotemporal nerve a branch of the trigeminal nerve (cranial nerve V); these parasympathetic fibers do not arise within the trigeminal nerve. Preganglionic parasympathetic fibers, from the glossopharyngeal nerve (cranial nerve IX), pass from its tympanic branch via the lesser petrosal nerve to the otic ganglion, where they synapse on postganglionic cell bodies. Postganglionic parasympathetic fibers from it join the auriculotemporal branch of the mandibular division of the trigeminal nerve, to reach the gland affecting the secretomotor functions. Also some evidence suggests that the facial nerve may supply parasympathetic innervation to the parotid gland in addition to that from the glossopharyngeal nerve.

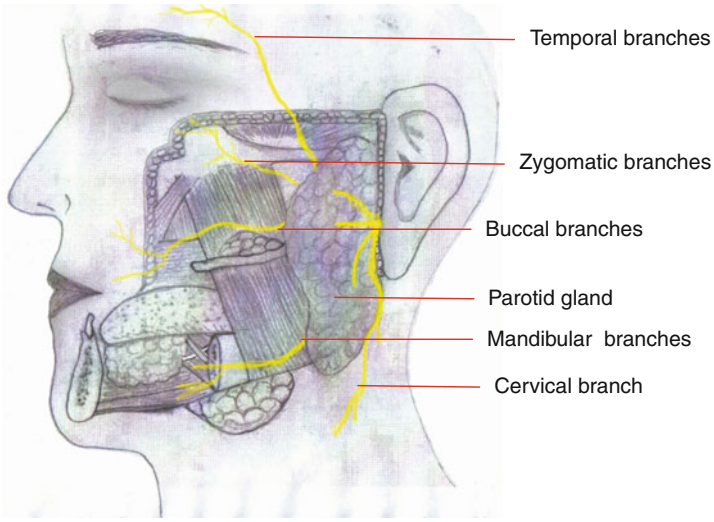

Fig. 5.20 An illustration showing temporal, zygomatic, buccal, mandibular and cervical branches of facial nerve

Facial Nerve

Facial nerve is closely related to the parotid gland (Fig. 5.20). The facial nerve exits the cranium through the stylomastoid foramen to inter the parotid gland where it forms a loop from which its five terminal branches originate. These branches provide motor innervation to the muscles of facial muscles of expression. Facial nerve communicates with the glossopharyngeal and vagus nerves and with the great auricular nerve of the cervical plexus while exiting the parotid gland.

The auriculotemporal nerve from the mandibular division of the trigeminal nerve communicates with the facial nerve after it has entered the substance of the parotid gland giving these branches: the posterior auricular, digastric, stylohyoid, and parotid plexus with its terminals.

The posterior auricular nerve arises near the stylomastoid foramen and ascends behind the ear. This branch gives motor innervation to the auricular and occipital muscles. The digastric and stylohoid branches provide motor innervations to the same-named muscles.

5.6.1.2 Submandibular Salivary Gland

Submandibular salivary gland is located in the digastrics triangle of the neck. It consists of larger superficial part and smaller deep part. It lies between the belly of digastric muscle and posteriorly stylomandibular ligament. Superiorly, it extends medially to the body of the mandible. Inferiorly, it overlaps the intermediate tendon

of digastric and the insertion of stylohyoid muscle. The inferior surface is covered by skin, platysma and deep fascia. It is crossed by the facial vein and the cervical branch of the facial nerve. Near the mandible the submandibular lymph nodes are in contact with the gland and sometimes may be embedded within it [2, 14].

The lateral surface is related to the submandibular fossa on the medial surface of the body of the mandible and the mandibular attachment of medial pterygoid muscle. The facial artery runs over its posterosuperior part, starting first deep to the gland and then emerges between its lateral surface and the mandibular attachment of the medial pterygoid to reach the lower border of the mandible.

The medial surface is related to mylohyoid muscle, from which it is separated by the mylohyoid nerve and vessels and branches of the submental vessels. Posteriorly, it is related to styloglossus, the stylohyoid ligament and the glossopharyngeal nerve, which separate it from the pharynx. In the middle part of the medial surface it is related to hyoglossus, from which it is separated by styloglossus, the lingual nerve, submandibular ganglion, hypoglossal nerve and deep lingual vein. Also, the medial surface is related to the stylohyoid muscle and the posterior belly of digastric muscle.

Deep Part of the Submandibular Gland

The deep part of the gland extends to the posterior end of the sublingual gland. It lies between mylohyoid inferolaterally, hyoglossus and styloglossus medially, the lingual nerve superiorly, and the hypoglossal nerve and deep lingual vein inferiorly.

Submandibular Duct

The submandibular duct is 5 cm long. It begins from numerous tributaries in the superficial part of the gland and emerges from the medial surface of the gland behind the posterior border of mylohyoid, then goes forwards between the sublingual gland and genioglossus muscle to open in the floor of the mouth on the summit of the sublingual papilla at the side of the frenulum of the tongue.

Vascular Supply and Lymphatic Drainage

Submandibular salivary gland receives branches of the facial and lingual arteries. The lymph vessels drain into the deep cervical group of lymph nodes (particularly the jugulo-omohyoid node), interrupted by the submandibular nodes.

Innervation

The secretomotor supply to the submandibular gland is derived from the submandibular ganglion. The submandibular ganglion is a peripheral parasympathetic ganglion.

The ganglion is connected with the facial nerve and its chorda tympani branch. There are three roots associated with the submandibular ganglion. The postganglionic fibers are secretomotor to the submandibular and sublingual salivary glands. Some fibers may also reach the parotid gland. The sympathetic root is derived from the plexus on the facial nerve. It consists of postganglionic fibers from the superior cervical ganglion. Sensory innervation of the gland is provided by the lingual nerve.

5.6.1.3 Sublingual Salivary Gland

The sublingual gland is the smallest major salivary gland. It is flat almond shaped and weighs 4 g. The sublingual gland lies above mylohyoid muscle and under the lining mucosa of the floor of the mouth, which is raised as a sublingual fold. The sublingual gland is seromucous, but predominantly mucous. The sublingual gland has 8–20 excretory ducts. The anterior part of the gland sometimes form a major sublingual duct (Bartholin's duct), which opens with, or near to, the office of the submandibular duct.

Vascular Supply, Lymphatic Drainage and Innervation

The arterial blood supply to the sublingual gland is from the sublingual branch of the lingual artery and the submental branch of the facial artery. Lymphatic drainage is to the submental lymph nodes. Innervation is via the submandibular ganglion.

5.6.2 Minor Salivary Glands

The minor salivary glands of the mouth are scattered all over the oral cavity and the oropharynx. They are most numerous at the junction of the hard and soft palate, lips and buccal mucosa. The minor salivary glands of the lateral aspects of the tongue, lips and buccal mucosa are seromucous whereas those in the floor of the mouth, palate, glossopharyngeal area and retromolar pad are predominantly mucous. The anterior and posterior lingual glands are mainly mucous. The anterior glands are enclosed within muscle near the ventral surface of the tongue and open by means of four or five ducts near the lingual frenum. The posterior glands are located in the root of the tongue. The deep posterior lingual glands are predominantly serous. Serous glands of (Von Ebner) spread around the circumvallate papillae, their secretion is watery.

5.6.3 Microscopic Anatomy of Salivary Glands

Salivary glands are formed by numerous lobes composed of smaller lobules (Fig. 5.21). These lobules are separated by dense connective tissue which continues with the

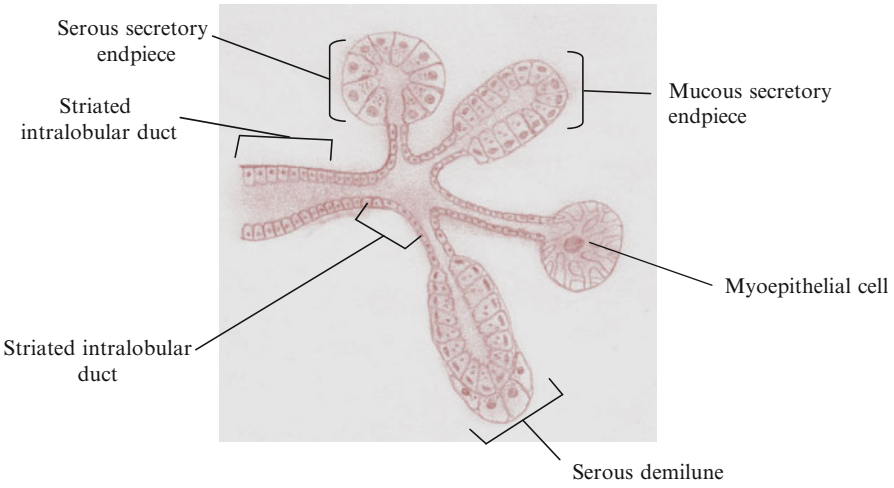

Fig. 5.21 An illustration showing the histological structures of salivary glands

outer capsule of the gland, and contains the collecting ducts, blood vessels, lymph vessels, nerve fibers, and small ganglia. Each lobule has a single duct, whose branches terminate at dilated secretory end pieces. Between the lobules a variable amount of adipose connective tissue are present.

In the submandibular gland, secretory units are predominantly serous acini, with some mucous tubules and acini.

In the sublingual gland mucous tubules and acini predominate, but serous cells also occur. Serous cells also secrete kallikrein, lactoferrin, and lysozyme, an antibacterial enzyme whose synthesis has been localized in particular to the serous demilunes of the submandibular and sublingual glands, and which is important in the defense against oral pathogens. In the parotid and submandibular glands, zymogen granules also show a positive periodic acid-Schiff staining reaction, which indicates the presence of polysaccharides, and some texts refer to these cells as seromucous. Mucous cells are cylindrical and have flattened basal nuclei.

5.6.3.1 Duct

The collecting ducts (Intercalated, striated and extralobular) function primarily as a medium for saliva but, together with the striated ducts, may also modify its content of electrolytes and secrete immunoglobulin A. Collecting ducts are metabolically relatively inert medium which run within interlobular connective tissue septa of the glands. They carry saliva to the main duct which opens on top of mucosal surface of the oral cavity. The lining epithelium of the collecting duct varies. It may be pseudostratified columnar, stratified cuboidal or columnar. It becomes a stratified squamous epithelium near the buccal orifice.

5.6.3.2 Myoepithelial Cells

Myoepithelial cells are contractile cells related to the secretory end pieces and ductal system. They have numerous cytoplasmic processes around the serious acini. They are termed basket cells. Myoepithelial cells associated with ducts are more fusiform in shape, and are arranged along the length of the duct [2].

5.7 Thyroid and Parathyroid Glands

5.7.1 Thyroid Gland

5.7.1.1 Gross Anatomy

The thyroid gland is an endocrine gland located in the anterior part of the lower neck. The thyroid gland is located deep to the sternohyoid muscle anterior to the 2nd and 3rd tracheal rings (Fig. 5.22). The thyroid gland is attached to the trachea

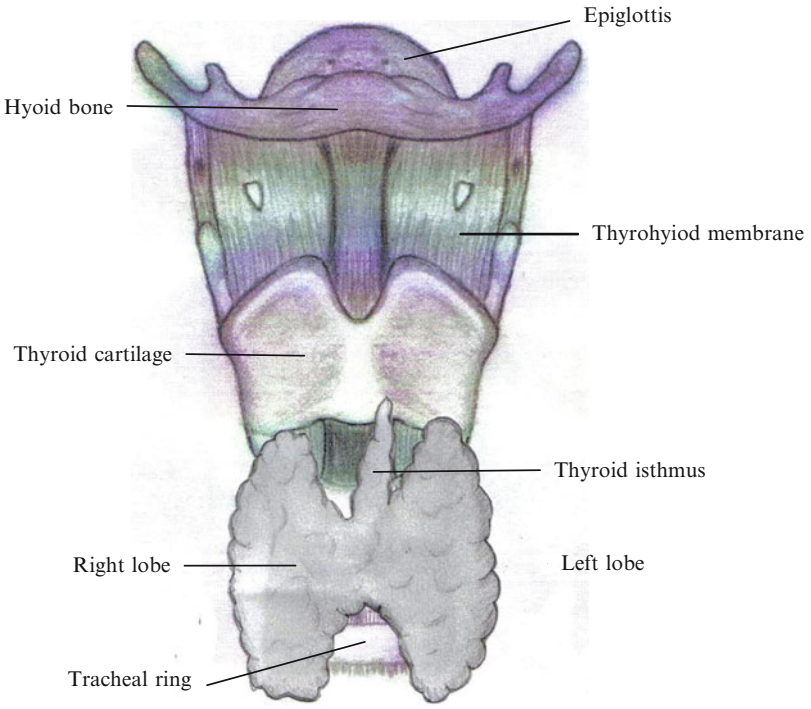

Fig. 5.22 An illustration showing the anterior view of thyroid gland in relation to the larynx and trachea

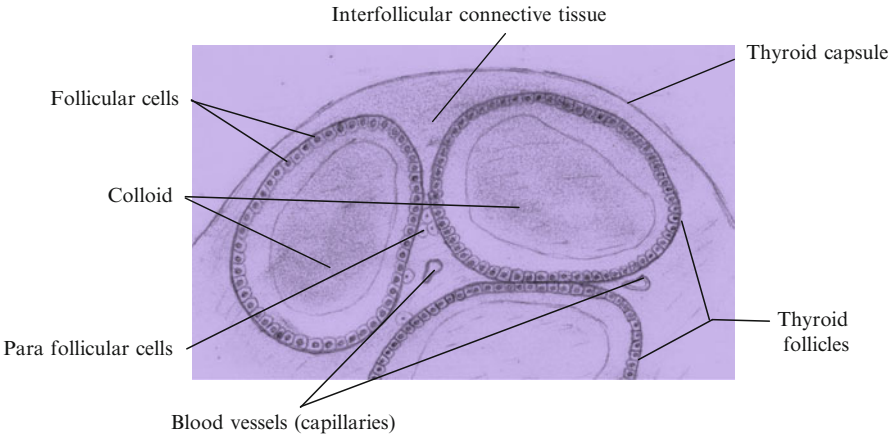

Fig. 5.23 An illustration showing the microscopic histological structures of thyroid gland

by the lateral suspensory (Berry) ligaments. It is butterfly shaped, has of two oblong lobes lying on either side of the trachea and connected by a narrow band of tissue called the isthmus. In normal adults the thyroid gland weighs 10–15 g. The thyroid gland is surrounded by a firmly attached true capsule, which is thin and adheres closely to the gland. This capsule may extend within the substance of the gland to form numerous septae, which divide the gland into lobes and lobules [15].

5.7.1.2 Microscopic Anatomy of Thyroid Gland

The microscopic structure of the thyroid is unique. The lobes of the gland, as well as the isthmus, contain many small globular sacs called follicles (Fig. 5.23). Each lobe may have 20–30 follicles. The follicles are lined with follicular cells and are filled with a fluid known as colloid. This colloid contains an iodinated glycoprotein, iodothyroglobulin, a precursor of thyroid hormones. Follicles vary in size, depending on the degree of distention, and they are surrounded by dense plexuses of fenestrated capillaries, lymphatic vessels, and sympathetic nerves. Between these follicles lie the arafollicular cells or C-cells.

Thyroid epithelial cells are responsible for synthesis of thyroid hormones (thyroxine three and four).

5.7.1.3 Vascular Supply and Innervation

Thyroid gland receives its arterial supply from the superior and inferior thyroid arteries. The superior thyroid artery is the first anterior branch of the external carotid artery.

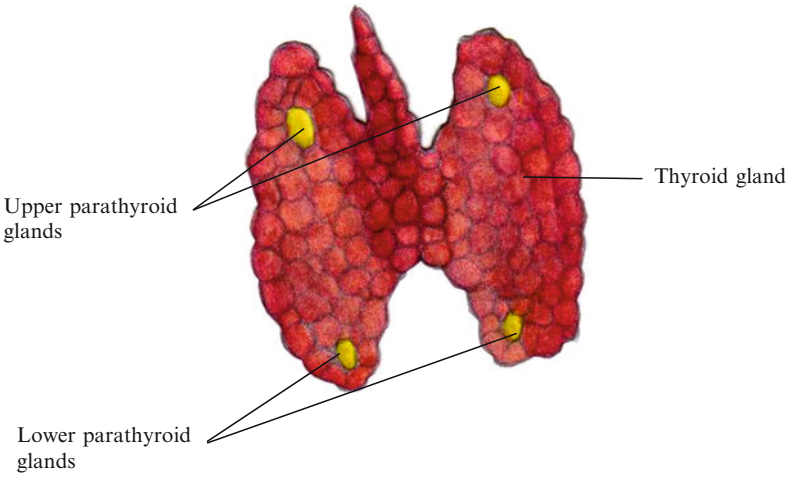

Fig. 5.24 An illustration showing the posterior view of thyroid gland and parathyriod glands

Three pairs of veins provide venous drainage for the thyroid gland. These are the superior thyroid vein, the middle thyroid vein, and the inferior thyroid vein.

Lymphatic drainage of the thyroid gland is via pretracheal, paratracheal, prelaryngeal lymph nodes.

The autonomic nervous system is the source of innervation of the thyroid gland. Parasympathetic fibers come from the Vagus nerves, and sympathetic fibers are distributed from the superior, middle, and inferior ganglia of the sympathetic trunk. These small nerves enter the gland along with the blood vessels.

5.7.2 Parathyroid Glands

5.7.2.1 Gross Anatomy

The parathyroid glands are small endocrine glands in the neck that produce the parathyroid hormone. There is usually 4–8 parathyroid glands located on the posterior surface of the thyroid gland (Fig. 5.24), or, in rare cases, within the thyroid gland itself. Parathyroid glands control the calcium level in the blood and within the bones.

The parathyroid gland size is about the size of a grain of rice. It usually weighs between 25 and 40 mg. The parathyroid glands are named for their proximity to the thyroid but its function is completely different from that of the thyroid. The parathyroid glands are quite easily recognizable from the thyroid as they have densely packed cells, in contrast with the follicular structure of the thyroid. However, at surgery, they are harder to differentiate from the thyroid tissue or fat tissue.

5.7.2.2 Microscopic Anatomy of Parathyroid Glands

On the histological level, they distinguish themselves from the thyroid gland, as they contain two types of cells: parathyroid main cells which are more in number, smaller in size and darker in color. Their function is production of the parathyroid hormone (calcitonin) which plays a role maintain the normal calcium level in blood. The second type of cells is oxyphil cells which are fewer in number, lighter in color and larger in size. The main function of the oxyphil cells is to provide support for the principle cells. Also provide a reserve supply of parathyroid hormone

5.7.2.3 Vascular Supply and Innervation

Blood supply and venous drainage to the parathyroid glands are basically that of the thyroid glands.

Innervation of the parathyroid glands varies from the thyroid glands. The Vagus nerve provides the pharyngeal branches so that the neurons reach the parathyroid glands. Neurons from the cervical sympathetic ganglia also are driven to the parathyroid glands.

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Chapter 6
Screening and Patient Examination

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Contents

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Abstract Cancer of the head and neck including the oral cavity remains among the top ten malignancies in the US and worldwide. Among these cancers squamous cell carcinoma originating from the surface epithelium is responsible for over 90% of the malignancies diagnosed in this region. Significant advances in the treatment of these malignancies over the last several decades have not been matched by improvement in survival. The main reason for this failure to improve on outcomes in head and neck and oral cavity cancers is delay in diagnosis. Late diagnosis means advanced stage disease often with presence of regional and even distant metastasis that negatively impact on survival. This disturbing fact maybe difficult to understand and explain given the accessibility of the region that makes it amenable to frequent inexpensive and non invasive examinations by health care providers. The importance of a detailed systematic thorough clinical examination of the head, neck and oral cavity cannot thus be emphasized enough. It is the goal of this chapter to provide a comprehensive review of a detailed clinical examination along with an up to date review of the available adjunct diagnostic aids. In addition guidelines for screening high risk population along with follow up schemas for those diagnosed with head, neck and oral cavity cancers will be provided based on the currently available "evidence based" information.

Keywords Head and neck screening • Endoscopy

Abbreviations

CN	Cranial Nerve
SCM	Sternocleidomastoid
OPLs	Oropharyngeal Lesions
GI	Gastrointestinal
IR	Incidence Ratio
ADA	American Dental Association
OSCC	Oral Squamous Cell Carcinoma
FVL	Fluorescence Visualization
FOB	Fiberoptic Bronchoscope

6.1 Basic Head and Neck Examination

6.1.1 Extraoral Examination

The head and neck examination should be performed with the patient seated in a comfortable position with the head held upright and still. Facial features (eyelids, eyebrows, palpebral fissures, lips, nasolabial folds) should be examined for shape

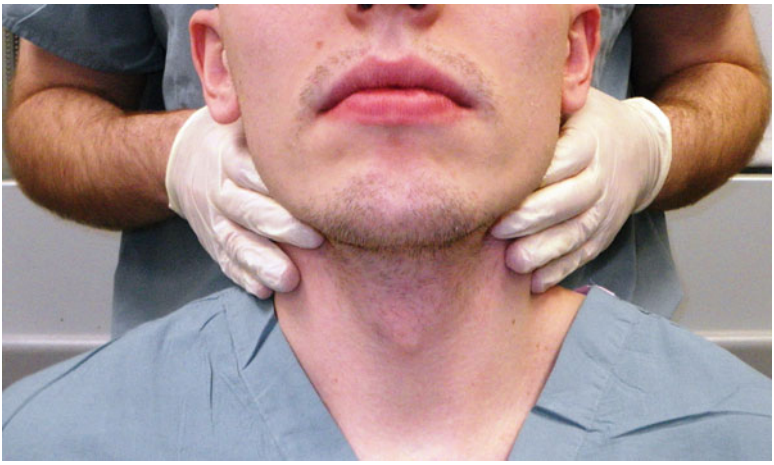

Fig. 6.1 Cervical Lymph Node examination anterior neck

for the general examination purposes and presence of lesions, masses and symmetry at rest, during function and expressions when screening for head and neck cancer purposes. In addition to evaluation for obvious or identifiable lesions or abnormalities the detailed clinical examination includes examination of the 12 cranial nerves (CN I–XII). The details of cranial nerve clinical examination are beyond the scope of this chapter but certain CN dysfunction may be elicited during the extraoral and/or intraoral examinations and require further attention as this may be associated with occult disease processes. This will be mentioned when appropriate in the contents of each examination. The clinician needs to be reminded that advanced stage skin cancers of the scalp and face are often associated with neurologic findings (usually cranial nerves seven or five dysfunction) as are salivary gland malignancies (most commonly parotid tumors) and may even present with lymph node involvement [1].

Head and neck examination starts with inspection and palpation of the face and neck with emphasis on examination of the cervical lymph nodes, sternocleidomastoid (SCM) and trapezius muscles, alignment of the trachea, palpation of thyroid and cricoid cartilages, hyoid bone, thyroid, parotid and submandibular glands. The neck examination is best performed by standing behind the patient and using simultaneously with both hands evaluate for differences between the two sides (Fig. 6.1). A systematic examination of the cervical lymph nodes starts with the submental and submandibular nodes (levels Ia and Ib respectively) by palpation of the neck under the inferior border of the mandible to the hyoid bone. Asking the patient to gently tilt the head towards the side been palpated allows for easier palpation in some individuals and those with thick necks (Fig. 6.2). It is not uncommon to identify mildly enlarged lymph nodes in this region, 1–1.5 cm that when soft, freely movable and not tender, usually require no further investigation other than follow up. The superficial and deep jugular chain lymph nodes (levels II–IV) are examined then by

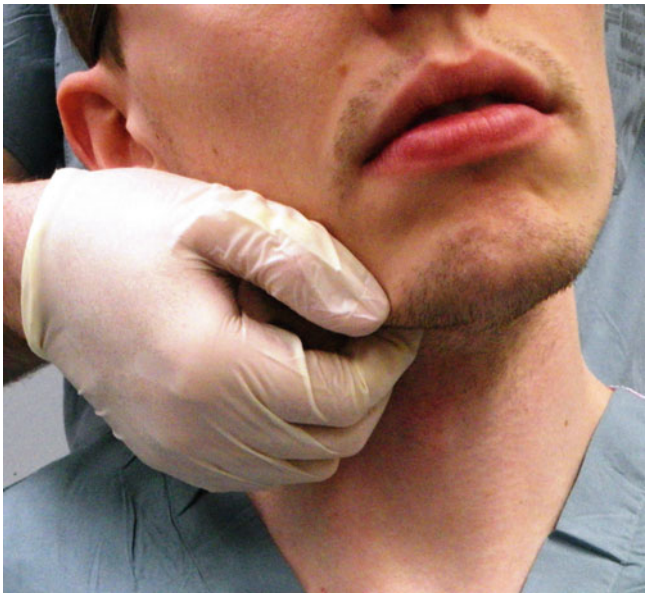

Fig. 6.2 Cervical Lymph Node examination level Ib –submandibular region

palpating the neck deep to the anterior border of SCM from its attachment at the mastoid process to the clavicle (Fig. 6.3). In addition to the lymph nodes the great vessels are palpated here as well. The clinician is cautioned when palpating this region in older patients with atherosclerotic disease as aggressive manipulation may risk atherosclerotic plaque dislodgment and not to mistaken the carotid bulb for a pathologic mass. The patient's head may be gently tilted down and away from the side that is been palpated for more effective examination. The posterior triangle of the neck between the posterior border of the SCM, anterior border of the trapezius muscle and the clavicle that contains the level V lymph nodes is palpated next. Finally the thyroid gland and peritrachea (level VI) lymph nodes are examined. Palpation of the thyroid gland requires gentle touch as often nodules and asymmetries can be missed if someone presses too hard (Fig. 6.4). The mobility of the hyoid bone, thyroid and cricoid cartilages can be evaluated during swallowing and by gentle manipulation with the thumb and index fingers while standing in front of the patient [1–3].

Abnormally enlarged lymph nodes, glands or masses should be further examined for consistency (firm or soft), associated symptoms upon palpation (painful or painless), mobility in relation to overlying skin and underlying structures (fixed or freely movable). The eyes, ears, nose and paranasal sinuses should be inspected for lesions as well as for potential direct involvement from advanced adjacent skin or oral cavity or nasopharyngeal cancers. Detailed examination of these organs is outside the scope of this chapter and can be found in physical diagnosis textbooks [2, 4, 5].

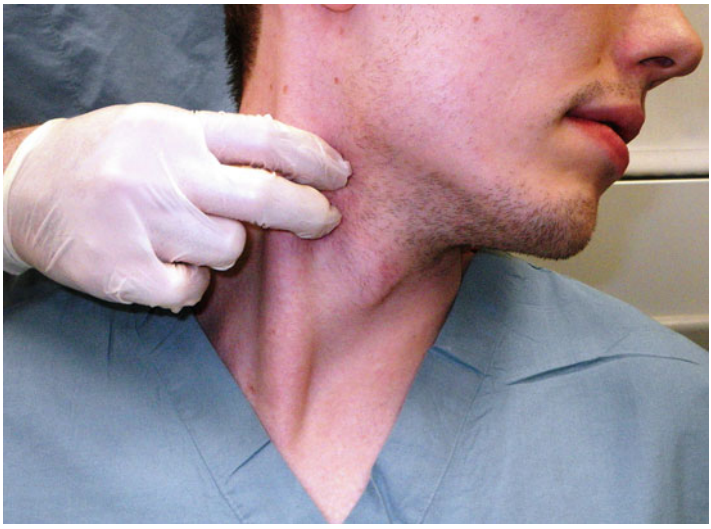

Fig. 6.3 Cervical Lymph Node examination lateral neck

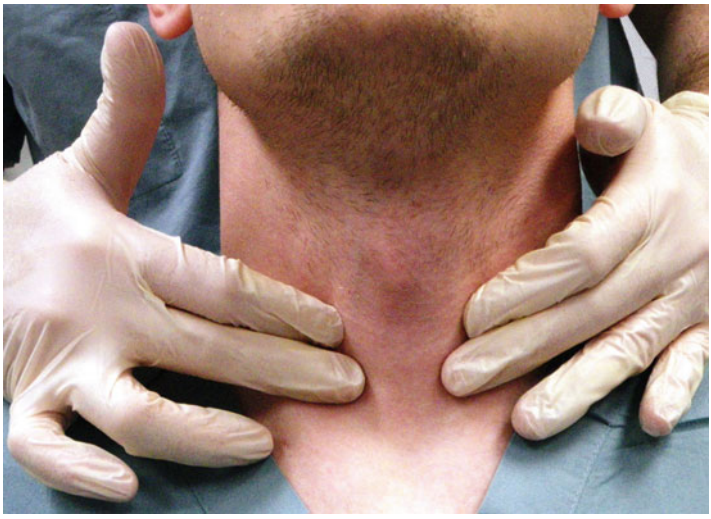

Fig. 6.4 Palpation of the thyroid gland

6.1.2 Intraoral Examination

A systematic approach to the intraoral examination involves inspection and palpation of the entire oral cavity starting at the lips and progressing in an organized fashion towards the oropharynx. Utilization of a good external light source, a dental mirror and gauze are paramount for access and effective visualization of all regions.

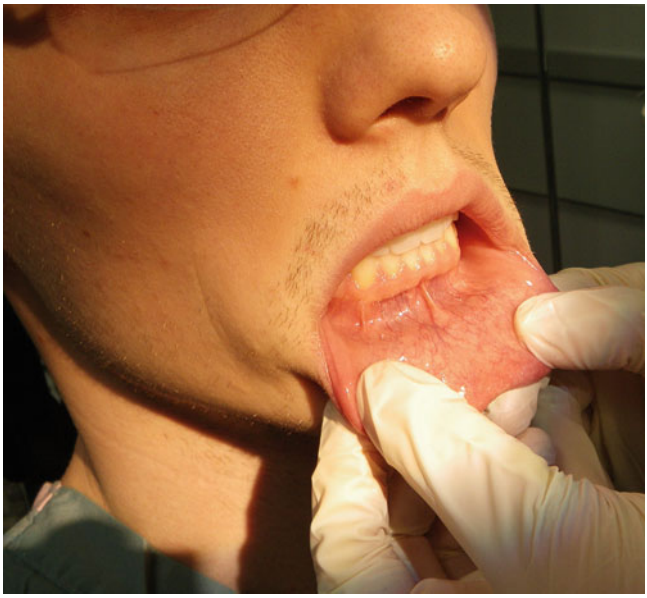

Fig. 6.5 Examination of the mucosa of the lower lip

Any removable dental appliances should be removed prior to examination. The clinical examination of the oral cavity for cancer screening purposes should focus on identification of mucosal surface textural or color irregularities, presence of growths, ulcerations and submucosal masses as well as evaluation of tongue and soft palate mobility and tonsillar and pharyngeal arches symmetry. The external surface and vermillion of the lips are examined first, then each lip is everted and retracted so that the maxillary and mandibular vestibles along with the buccal mucosa can be visualized next (Figs. 6.5 and 6.6). With the mouth open the hard and soft palate, tonsillar pillars, dorsal surface of the tongue can be directly visualized and palpated. Any symmetry of the tonsils in adult patients requires further investigation especially in high risk population [6].

Inability to open the mouth too wide could be normal for some patients, but true restriction, inability to open the mouth more than 10–15 mm, known as trismus, is a pathologic finding most commonly associate with advanced disease (cancers involving the muscles of mastication or invading the masticatory spaces) and requires further investigation that involves additional examination means and imaging. The patient is asked to say "ah" so the soft palate elevates to reveal the posterior oropharyngeal wall mucosa for visual inspection while the symmetry of the soft palate upon elevation is examined and function of the vagus and glossopharyngeal nerves is evaluated (Fig. 6.7). The patient is then asked to protrude the tongue and move it from side to side, then touch the roof of the mouth and the skin of the lower lip in order to evaluate the ventral surface as well as any restrictions in tongue mobility (Figs. 6.8, 6.9 and 6.10). This maneuver will further reveal any dysfunctions

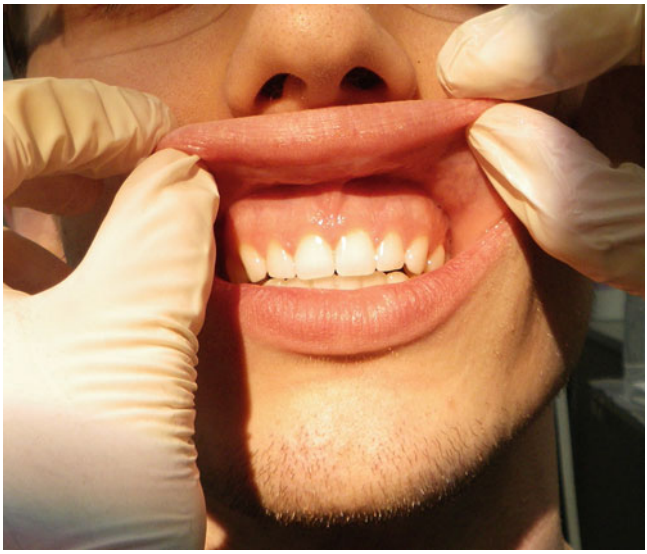

Fig. 6.6 Examination of the mucosa of the upper lip

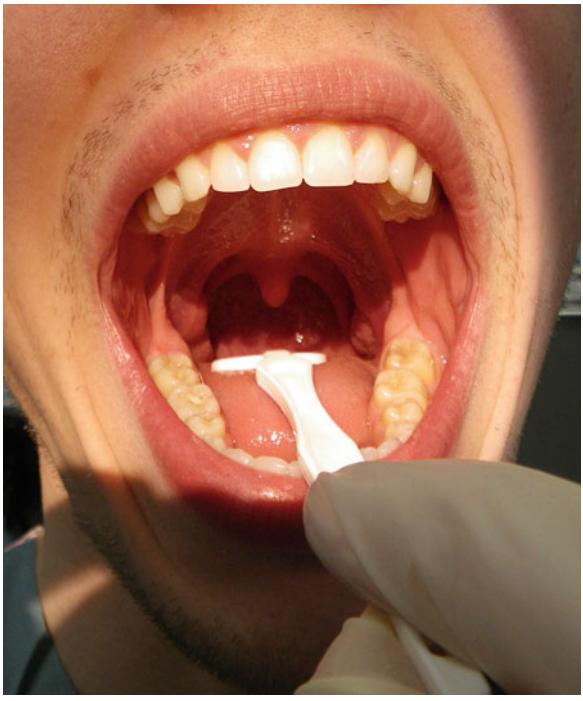

Fig. 6.7 Direct examination of the oropharynx

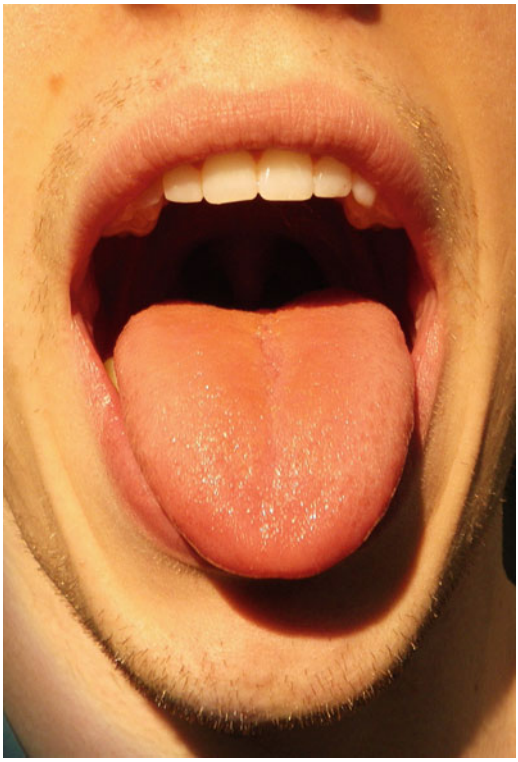

Fig. 6.8 Assessment of tongue mobility during protrusion

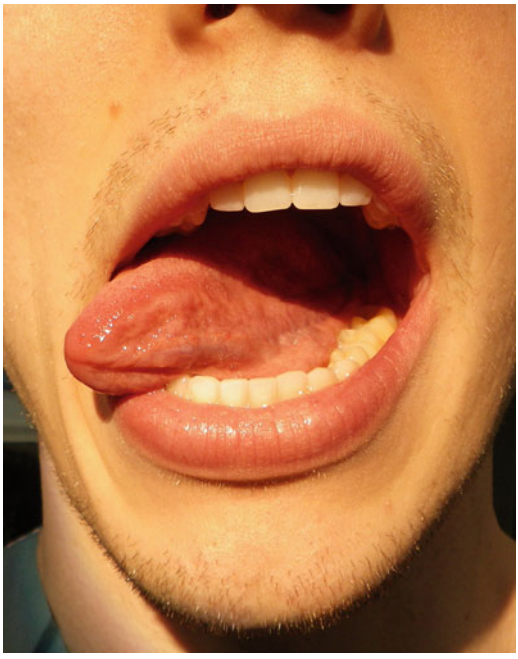

Fig. 6.9 Assessment of tongue mobility during lateral movement

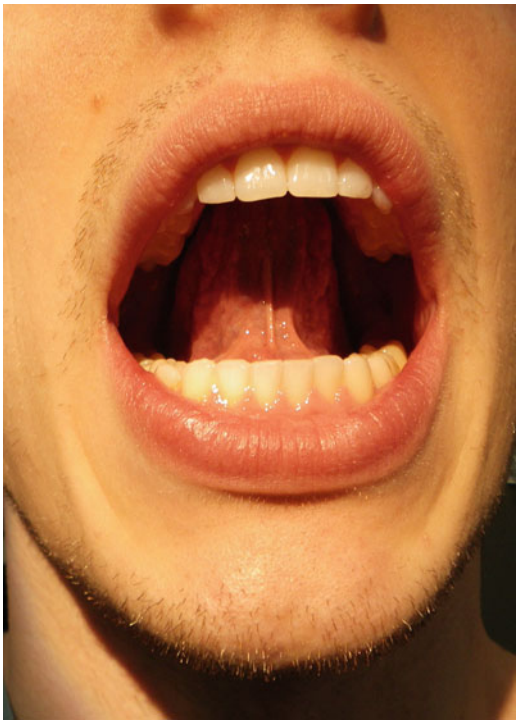

Fig. 6.10 Assessment of tongue mobility and ventral surface

of the hypoglossal nerve as asymmetric tongue protrusion or inability to move the tongue implies nerve impairment, when mechanical limitation from mass effect is excluded. Then the tongue is retracted with the use of gauze so the lateral aspects of it and the adjacent floor of mouth can be visualized and inspected (Fig. 6.11). The dental mirror is used at this point to visualize the lingual aspects of the gingiva as well as the base of the tongue (Fig. 6.12). In addition to visualization and inspection, palpation of the lips, vestibles, buccal mucosa and oral tongue is performed next. Bimanual palpation, through the ipsilateral floor of the mouth and skin, of the sublingual and submandibular glands follows along with examination of the orifices and saliva flow from Stenson's and Wharton's ducts. Palpation of the base of the tongue is the last task to be performed as it may cause severe gauge reflex, may not be possible for all patients and may prevent completion of the remaining of the examination if attempted early on during this process. Gag reflex examination is important for evaluation of the functionality of the vagus and glossopharyngeal nerves and should be done at the completion of the intraoral examination and after informing the patient. This is done by gently touching the soft palate or the base of the tongue or the posterior pharyngeal wall, based on patient's tolerability, with the dental mirror or a tongue depressor. This maneuver will elicit a gag reflex in all patients with intact CN XI and XII [1, 3, 5].

Once an abnormality is identified the need for further interrogation for establishment of a diagnosis should be considered and is based on several criteria that include

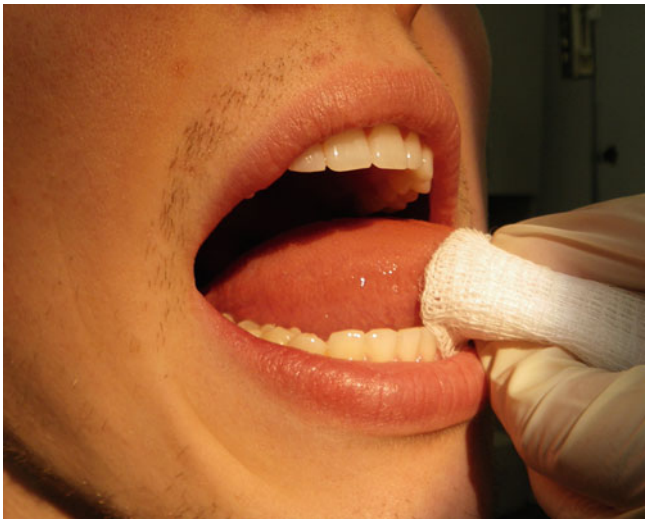

Fig. 6.11 Examination of the lateral surface of the tongue

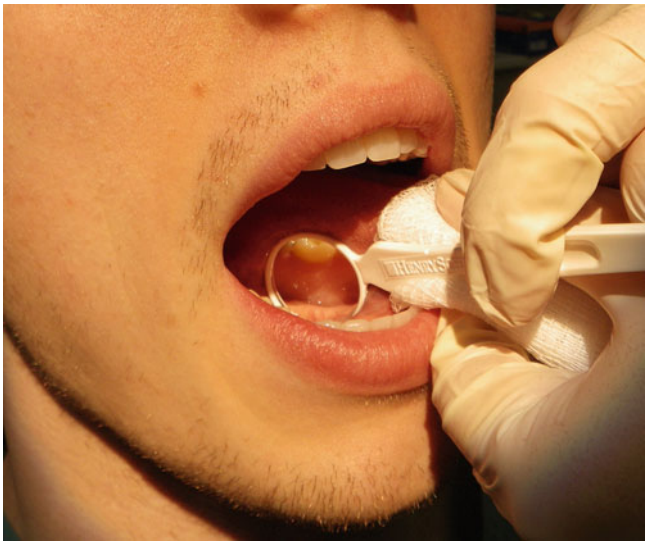

Fig. 6.12 Indirect examination of the lingual mucosa of the mandible

the lesion's location, duration, characteristics, associated symptomatology or lack of as well as patient's risk factors. The guidelines for further investigation of a pathologic finding, ultimately involving tissue sampling for definitive diagnosis, are well established and extensively covered in several well written head, neck and oral pathology textbooks and are not the focus of this chapter [6, 7].

Although conventional clinical examination is the mainstay of screening for oral cancer, its actually utility remains unclear as studies have shown controversial results in regards to detection of premalignant lesions and early cancers. Yearly cancer related checkups are recommended by the American Cancer Society may allow for identification of early lesions by dental and primary health care providers. Interestingly though in a recent study only about 13% of Americans report receiving an oral examination and the knowledge of the COE process has been questionable among physicians [8]. Systemic reviews of seven studies evaluating COE as a method for detecting early cancerous lesions, sensitivity ranging from 60 to 97% and specificity ranging from 75 to 99% were reported, which are comparable to rates found in other cancer screening programs [8–12]. This suggests that COE may be an adequate screening method to identify oral lesions. Shortcomings of this method include the inability to detect sub-clinical abnormalities or discriminate between benign lesions and those with a high-risk of malignancy which may require the use of adjunctive diagnostic techniques. Further, the effectiveness of COE screening to reduce disease-related mortality remains to be determined.

6.1.3 Adjuncts to Screening and Examination

The limitations of conventional oral examination and histopathology of OPLs has spurred the development of diagnostic aids and adjunctive techniques to enhance early detection of oral cancer. The clinical role for these adjuncts includes screening for evidence of occult disease or abnormal changes and assessment of the biologic potential in clinically apparent lesions. The easy accessibility to the oral cavity permits the use of relatively non-invasive procedures, such as *in vivo* light-based methods to enhance visualization of abnormal mucosa or brush cytology.

Brush cytology is a noninvasive method to obtain epithelial cells from accessible tissue surfaces such as the oral and cervical mucosa (and potentially the GI and respiratory tract). In its most refined form, a cytology brush, with a 2-cm brush consisting of densely packed 2-mm bristles, is used to obtain approximately 1,000,000 epithelial cells including supra basal nucleated epithelial cells and a minority of inflammatory cells from the mucosa . There are no fibroblasts present unless an ulcer is sampled. Brush cytology actively removes cells from the mucosa, unlike exfoliated cell collection which relies on vigorous swishing of the mouth to dislodge superficial sloughing cells. Over the last 30 years the acquisition of cervical mucosal cells by brush cytology and similar non-surgical methods has become standard clinical practice for the preventive screening for cervical carcinoma. After transfer to microscope slides, the cells are stained with various DNA stains, such as the Papinicolaou stain. Histomorphometric analysis is used to determine if premalignant or malignant changes have occurred, such as an increase in nuclear cytoplasmic ratio and aberrant chromatic nuclear staining [13]. A positive finding is followed up by a surgical biopsy. Pap smear screening has been credited with a significant reduction in the rate of cervical cancer incidence in the United States.

The OralCDx system is one method using a brush to collect cells from the oral mucosa of a suspicious lesion, followed up by automated histomorphometric analysis of stained oral cytology smears to determine if a surgical biopsy is required [14]. This approach to oral cancer detection was an advantage over earlier methods in that it relies on computerized assisted analysis to evaluate the malignant state of the stained cells [15]. Still, after several years of usage, the accuracy of this test is not clear especially in early or premalignant lesions. Unfortunately in some of the largest studies of its utility as a screening tool, lesions that tested negative by OralCDx were not routinely confirmed by biopsy, making the true sensitivity of this tool unknown [16–19]. While brush oral cytology, coupled with cell staining, may not fulfill its promise of making screening practical, it is a step in the right direction [20, 21]. Oral cytology cell can be stained to specifically measure changes in poidy to aid in diagnosis [22–24]. Both mutations and epigenetic changes such as promoter hypermethylation can be detected in DNA of cells obtained through tissue biopsy, brush cytology, or exfoliated cells [22–26]. These changes have been well documented with OSCC in tissue obtained by surgical biopsy and, as expected, the approach has shown some success in identifying malignancies.

6.2 Light Based Detection Systems

6.2.1 ViziLite® - Chemiluminescent Device

The ViziLite® device (Zila Pharmaceuticals, Phoenix, AZ) is a system proposed for visualization of oral lesions that involves an oral rinse with 1% acetic acid for 1 min followed by visual examination under chemiluminescent light. Acetic acid in theory improves visibility because it removes the glycoprotein barrier, dehydrates the oral mucosa so neoplastic cells that demonstrate a high nuclear/cytoplasmic ratio and density reflect more light than normal mucosa and appear "acetonwhite." This effect is enhanced when visualized under chemiluminescent light at 490–510 nm wavelengths [27–29]. Literature reporting the efficacy of ViziLite® in detecting oral malignant and pre-malignant lesions and the benefit of this method over current techniques is limited [27–30]. In the study by Ram et al. it was suggested that ViziLite® is superior to toluidine blue for detection of OSCC and epithelial dysplasia and the reported sensitivity was 100%. However, ViziLite® generated a high false-positive rate and demonstrated low specificity (only 14%) as it failed to differentiate benign conditions showing excessive keratinization and/or inflammation. This harbors the risk of unnecessary biopsies [28]. In their study Huber et al. reported the identification of one subclinical lesion with ViziLite® "acetowhite" positive results, verified as atypical using the OralCDx system, suggesting possible utility in detection of occult epithelial abnormalities [31]. The clinical value and widespread acceptance of the ViziLite® system to enhance standard visual examination remains to be determined.

6.2.2 *VELscope® - Autofluorescence Visualization*

The VELscope® (LED Dental Inc. Vancouver, British Columbia, Canada) is an FDA cleared hand-held device for the direct visualization of tissue fluorescence in the oral cavity. Tissue autofluorescence is produced by naturally occurring fluorophores present in epithelial cells or tissue matrix after excitation at suitable wavelengths of light, typically in the ultra violet to blue light range (<450 nm). Cell or matrix constituents contributing to autofluorescence include collagen, elastin, keratin, reduced nicotinamide adenine dinucleotide (NADH), flavins (FAD^+, FMN, and riboflavin) and aromatic amino acids (tryptophan, tyrosine, and phenylalanine). Autofluorescence emitted by these endogenous fluorophores is subjected to absorption and scattering events in the tissue prior to detection or visualization, which alters the measurable autofluorescence profile. Under diseased conditions, fluorophore concentrations as well as the light scattering and absorption properties of the tissue are altered due to a variety of changes in cell metabolism, blood supply, and tissue architecture (e.g. nuclear size distribution, collagen 25 content, and thickness of the epithelium). Analysis of tissue autofluorescence has been utilized to detect cancers of the lung, bladder, gastrointestinal tract, colon, cervix, and head and neck [30, 32–37].

The VELscope® utilizes blue excitation light (400–460 nm) to excite endogenous green-red fluorophores present in oral epithelium whose emission in the visible range (>475 nm) can be detected by the unaided human eye. Fluorescence visualization loss (FVL), or a decrease in visible autofluorescence in this wavelength range, is found in high-risk oral premalignant lesions and SCC. In a clinical study examining 50 oral lesions, using histology as the diagnostic standard, the device exhibited a sensitivity of 98% and specificity of 100% when discriminating normal mucosa from high-risk premalignancy (severe dysplasia/CIS) or invasive carcinoma. In addition, the VELscope® optical device has demonstrated potential for detection of occult oral lesions in patients previously treated for OSCC to identify second primary and recurrent tumors, as well as assessment of tumor margins to aid surgical excision [32–37].

Excellent critical reviews on the available adjuncts to clinical examination for detection of oral malignant and premalignant lesions can be found in the recently published work by Lingen et al. and Patton et al. [38–40]

6.3 Endoscopy

6.3.1 *Laryngoscopy*

Laryngoscopy: Examination of the internal laryngeal structures is not possible with conventional clinical examination and requires utilization of special equipment: flexible or rigid endoscopes. Laryngeal endoscopy is used to examine the vocal fold

Fig. 6.13 Rigid endoscopes

structure and gross function. Further details of vocal cord vibration patters and qualification of vibration patters can be examined with videostroboscopy, or high speed digital imaging. The later modalities are beyond the scope of this chapter and details can be found in textbooks specifically devoted to these types of examinations.

Endoscopy can be performed either under general anesthesia in the operating room which provides for a complete detailed examination in addition to the ability to obtain biopsies if deemed necessary or under topical anesthesia. Rigid scopes are usually 70 or 90° and have the advantage of high resolution with bright, clear pictures. The combinations of large selection of viewing angles and excellent contrast with accurate magnification of structures are the main advantages of this examination (Fig. 6.13). Phonation though with rigid endoscopy is limited to sustained vowels, most commonly "ee". The laryngeal structures examined are the valleculae, pyriform sinus, epiglottis, aryepiglottic folds, ventricular folds and posterior glottis rim. The examination is performed in the following order: at rest and deep breathing, easy cough or throat clear followed by laryngeal diadochokinesis ("ee" and "hee"). Arytenoid and vocal fold motion is examined so the integrity of the cricoarytenoid joint and recurrent laryngeal nerve is assessed [41].

The patient is bending slightly forward from the hips while maintaining a straight back. With the neck and chin extended and the tongue protruded the examiner passes the 70° scope just under the uvula and advances it until the epiglottis is visualized. When the patient sustains an "ee" the epiglottis moves anteriorly and the vocal folds can be visualized. When the 90° scope is used there is no need for the patient to bend forward of extend the neck [41].

When the procedure is performed under general anesthesia the patient is in the supine position the examination can be combined with other procedures namely biopsy or laser ablation, and addition areas such as the anterior commissure maybe be visualized. Over ten different types of laryngoscopes are available and used for

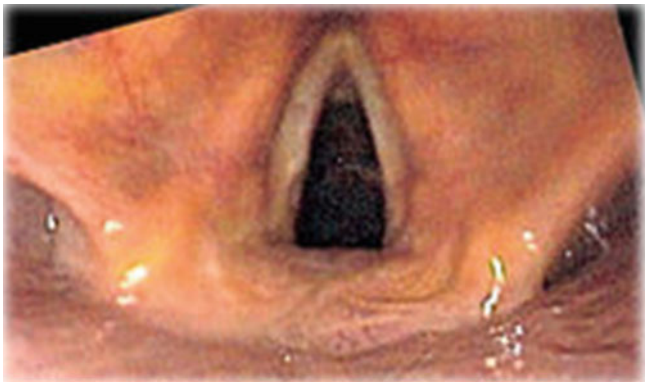

Fig. 6.14 Glottic opening image during endoscopy

different procedures by otolaryngologists. The procedure is as follows: a dental guard is used to protect the upper dentition and the patient's mouth is opened using the right hand. The laryngoscope held with the left hand is inserted from the right side of the mouth and is swiped to the left directing the blade in an outward and upward direction so the tongue is moved out of the way. The scope is then moved from right to left so the entire base of the tongue, valleculae and ventral surface of the epiglottis can be examined. Then the tip of the epiglottis is elevated so the vocal folds, anterior commissure and dorsal surface of the epiglottis ad entire glottic opening can be examined (Fig. 6.14) [41].

Another method of examination of the laryngeal structures that allows for dynamic examination of the larynx is with flexible endoscopes. The procedure can be performed under topical anesthesia of the nasal cavity with vasoconstriction and the scope can be advanced either through the inferior or middle meatus of the nose. The primary disadvantage of flexible endoscopy is that light transport and magnification of the image is inferior to those of rigid endoscopy and there is distortion of the periphery of the image [41]. Examination of the nasopharynx, oropharynx, base of tongue, pre-epiglottic space, valleculae, pyriform sinuses, vocal folds at rest and upon phonation is achieved with flexible scopes [6].

6.3.2 Tracheobronchial Endoscopy

Tracheobronchial Endoscopy is minimally invasive procedure that can be used for diagnostic evaluation or intervention. A flexible fiberoptic bronchoscope (FOB) can be used to evaluate voice changes, hoarseness, or chronic non-resolving or worsening cough, wheezing or hemoptysis as well as assist with intubation, for removal of foreign body. More importantly though a detailed thorough examination of the airway mucosa and tissue biopsy can only be achieved with tracheobronchial endoscopy.

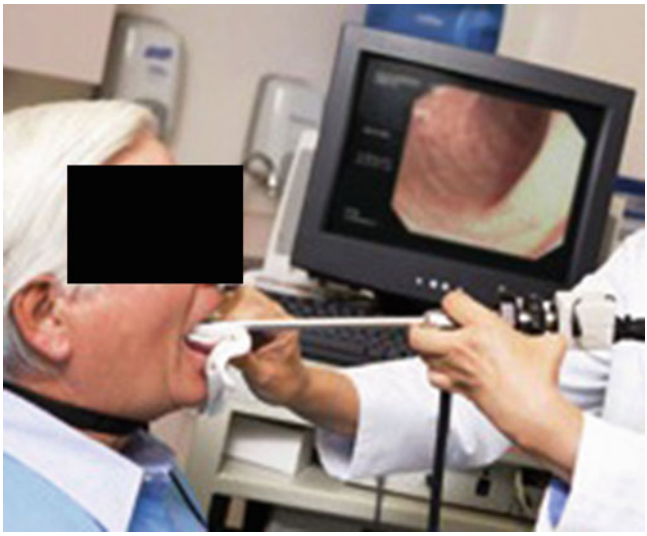

Fig. 6.15 Office setting indirect examination with rigid scope

The diagnostic yield of the procedure is regarded high; however it varies considerably depending on the indications and techniques used during the procedure [42–45]. Although the examination can at least in theory be performed under topical anesthesia, intravenous sedation or general anesthesia allow for superior access and make the procedure easier for the patient [46–48].

A FOB or a rigid bronchoscope can be used for examination of the airway structures. A flexible bronchoscope is longer and thinner than a rigid bronchoscope. It contains a fiber optic system that transmits an image from the tip of the instrument to an eyepiece or video camera at the opposite end. Using Bowden cables connected to a lever at the hand piece, the tip of the instrument can be oriented, allowing the practitioner to navigate the instrument into individual lobe or segment bronchi. Most flexible bronchoscopes also include a channel for suctioning or instrumentation, but these are significantly smaller than those in a rigid bronchoscope. Flexible bronchoscopy causes less discomfort for the patient than rigid bronchoscopy and the procedure can be performed easily and safely under moderate sedation. It is the technique of choice nowadays for most bronchoscopic procedures [49] (Fig. 6.15).

When the FOB is used the patient is placed in sitting or supine position and the bronchoscopist is positioned at the head of the bed in front of the patient. The nasal route maybe preferred as it tolerated easier it causes less gag reflex in the non-intubated patient and the nasopharynx can be examined as well. After adequate anesthesia, vasoconstriction and administration of medications to suppress cough and minimize secretions the scope is advanced through the nasopharynx, oropharynx towards the laryngeal opening in the manner described earlier for laryngoscopy purposes. After advancing the scope through the vocal cords the bronchial segments can be examined then in orderly systematic fashion keeping in mind the

regional anatomy. It is expected for the patient to experience an urge to cough when the scope is advanced through the cords and further advancement should be held at this point to allow for the patient to relax and catch their breath prior to continuing [50].

The rigid bronchoscope has a larger lumen than the narrow lumen of the flexible bronchoscope and allows for therapeutic approaches such as electrocautery to help control bleeding, forceps for biopsy purposes or for foreign body retrieval [49]. Rigid endoscopy is performed under general anesthesia and ventilation is usually through the scope. After introducing the instrument, the epiglottis is gently lifted with the end of the bronchoscope, after which the larynx and vocal cords can be seen. Once the vocal cords have been visualized, the bronchoscope is turned 90° vertically in order to pass through the vocal cords. This offers the least resistance and avoids damage to the vocal cords. After entering the upper trachea, the bronchoscope is turned back to its original neutral position. Ventilation is initiated via the side port. The bronchoscope is gently advanced toward the carina, and systematically inserted into each mainstem bronchus. Anatomic, airway, and mucosal abnormalities are noted. Telescopes may be inserted into the rigid bronchoscope to visualize the distal segments, requiring the angled 30° and 90° scopes to see particularly the right upper lobe orifice. The head is usually turned to the left to enter into the right mainstem bronchus, and turned to the right to enter into the left mainstream bronchus. Once the preliminary examination is completed, the purpose for which the procedure was performed should be addressed (*eg,* dilation, stent insertion, laser ablation, extraction of foreign bodies). Cautery, forceps, and suction should be readily available. If a more detailed examination, washings, laser/photodynamic ablation, or stent insertion is required, a flexible bronchoscope can be inserted through the rigid bronchoscope [51, 52].

6.4 Guidelines for Screening and Follow Up

Despite the overall decrease of incidence ratio (IR) of oral and oropharyngeal cancers, the IR of cancers of the oral tongue, oropharynx and tonsil is increasing. Even more importantly the age adjusted IR of oral and oropharyngeal cancer in the US between 2002 and 2006 was found to be more than twice as high among men as among women (15.9 versus 6.0) as was the mortality rate (4.0 versus 1.5). Unfortunately and despite these findings no standards exists regarding screening for oral cancer or evaluation for recurrence after cancer treatment [53]. In 2010 a panel convened by the American Dental Association (ADA) Council on Scientific Affairs developed a report to address recommendations regarding screening for oral squamous cell carcinoma and the use of adjunctive screening aids to visualize and detect potentially malignant as well l as malignant oral mucosal lesions. After review of 332 systematic reviews and 1,499 recent clinical studies the panel selected five systematic reviews and four studies to use for their recommendations. The panel concluded that insufficient evidence exists to support an evidence based

recommendation. Regardless of this and due to the significance of the disease process the panel provided their conclusions and recommendations [54].

At present no generally accepted protocols exist regarding follow up after cancer treatment. Patients are at risk for local regional recurrence or second primary cancer development during the first 1–3 years after successful treatment of head and neck cancer so clinicians offer follow up regiments based on this acceptance and mainly based on experience. If the patient remains cancer free after 5 years then an as needed follow up regiment can be established. On follow up cancer surveillance and monitoring is accomplished with the combination of clinical examination in addition to timely imaging and or endoscopy if indicated.

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Chapter 7
Benign Neoplasms of the Head and Neck

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Contents

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Abstract This chapter describes a new approach to developing a differential diagnosis, based on collating a lesion's tissue of origin and the disease process that is taking place. For the purposes of this approach, disease processes are categorized as Developmental, Allergic-Immune, Metabolic, Infectious, Environmental, or Neoplastic, yielding the mnemonic acronym DAMIEN. General characteristics of benign neoplasms and precancerous lesions are discussed. This is followed by a review of benign tumors that may occur at many different sites in the head and neck. This review is organized by tissue type and illustrated by clinical examples in many cases. Finally, there is a discussion of benign neoplasms that are specific to various anatomical sites.

Keywords Neoplasia • Dysplasia • Differential diagnosis • Benign pathology • Head and neck

Abbreviations

CGCG	Central Giant Cell Granuloma
CIS	Carcinoma in situ
CNS	Central nervous system
COF	Central Odontogenic Fibroma
CT	Computed tomography
DAMIEN	**D**evelopmental **A**llergic/Immune, **M**etabolic, **I**nfectious, **E**nvironmental, or **N**eoplastic
FD	Fibrous Dysplasia
H&E	Hematoxylin and eosin stain
HHV	Human Herpesvirus
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
KCOT	Keratocystic Odontogenic Tumor (Odontogenic Keratocyst)
LCH	Langerhans Cell Histiocytosis
MEN	Multiple Endocrine Neoplasia
MRI	Molecular resonance imaging
OD	Osseous Dysplasia
OKC	Odontogenic Keratocyst (Keratocystic Odontogenic Tumor)
PA	Pleomorphic Adenoma
PGCG	Peripheral Giant Cell Granuloma
PVL	Proliferative Verrucous Leukoplakia
VHL	Von Hippel Lindau Syndrome
WHO	World Health Organization

7.1 The DAMIEN Approach to Differential Diagnosis

7.1.1 Formulating a Differential Diagnosis

When attempting to make a clinical diagnosis of an unusual mass, experienced clinicians quickly make conscious or subconscious reference to previous experiences, a process that may be called "pattern recognition" [1]. Less experienced clinicians may find a diagnostic algorithm useful in formulating a diagnostic hypothesis or clinical differential diagnosis. While a number of such algorithms have been put forth, we will base our current discussion on a system developed over the past decade by oral pathologist Sara Gordon, first author of this chapter, which collates the probable tissue of origin, and the probable disease process, forming a diagnostic matrix as shown in Fig. 7.1. For the purposes of forming a differential diagnosis, disease processes can be categorized as **D**evelopmental, **A**llergic/Immune, **M**etabolic, **I**nfectious, **E**nvironmental, or **N**eoplastic. Some diseases overlap these categories, as we shall explain in the case of neoplasms. We call this the DAMIEN method, because our disease processes form the acronym DAMIEN. The name is also an historical acknowledgement of Damien, the patron saint of healing, in recognition that excellent care must be based on accurate diagnosis. The philosophical roots of this approach are grounded in the work of Norman Wood and Paul Goaz. In their classic textbook "Differential Diagnosis Of Oral & Maxillofacial Lesions", they suggested a differential diagnosis technique based on the clinical characteristics of lesions [2].

7.1.2 Determining Tissue of Origin

Tissues of origin may include the following:

- **Surface tissues:** Epithelial cells and melanocytes.
- **Sub-surface tissues:** Glands; blood vessels; blood cells; fibrous, fatty, muscular, or neural soft connective tissue; bone, cartilage, or odontogenic tissues; and others.

Clinical examination will often suggest a general or specific tissue of origin. Characteristics of the lesion such as soft or hard texture, apparent encapsulation, color, and clinical history are aspects that can guide the clinician. For example, a bony hard mass is likely composed of bone or cartilage. Neural lesions may be situated over a foramen and often present with symptoms of neural dysfunction such as loss of motor function, loss of sensation, or stabbing pain. Vascular lesions are often red, may feel pulsatile, and can frequently be blanched with applied pressure, a technique called diascopy.

Wood and Goaz proposed that lesions caused by growth of surface tissues frequently present with a rough surface, reflecting that the surface is growing faster

	D Development	**A** Allergic - Autoimmune	**M** Metabolic	**I** Infectious (B, V, F)	**E** Environment	**N** Neoplastic (B, M)
ON SURFACE						
Squamous cells						
Melanocytes						
UNDER SURFACE - SOFT						
Salivary Glands						
Sebaceous Glands						
Blood vessels						
Blood cells						
Fibrous						
Nerve						
Fat						
Muscle						
UNDER SURFACE - HARD						
Bone						
Cartilage						
Odontogenic						
OTHER						

Fig. 7.1 Damien Approach. An initial approach to differential diagnosis of a difficult lesion can include determination of the probable disease process (*horizontal axis*) and tissue of origin (*vertical axis*)

than the underlying tissues. Lesions caused by growth of tissues underneath the surface are more likely to present as dome-shaped enlargements, and the depth of the lesion may be estimated by the acuity of the dome shape.

The tissue of origin may also be surmised from knowledge of underlying anatomy, using the “Circle Rule”, in which the tissue that would normally be present at

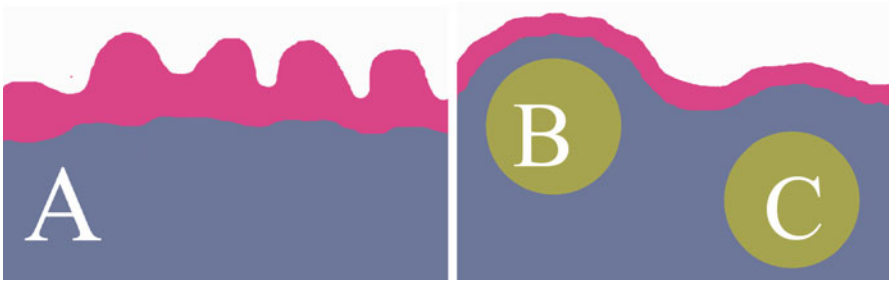

Fig. 7.2 Shape of Lesions. A rough mucosal lesion (*A*) is usually caused by an increase in the overlying epithelium, with no corresponding growth of the underlying tissues, causing the excess tissue to pile up on the surface. A growth located close to the surface, but in the connective tissue (*B*), will usually cause a smooth dome-shaped lesion. A growth located deeper in the connective tissue (*C*) causes a less acute rise in the surface of the mucosa. The tissue of origin may be estimated by turning the surface architectural change into an imaginary circle, and then visualizing what tissues would normally be present at the center of that circle (the Circle Rule). *Pink indicates* epithelium; *blue indicates* connective tissues

the epicenter of a spherical lesion is the most likely tissue of origin. These concepts are illustrated in Fig. 7.2.

7.1.3 Determining Disease Process

Developmental conditions may be congenital or acquired, but are determined by developmental processes, which may include genetic influences interacting with the environment. Once a developmental condition has developed, it tends to be stable. An example of a developmental condition of the head and neck is Cleft Palate.

Allergic/Immune conditions are mediated by the immune system, as the name suggests. These conditions often present with inflammation, and may represent hypersensitivity disorders or actual allergies. A common example of an allergic/immune condition in the oral cavity is Lichenoid Mucositis.

Metabolic conditions often have systemic effects. They can include hormonal or nutritional disorders. Two common examples of metabolic conditions with head and neck manifestations are Type 2 Diabetes Mellitus and Iron Deficiency Anemia.

Infectious conditions are familiar to everyone. The majority of dental disease, for example, is caused by infection. The most common infectious agents are bacteria, viruses, and fungi. Infectious conditions may be acute or chronic, and often display inflammation. Examples of common head and neck infections are Dental Caries (*Streptococcus mutans*), Herpes Labialis (*Human Herpesvirus Type 1)*, and Candidiasis (*Candida albicans*).

Environmental conditions are caused by a reaction to physical, chemical, thermal, electromagnetic, or other environmental stimuli. The clinician should search

the patient history for such a trigger. Characteristically, but not always, these conditions begin to resolve within 10 days when the stimulating environmental factor is removed. A common oral example is an ulcer on the lateral tongue caused by contact with a sharp tooth. However, some lesions persist after the stimulus is resolved; an example is a "Fibroma", focal fibrous hyperplasia caused by trauma.

Neoplastic lesions may be either benign or malignant, and are the focus of this chapter. Diseases classified as developmental, allergic/immune, metabolic, infectious, or environmental are the subject of the next chapter.

When a clinician considers both the most likely tissue of origin and disease process for a given lesion, this collation frequently suggests a potential diagnosis. For example, if a lesion seems to originate in salivary gland and appears to be a benign neoplasm, it would be reasonable to include various benign salivary gland tumors on the differential diagnosis. If a velvety red lesion on the lateral tongue does not appear to be caused by trauma or any other non-neoplastic cause, then a working diagnosis of epithelial dysplasia or early Squamous Cell Carcinoma may be appropriate.

7.1.4 Characteristics of Neoplasia

The US National Cancer Institute defines a **Neoplasm** as "an abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Neoplasms may be benign (not cancer), or malignant (cancer)" [3]. A neoplasm is regarded as a cell line that is monoclonal, or derived from one originating cell. This cell line developed the ability, through mutations, to undergo unregulated and independent growth free of normal external signaling. A benign neoplasm is capable of only localized growth, and is usually encapsulated or contained by a basement membrane. These characteristics generally make it freely moveable on palpation, and well circumscribed on imaging. A malignancy is a neoplasm that has also developed the ability to invade and metastasize, so it may feel indurated on palpation, indicating that it has invaded surrounding tissues. On imaging such as radiographs, it may appear poorly defined, also a reflection of its invasion of surrounding structures.

While this definition may seem straightforward in theory, the distinction clinically and pathologically between benign and malignant tumors is not always simple. For example, the benign odontogenic tumor, Ameloblastoma, has a high potential for recurrence and may be so destructive that it leads to considerable morbidity. Its destructive potential is similar to that of the malignant skin tumor Basal Cell Carcinoma, which like the Ameloblastoma rarely metastasizes but behaves in a locally aggressive manner. Other tumors may be benign, yet have the potential for malignant transformation, such as the benign salivary Pleomorphic Adenoma.

As will be discussed elsewhere, a patient may possibly be at increased risk of tumors because of a variety of influences. Germline genetic mutations (**D**evelopmental) are present in a number of familial cancer syndromes such as Li-Fraumeni syndrome, and may predispose the patient to cancers in multiple

organs. Prolonged inflammation (**A**llergic/Immune) may play a role in increased risk of malignancy associated with some conditions such as Lichen Planus. Some **M**etabolic derangements are known to increase the risk of specific malignancies, such as the association between hyperestrogenism and Endometrial Adenocarcinoma. Certain specific **I**nfections are associated with malignancy, including some Human Papillomaviruses (HPV), some Human Herpesviruses (HHV), HIV, and others. However, the most consistent observed etiology is **E**nvironmental. The most common environmental causes of neoplasia are tobacco, alcohol, betel nut (quid) use, and excessive sunshine exposure. Whatever the predisposing factors, a neoplasm is defined by its potential for unregulated cell replication.

7.2 Benign Neoplasms Common to Multiple Locations

Because many cell types occur in multiple anatomic locations within the head and neck, it is unsurprising that a variety of tumors of the head and neck can occur in any one of several different sites. For example, mucosa forms the surface of the aerodigestive tract so Squamous Cell Carcinoma may occur throughout the oral cavity, nasal mucosa, pharynx, larynx, or esophagus. Other tumors are site-specific, such as odontogenic tumors, which are unique to tooth-forming tissues of the jaws. In the following discussions, we will emphasize benign neoplasms what have a special significance in the head and neck.

7.2.1 Epithelial

There are few true benign neoplasms of surface epithelium. The family of **Squamous Papillomas** includes a variety of benign exophytic epithelial tumor-like growths. Most of these are caused by assorted specific subtypes of Human Papillomavirus (HPV) infection, discussed in more detail elsewhere, and are more accurately diagnosed as Verrucae, Condylomas, and other specific viral infections. Such lesions arise on a number of different head and neck sites, including oropharyngeal, laryngeal, hypopharyngeal, auricular, and sinonasal.

In the oral cavity, the most common papillary lesions are Papillomas and Verrucae (warts). Most lesions clinically diagnosed as **Papilloma** have no definite viral etiology. Some clinicians may refer to these lesions as fibroepithelial polyps. HPV types 2 and 4 usually cause **Verruca Vulgaris**. A general guide to the clinical differential diagnosis of these lesions is suggested in Fig. 7.3, although biopsy is recommended. **Genital Warts (Condyloma Acuminatum)** are spread to the oral cavity by sexual activity. These lesions are also papillary but generally larger, often multiple, and more extensive than the Papilloma, which is a solitary lesion. Genital Warts are caused by HPV 6, 11, and others. **Focal Epithelial Hyperplasia (Heck's Disease)** is usually found in children; multiple flat nodules affect the oral mucosa. HPV 13 and 32 cause this disease [4].

Fig. 7.3 Papillomatous Lesions. Papilloma and Verruca Vulgaris appear similar clinically. However, a Papilloma (*left*) is more likely to appear as rounded exophytic projections on a stalk, somewhat like a letter P, while a Verruca (*right*) is more likely to have sharp-tipped projections like the letter V, or W for Wart. Pink indicates epithelium and blue indicates connective tissue

Conjunctival Papillomas are benign corneal masses that have been associated with infection with several types of Human Papillomavirus, especially types 6 and 11 but also with HPV types 16, 18, 33, and 45. Found in patients over a wide range of ages, they are usually solitary but may occasionally be multiple, especially in children. They may be sessile or pedunculated. They may cause a foreign-body sensation, and if located near the limbus or the bulbar conjunctiva, they may interfere with vision. Surgery, laser, cryotherapy, and medications may be used to treat these lesions [5–10].

Sinonasal Papillomas will be described separately, since they form a heterogeneous group clinically and microscopically.

7.2.2 Premalignant Epithelial

The World Health Organization distinguishes between precancerous lesions and precancerous conditions. A **precancerous lesion** is "a morphologically altered tissue in which cancer is more likely to occur than its apparently normal counterpart". A **precancerous condition** is "a generalized state associated with significantly increased risk of cancer" [11].

The mucosa of the head and neck, including the oropharynx, hypopharynx, and larynx, is a relatively common site for **dysplasia**, a precancerous lesion that is also known as intraepithelial neoplasia. These precancerous changes are usually related to environmental carcinogen exposures, especially tobacco and ethanol. Oral dysplasia and cancer are most likely to develop on the lateral tongue, ventral tongue, floor of the mouth, and retromolar trigone. In some parts of the world, smokers may place the lit end of the cigarette in the mouth, a practice known as reverse smoking. Palatal precancers and cancers are more common in patients who are reverse smokers.

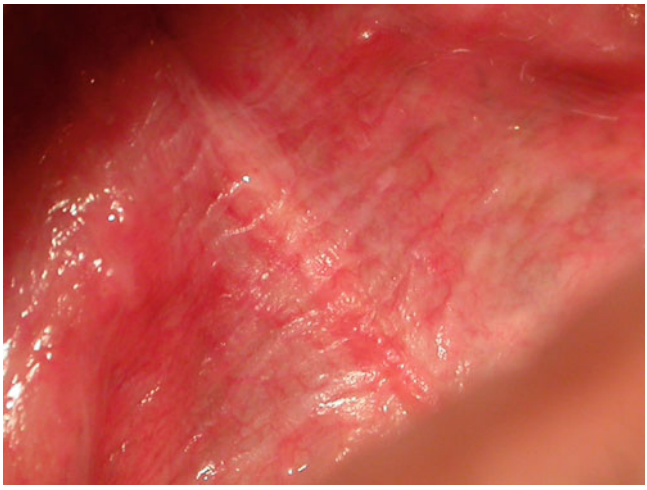

Fig. 7.4 Corrugated Leukoplakia. This subtle corrugated white lesion on the floor of the mouth of a middle-aged female smoker is highly suspicious for the presence of dysplasia. It requires thorough examination techniques to detect such lesions. This is a high-risk site for oral cancer, and lesions such as this should be promptly biopsied

There is growing acknowledgement of the role for high-risk Human Papillomavirus (HPV), especially types 16 and 18, in the development of head and neck Squamous Cell Carcinoma, although this risk varies by site as will be discussed elsewhere [12–14]. It is most likely that HPV infection works synergistically with other risk factors to cause premalignant and malignant epithelial lesions [15]. Presence of high-risk HPV appears to be related to the number of oral and genital sexual partners, although this may not be the sole route of viral transmission, and in particular, HPV16 may predict the risk of progression from intraepithelial neoplasia to invasion [16–18].

Dysplastic epithelial lesions, when visualized clinically, generally exhibit changes in color and contour. Their color is usually a combination of red and white. White lesions of uncertain etiology are often referred to as **leukoplakia**, defined by the World Health Organization as "whitish patch or plaque that cannot be characterized clinically or pathologically as any other disease, and is not associated with any physical or chemical causative agent, except the use of tobacco" [19]. Predominantly red lesions with no apparent cause are sometimes described as **erythroplakia**, and mixed lesions as **erythroleukoplakia**. These terms imply an increased risk of dysplasia, yet a biopsy is required to determine the actual diagnosis, which may range from inflammation or infection through dysplasia to outright malignancy. Thus, the terms "leukoplakia", "erythroplakia", and "erythroleukoplakia" are not histopathologic diagnoses, but clinical designations that indicate suspicion for increased risk of neoplasia.

Mucosal lesions usually appear white because the intervening surface is hiding the underlying blood. A white wrinkled or corrugated surface may indicate that the surface epithelium is growing at a faster rate than the underlying tissues. Up to 20% of leukoplakic lesions hold a risk of malignant transformation [20]. See Figs. 7.4 and 7.5.

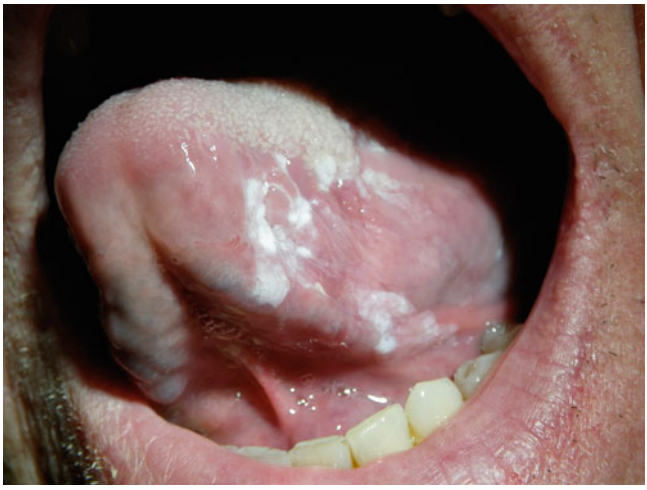

Fig. 7.5 Leukoplakia. This multifocal rough white lesion is located on the lateral tongue of a 57-year-old male with a long history of tobacco use. These are high-risk attributes. It could clinically be termed a leukoplakia, a white area that cannot be attributed to any non-neoplastic condition. Biopsy showed it to be moderate epithelial dysplasia

Lesions generally appear red because the underlying blood is more readily apparent, whether due to epithelial atrophy, vascular dilation, or vascular hyperplasia. Erythroplakic mucosal lesions are considered higher risk for malignant transformation [21].

Dysplasia is graded as low, moderate, or high depending on the proportion of the epithelial thickness exhibiting atypical changes (Fig. 7.6). When full-thickness changes are present, the lesion may be referred to as "**carcinoma *in situ***" [22]. As the grade of dysplasia becomes more severe, the risk of malignant progression increases. Silverman estimated the risk of malignant transformation in dysplasia as 36%, although there is not universal agreement on this estimate [23]. The presence of any invasion of the underlying connective tissue heralds the progression to malignancy. This distinction is important because the epithelium contains no vascular, lymphatic, or neural elements; the invasive lesion has propelled itself through the basement membranes, thereby gaining the potential for lymphovascular metastasis. Malignancy is discussed elsewhere.

It has long been acknowledged that some patients appear to have increased risk of malignancy in multiple mucosal sites, a term called "field cancerization". A distinctive form of this condition is seen in patients with **Proliferative Verrucous Leukoplakia (PVL)** [24]. These patients do not always fit the classic profile of high-risk patients; they are frequently female non-smokers and non-drinkers. However, they develop multifocal rough or verrucous white areas, such as that shown in Fig. 7.7, that are often refractory to therapy and exhibit a high risk of malignant transformation into low-grade Verrucous Carcinoma or conventional

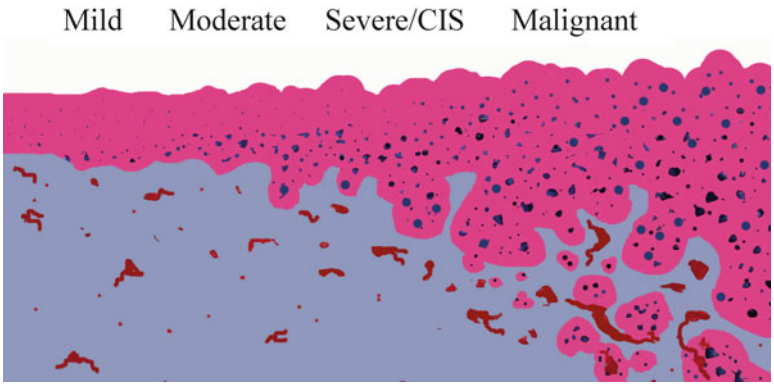

Fig. 7.6 Progression of Dysplasia. *Left to right*: Dysplasia begins at the basal layer of the epithelium (*pink*), because in normal epithelium, this is where all proliferating cells are located. As epithelium becomes increasingly dysplastic, the epithelium begins to thicken, giving in a white appearance clinically. Abnormal cells occupy an increasingly larger proportion of the epithelium as dysplasia grade increases from mild to severe. The nuclei (*black dots*) become larger, darker, and more distinct, reflecting the genetic changes in the dysplastic cells. The rete pegs become bulbous and the surface becomes rough. When dysplastic cells occupy the full thickness of the epithelium, the lesion is called carcinoma in situ. When the abnormal epithelium begins to invade the underlying connective tissue (*blue*), the lesion has become malignant or cancerous. Neoplastic epithelial cells release cytokines that promote blood vessel growth (*red*), so as dysplasia becomes severe, the lesion is more likely to look erythematous. Cancer often invades the blood vessels or lymphatics in order to metastasize to other regions

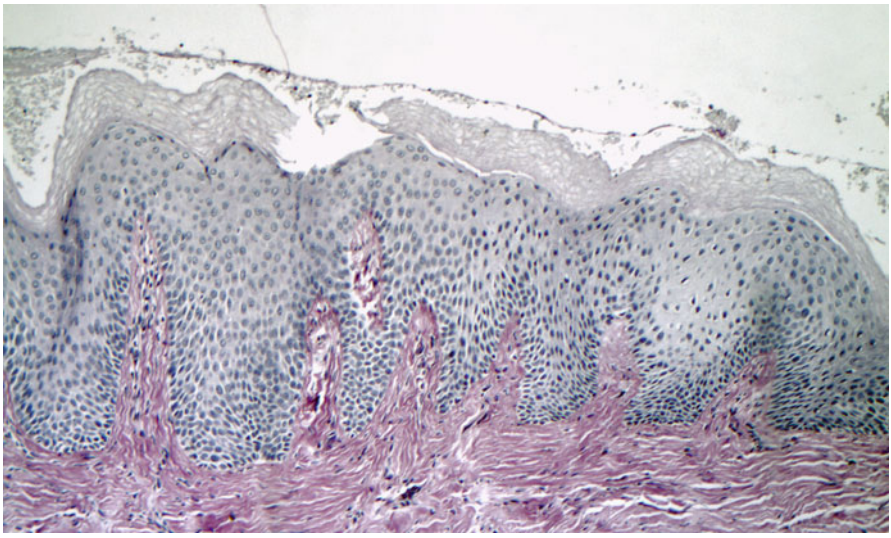

Fig. 7.7 Atypical Verrucous Hyperplasia. This oral biopsy shows an irregular rough-surfaced proliferation of keratinocytes, exhibiting cellular crowding, dyskeratosis, and mild nuclear hyperchromasia. Clinically, the patient had recurrent multifocal warty white lesions, clinically consistent with Proliferative Verrucous Hyperplasia (H&E, 40×)

Squamous Cell Carcinoma. Attempts to demonstrate association between HPV and PVL has met with mixed results [25–27].

A number of other precancerous conditions also carry a significantly increased risk of cancer. In **Oral Submucous Fibrosis** (associated with betel nut use), the oral cavity becomes stiffened due to excessive fibrosis, and there is a high risk of Squamous Cell Carcinoma. This condition is seen in areas such as south-east Asia where betel nut (quid, paan, etc.) use is common. **Xeroderma Pigmentosum,** an autosomal recessive disease with defective repair of DNA damage, is another such condition; many malignancies in these patients occur on sun-exposed surfaces but they can also occur on mucosa. In adult patients with **Epidermolysis Bullosa,** a group of inherited blistering skin diseases, Squamous Cell Carcinoma is the most common cause of death, and it can develop on mucosa or skin [28]. **Plummer-Vinson Syndrome** (also known as Patterson-Kelly Syndrome and as Sideropenic Dysphagia) is a combination of iron deficiency anemia, esophageal webs, and dysphagia associated with a raised risk of esophageal, oral, and pharyngeal Squamous Cell Carcinoma. Some forms of **Lichen Planus** may be associated with increased oral cancer rates, although the nature of this association is controversial and unclear. **Lupus Erythematosus** has also been associated with higher cancer rates, particularly of the lip [29].

7.2.3 Melanocytic

Melanocytic Nevi, commonly known to patients as moles, are localized clusters of benign melanocytic cells, which are of neural crest origin. They may be hamartomas or benign neoplasms, based on clonality studies [30].

Most humans exhibit a number of small melanocytic nevi without risk of malignant transformation; Caucasian adults typically have 10–40 nevi on their skin (see Fig. 7.8) [31]. Very large melanocytic nevi, such as so-called "garment nevi", have an increased risk of transformation to malignant Melanoma [32, 33]. The number and size of nevi on skin, and the risk for transformation to Melanoma, is also increased in patients with **Dysplastic Nevus Syndrome**.

Mucosal melanocytic nevi are very similar to nevi on skin. However, they are less common, found in about 0.1% of the population. Like skin nevi, they evolve through junctional, compound, and intramucosal stages as the nevus cells gradually migrate from the epithelium, past the rete pegs, and into the submucosal tissues. Unlike skin nevi, they are not hair bearing [34].

Blue Nevi, in which the melanocytic cells are spindle shaped and located deeper in submucosal tissues, are more common in the oral cavity than on skin, accounting for a quarter to a third of oral nevi. They are most common on the hard palate, buccal mucosa, and gingival respectively, and distinctly uncommon on the tongue and the floor of the mouth [31].

Nevus of Ota or **Oculodermal Melanocytosis** is a diffuse gray-brown color, usually in a region innervated by the first or second branch of the trigeminal nerve. It is

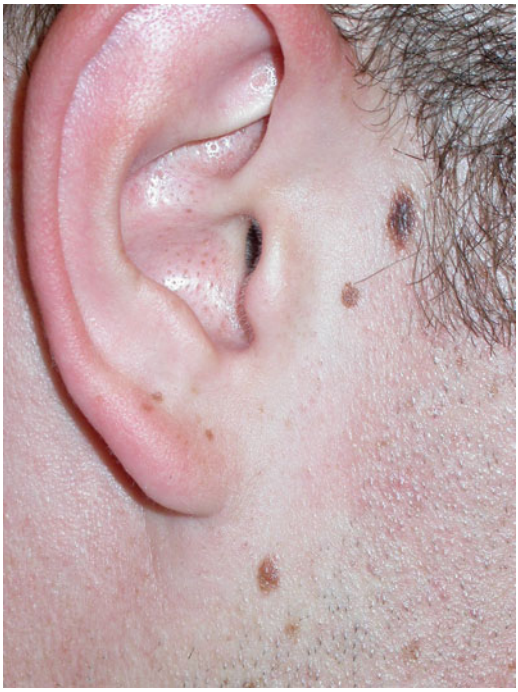

Fig. 7.8 Melanocytic Nevi. Multiple nevi on the skin of a young Caucasian male. Most people have multiple nevi

usually seen on the eye and surrounding skin, but may also include other nearby mucosa including oral or ear. It is more common in patients of Asian ancestry. A Nevus of Ota is seen in Fig. 7.9. Such nevi may be mistaken casually for bruises, although they are unchanging over time and they do not display the multicolor evolution of an ecchymosis. These lesions microscopically resemble the blue nevus. The Nevus of Ota can rarely be associated with the development of melanoma. Diagnosis of Nevus of Ota is generally a clinical one, but biopsy of suspected Melanoma may be necessary. Cosmetic removal of the lesion can be attempted with laser [35–37].

Melanoacanthoma (Fig. 7.10) is an unusual, benign, but alarming proliferation of melanocytes and keratinocytes that presents as a rapidly expanding pigmented macule of oral mucosa, often the buccal mucosa. Because it is probably a reaction to an environmental stimulus rather than a neoplasm, some authors prefer the term **Melanoacanthosis**. It is most common in young Black females, but can occur in other demographic groups. Oral Melanoacanthoma is not a premalignant lesion. However, biopsy is necessary to establish a definite diagnosis and distinguish this from a developing Melanoma, which despite its benign-sounding name is always malignant. Some cases spontaneously resolve [38–40].

In November 2011, the US Food and Drug Administration approved a new device called MelaFind to aid experienced and specially trained dermatologists in the clinical detection of Melanoma of skin. The dermatologist scans the lesion, and a diagnostic

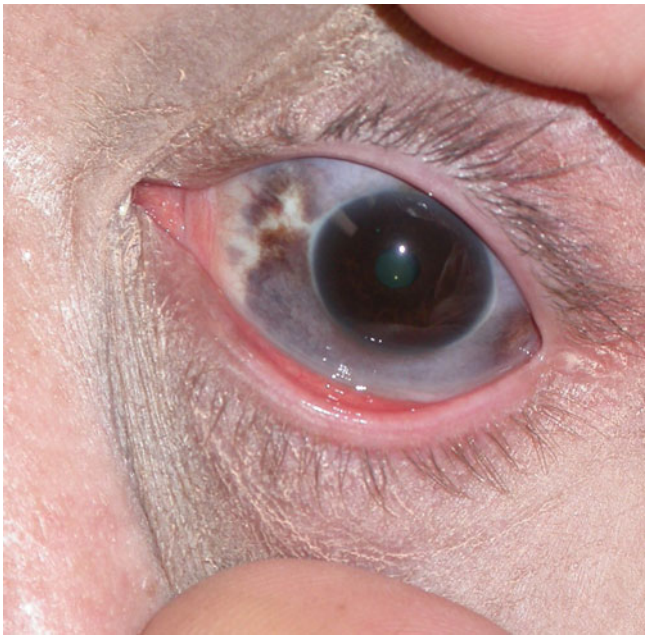

Fig. 7.9 Nevus of Ota. This Nevus of Ota affected a middle-aged woman of mixed Caucasian and Native American ancestry. Note that the pigmentation affects the eye as well as the periocular skin. It had been present for most of her life. The patient and her husband were frustrated because strangers frequently misunderstood it as a sign of domestic abuse

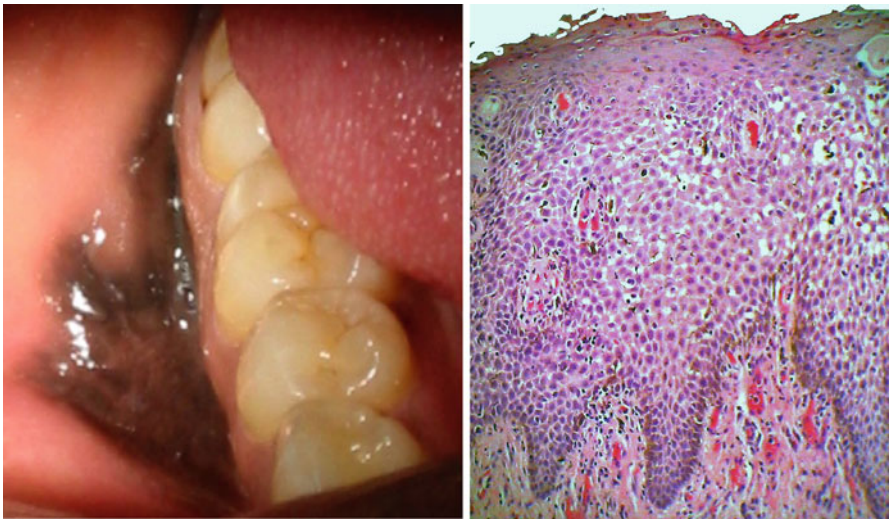

Fig. 7.10 Melanoacanthoma (Melanoacanthosis). This rapidly expanding pigmented macule on the buccal mucosa of a 27-year-old African-American woman (*left*) was very worrisome, as the patient believed that it was a Melanoma. Biopsy (*right*) revealed the benign melanocytic proliferation characteristic of Melanoacanthoma (H&E, 20×)

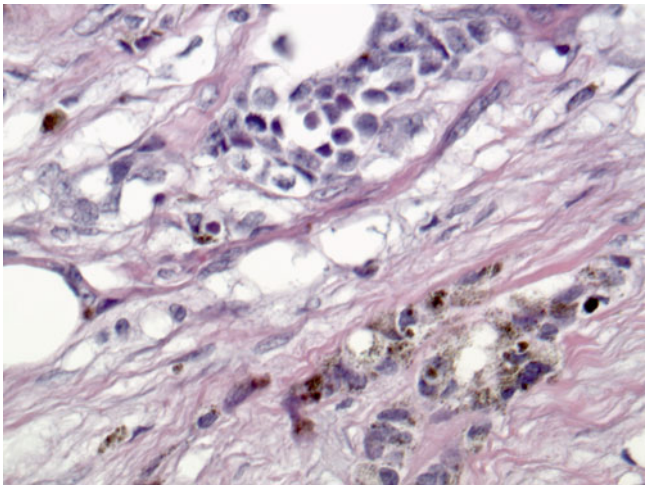

Fig. 7.11 Melanotic Neuroectodermal Tumor of Infancy. This unencapsulated tumor demonstrates the typical microscopic appearance: larger pigmented epithelioid cells, and smaller neuroblast-like cells in clusters (H&E, 63×)

algorithm in an attached computer determines the likelihood of the scanned lesion representing a melanoma. The technique is somewhat controversial and although the sensitivity is reportedly high, it appears to be subject to a relatively high rate of false positives [41].

Any lesion that raises suspicion of melanoma should be biopsied promptly. The American Academy of Dermatology advocates the "ABCDE" clinical criteria to raise suspicion that a melanocytic skin lesion may represent some stage in the development of a Melanoma, rather than a nevus: Asymmetry; Border irregularity; Color variation within the lesion; Diameter larger than 6 mm; and Evolution over time [42]. Lin et al. suggest these criteria may also be applicable to mucosal tissues [43].

Melanotic Neuroectodermal Tumor of Infancy is a rare, rapidly growing pigmented tumor arising in the jaw or skull of infants. It contains melanocytic and neuroectodermal cells as shown in Fig. 7.11. Patients may demonstrate high urinary levels of vanillylmendelic acid. Treatment is surgical, with a significant risk of recurrence and a small risk of metastasis [44].

7.2.4 Neural and Neuroendocrine

Nerve sheath tumors in the head and neck are similar to those in other body sites. Benign nerve sheath tumors include the **Schmannoma, Neurofibroma,** and **Palisaded Encapsulated Neuroma**. A Neurofibroma is shown in Fig. 7.12 and a Schwannoma is shown in Fig. 7.13. Treatment is surgical. Nerve sheath tumors may

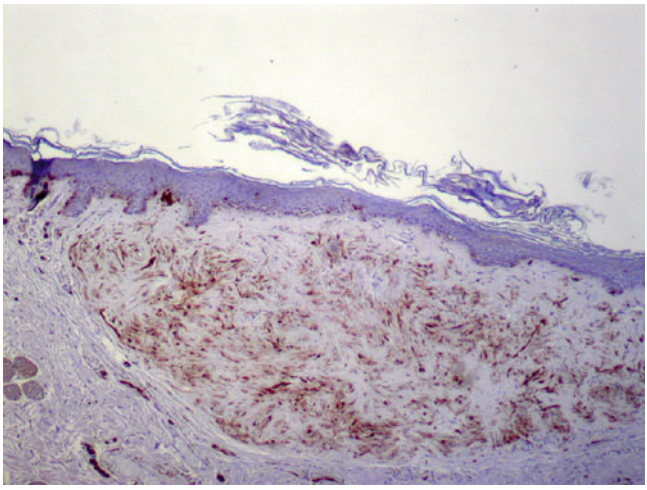

Fig. 7.12 Mucosal Neurofibroma. The delicate wavy spindle cells of this Neurofibroma of the oral cavity stain brown with S-100 stain (S-100, 20×)

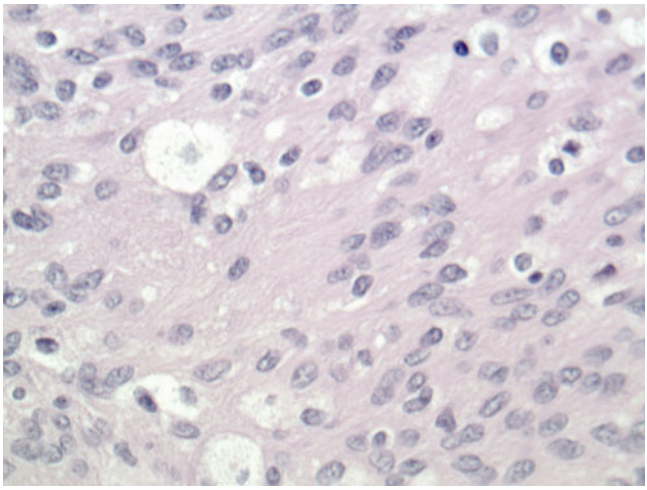

Fig. 7.13 Schwannoma. No neurites are seen in Schwannomas, which are encapsulated proliferations of Schwann cells. Identification of Antoni A areas aids microscopic diagnosis of a Schwannoma. In these areas, the spindle cells are arranged in rows separated by Verocay bodies composed of fibrillary cell processes, as shown above (H&E, 63×)

occasionally be seen on dental radiographs as a so-called "blunderbuss" widening of the inferior alveolar canal as seen in Fig. 7.14. Patients with multiple Neurofibromas should be evaluated for the possibility of **Neurofibromatosis**, which carries with it an increased risk of malignant transformation (Fig. 7.14).

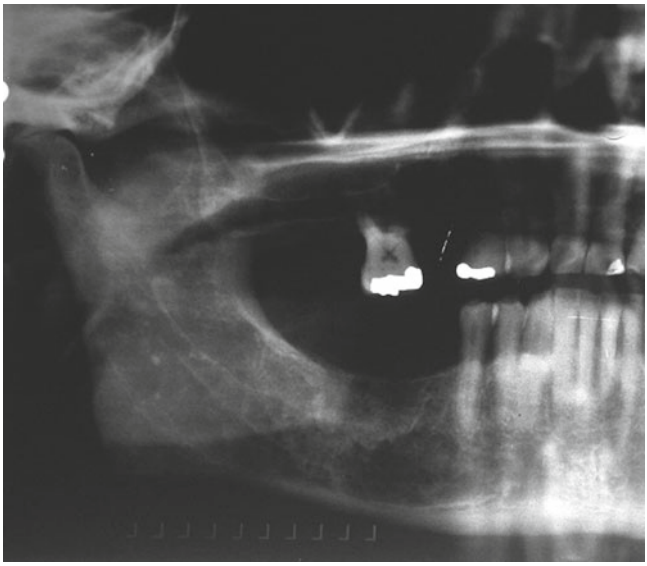

Fig. 7.14 Benign Nerve Sheath Tumor. The left inferior alveolar nerve canal displays a so-called "blunderbuss" widening. The lesion was asymptomatic. This patient had a history of brain tumor. He was referred for biopsy to determine which type of benign nerve sheath tumor was present, and further evaluation for the possibility of Neurofibromatosis, but was lost to follow-up

Mucosal Neuroma is the characteristic perioral lesion of **Multiple Endocrine Neoplasia (MEN) 2b** [45, 46]. This autosomal dominant syndrome is caused by mutation of the RET proto-oncogene. Other key features of the syndrome include: high rates of Medullary Carcinoma of the thyroid gland, a highly malignant tumor with early metastases; Pheochromocytoma of the adrenal gland, which causes significant hypertension; a Marfanoid body type, with long limbs and digits; elevated urinary vanillylmandelic acid levels; and other variable features. Mucosal Neuromas are usually multiple slow-growing nodulopapular lesions that are present from a young age. They are most commonly found on the lips, anterior tongue, and palate. Other sites such as the eyelids and intestinal tract may also be affected. Biopsy is required to confirm the diagnosis, and treatment is surgical. Mucosal Neuromas are not dangerous themselves. However, MEN2b patients have very high rates of a very aggressive form of Medullary Carcinoma of the thyroid, so prompt referral for evaluation of the syndrome can potentially save the patient's life (Fig. 7.15) [47].

Paraganglia are clusters of neuroendocrine cells that are associated with autonomic ganglia. They are part of the autonomic nervous system and are found along the large vessels of the head and neck, among other locations. **Paragangliomas** are rare tumors of paraganglia that usually occur in the paravertebral area but occasionally in the head and neck. They may occasionally occur along the bifurcation of the carotid artery ("Carotid Body Tumors") or the jugulotympanic area of the temporal bone ("Glomus Jugulare" and "Glomus Tympanicum" of the middle ear) as well as

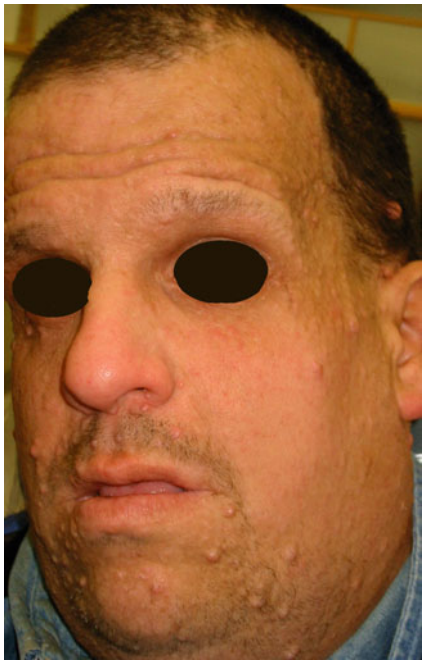

Fig. 7.15 Neurofibromatosis. This patient with confirmed Neurofibromatosis displays hundreds of Neurofibromas and café au lait spots on his skin and oral mucosa. His history includes CNS, optic nerve, and adrenal tumors. He is intellectually delayed and blind. His father and grandfather also had Neurofibromatosis, although their cases were milder. Some patients with Neurofibromatosis are deaf because of bilateral Schannomas on the acoustic nerve, but this patient is not deaf

other sites. A few head and neck Paragangliomas secrete catecholamine, and may cause significant hypertension. Occasionally, Paragangliomas of the head and neck are malignant. Paragangliomas may be associated with a familial syndrome in some cases [48–51].

7.2.5 Smooth and Skeletal Muscle

Adult Rhabdomyoma is a very rare benign tumor of skeletal muscle that usually presents as a mass in the branchial arch regions of older males [52, 53]. Treatment is surgical. Figure 7.16 shows the histologic features of an Adult Rhabdomyoma.

Leiomyoma is a benign smooth muscle neoplasm. Leiomyomas can arise in the smooth muscle of the uterus (Uterine Leiomyoma), scrotum, labia, or nipple (Genital Leiomyoma), the arrector pili muscle of skin (Piloleiomyoma), or the smooth muscle of the tunica media of veins and arteries (Vascular Leiomyoma or Angioleiomyoma). In the head and neck, the majority are solitary Angioleiomyomas. They are usually deeply sited nodules and many are painful. After surgical excision, few recur [54].

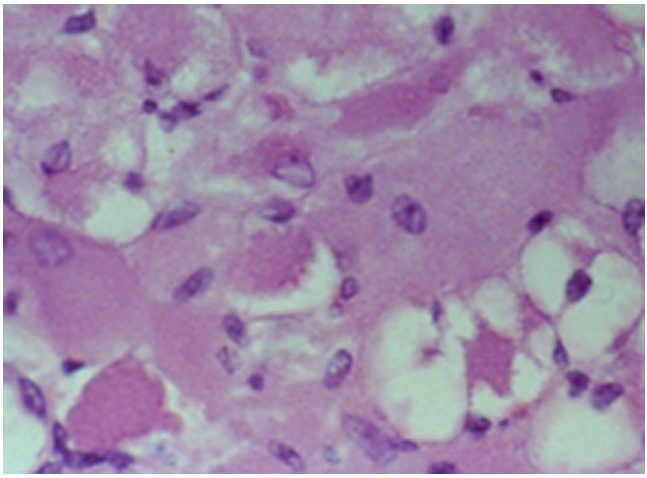

Fig. 7.16 Adult Rhabdomyoma. This biopsy from the submandibular region in a 71-year-old Caucasian male shows the characteristic granular cells and glycogen vacuoles. Electron microscopy demonstrated abundant mitochondria and Z-bands indicative of skeletal muscle origin (H&E, 63×)

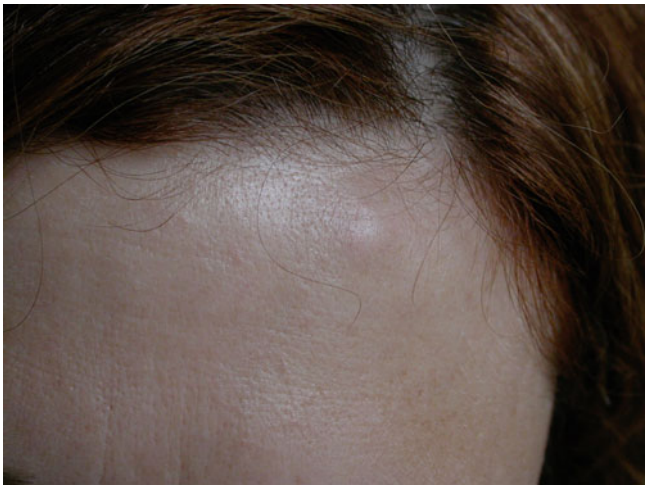

Fig. 7.17 Lipoma. This freely moveable subcutaneous nodule on the left upper forehead of a 42-year-old Caucasian female appears clinically to be a benign neoplasm of soft connective tissue. Biopsy demonstrated that it was a lipoma, the most common neoplasm of soft connective tissue

7.2.6 Adipose

Lipoma, a benign tumor of adipocytes, is considered the most common neoplasm of soft connective tissue, and consists of an encapsulated proliferation of mature-appearing fat cells [55]. It usually presents as a solitary freely-moveable deep-sited nodule on skin or mucosa (Fig. 7.17), and may sometimes have a yellowish

hue. A biopsy is used to confirm the diagnosis, and careful evaluation is especially important if the lesion is large and enlarging rapidly, as it is critical to rule out Liposarcoma. Treatment is surgical [56].

7.2.7 Vascular

The International Society for the Study of Vascular Anomalies classifies vascular anomalies as vascular tumors and vascular malformations. These terms are frequently confused, and the lesions they represent may have clinical overlap.

The most common benign vascular tumors are **Hemangiomas** (Juvenile Hemangioma, Rapidly Involuting Congenital Hemangioma, Noninvoluting Congenital Hemangioma). True Hemangiomas tend to grow, stabilize, and then involute. Other benign vascular tumors are the Kaposiform Hemangioendothelioma and Tufted Angioma.

Vascular Malformations represent developmental errors. They include high-flow (Arteriovenous Malformation) and low-flow lesions (venous, lymphatic and capillary types) (see Fig. 7.18). These lesions grow with the developing child but may expand secondary to trauma, hormonal changes, thrombosis, or sepsis [57–60].

Hemangioblastoma is a benign but potentially aggressive vascular tumor. It usually occurs in the central nervous system or spinal cord, but may occasionally occur on the optic or peripheral nerves. Treatment is usually surgical, but embolization, gamma knife, and anti-angiogenic treatment are sometimes used. About 25% of Hemangioblastomas are associated with the autosomal dominant von Hippel Lindau (VHL) syndrome. Besides vascular tumors, other features of VHL Syndrome include tumors of the kidneys and adrenal glands [61].

7.2.8 Fibrous

Fibroma (Fig. 7.19) is a common clinical diagnosis in the head and neck, especially in trauma-prone areas of the oral cavity. In most cases, lesions identified clinically as Fibromas are **Irritation Fibromas**, non-neoplastic reactive proliferations of fibrous tissue that are also termed Focal Fibrous Hyperplasia. These are discussed further in the next chapter.

A nodular unencapsulated proliferations of plump stellate fibroblasts that occurs orally on the gingiva, tongue, or palate is called **Giant Cell Fibroma** (Fig. 7.20); when similar lesions occur on the nose, they are called **Fibrous Papules of the Nose.** Treatment is surgical. The Giant Cell Fibroma is not to be confused with Peripheral Giant Cell Granuloma, a different condition.

Fibromatoses are aggressive infiltrating fibrous proliferations that may occur in many areas of the body; in the head and neck, they usually occur in the soft tissues around the mandible, the tongue, and the buccal mucosa. They can cause resorption of underlying bone. Treatment is surgical. They are most frequently seen in children and have a tendency for recurrence [62].

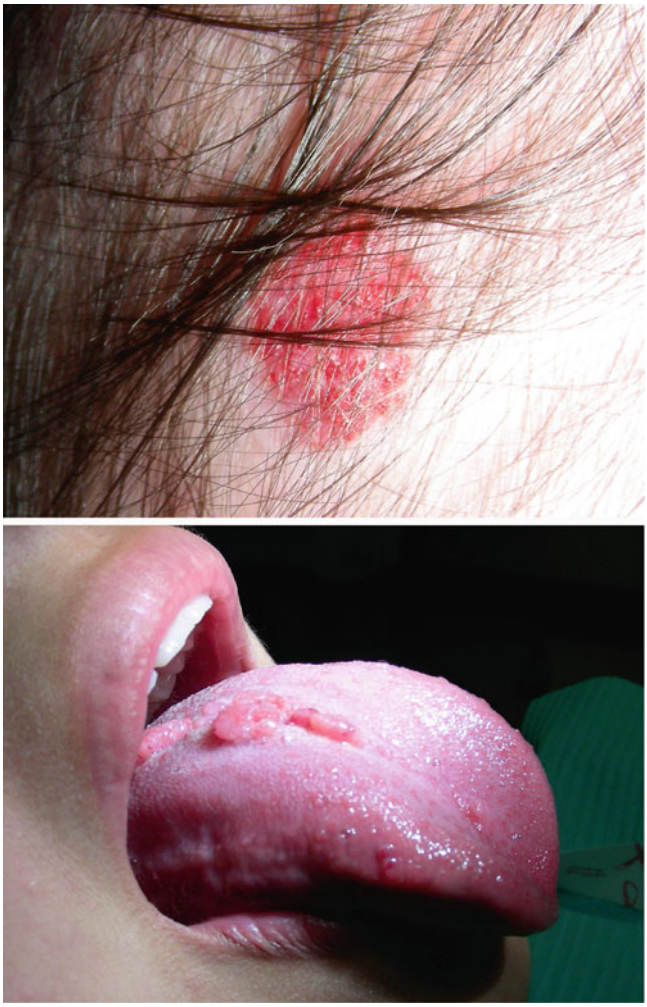

Fig. 7.18 Vascular Tumors and Malformations. *Top*: This sessile red lesion had been present on the scalp of this infant since birth, but later involuted. Clinically, the diagnosis was a Hemangioma. *Bottom*: This exophytic lesion had been present in a teenaged girl since birth, with no history of enlargement. Clinically, the diagnosis was a Lymphovascular Malformation. Neither lesion was biopsied

Gingival Fibromatosis is very different. Gingival enlargements referred to as "gingival fibromatosis" actually represent a collection of conditions. Most common is **Drug-related Gingival Overgrowth,** associated with the use of anticonvulsants such as phenytoin, calcium channel blockers such as nefedipine, cyclosporine, and occasionally other medications. This is not a true hyperplasia of gingival tissues, which would require an increase in cell number, but instead is an increase of collagen and extracellular matrix. Gingival enlargement can also be sporadic or associated with a number of syndromes and hereditary conditions.

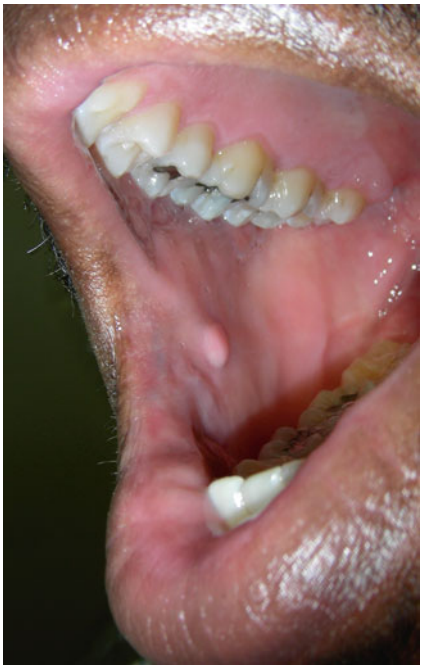

Fig. 7.19 Irritation Fibroma. The smooth-surfaced exophytic nodule on the buccal mucosa is typical of an irritation fibroma, also called Focal Fibrous Hyperplasia. It represents an unencapsulated submucosal mass of reactive fibrous tissue, and once excised, it should not recur. Such lesions are common intraorally, especially on the buccal mucosa, because patients frequently bite their cheeks accidentally

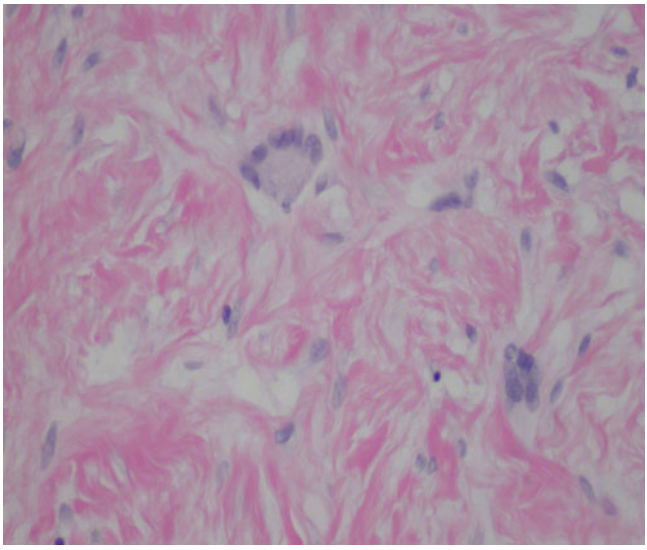

Fig. 7.20 Giant Cell Fibroma. This nodular gingival mass was composed of stellate and kite-shaped fibroblasts (H&E, 63×)

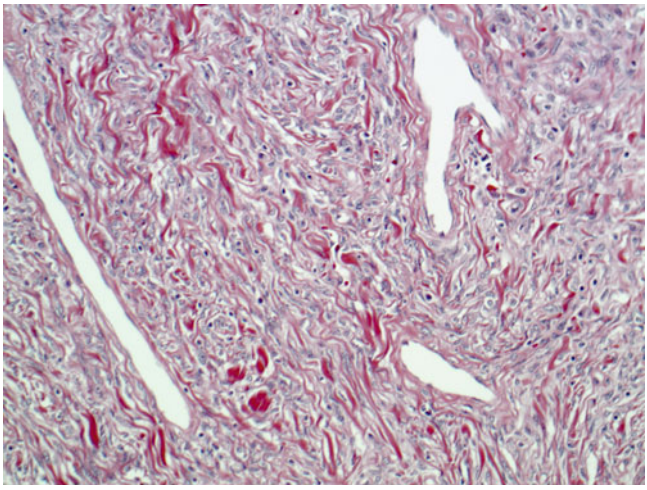

Fig. 7.21 Solitary Fibrous Tumor. This Solitary Fibrous Tumor of the buccal mucosa shows the spindle cells with collagen fibers. Blood vessels show the irregular "stag-horn" branching that is also seen in hemangiopericytomas (H&E, 20×)

Myofibroma is a benign neoplasm of myofibroblasts, which have features of both fibroblasts and muscle cells. Myofibromas tend to occur in the maxillofacial region, especially the mandible, lips, tongue, and buccal mucosa. Treatment is surgical. **Myofibromatosis** is the presence of multiple Myofibromas, and although this condition is also benign, it can be aggressive [63].

Solitary Fibrous Tumors are rare neoplasms composed microscopically of circumscribed collections of spindle cells with hypo- and hyper-cellular areas (Fig. 7.21). Diagnosis is aided by their positive reaction to CD34, CD99, and Bcl2 stains. The oral cavity (buccal mucosa, tongue, and lip) is the most common site within the head and neck, although they have been reported in other sites including sinonasal and subcutaneous areas. Treatment is surgical. They may occasionally show malignant features [64].

7.2.9 Bones and Joints

Torus Palatinus (midline of hard palate) and **Mandibular Tori** (on the anterior lingual aspect of the mandible, usually bilaterally) are variations of normal anatomy that are non-neoplastic. They are discussed in the next chapter.

Osteoma is a well-defined benign mass of bone that may occur in the head and neck. It is the most common tumor-like lesion of bone in the oral region, and occurs over a wide age range [65]. Osteomas are normally asymptomatic and non-aggressive. If treatment is necessary, it is surgical. Multiple Osteomas may be associated with **Gardner's**

Syndrome, which has numerous other features including multiple supernumerary (extra) and impacted teeth, and a very high risk of colon adenocarcinoma.

Osteoblastoma and **Osteoid Osteoma** are closely related benign neoplasms of osteoblasts, so they are bone-producing tumors. Both can cause spontaneous pain. Osteoid Osteoma does not generally occur in the jaws. Osteoblastoma, which can reach greater sizes than Osteoid Osteoma, occasionally occurs in the jaws and skull. It usually occurs in young adults, and favors the frontal, temporal, ethmoid, occipital bones, and jaws. When they occur in the jaw, most Osteoblastomas cause spontaneous pain, loosen, and resorb the roots of adjacent teeth. Treatment is surgical. When Osteoblastomas are removed, they should not recur, but pathologists recognize the existence of an aggressive form that is prone to recurrence [66, 67].

Osteochondroma tends to occur in younger patients, and is a benign hamartomatous projection of bone with a cartilaginous cap. It is rare in the jaws, where it tends to favor the posterior mandible. Treatment is surgical. Although benign, the Osteochondroma has been reported to undergo malignant transformation [68, 69].

Chondromas are benign neoplasms of chondroblasts, forming mature hyaline cartilage. Treatment is surgical. Because this lesion is uncommon in head and neck, there should be a high index of suspicion for a low-grade chondrosarcoma. The **Chondroblastoma** and **Chondromyxoid Fibroma** are other rare benign cartilaginous neoplasms that may occasionally arise in the head and neck. In the jaws, most chondromatous neoplasms are malignant [70, 71].

A variety of bone tumors may exhibit giant cells. The most common of these in the head and neck is the **Central Giant Cell Granuloma (CGCG)**. The CGCG forms a painless and well-defined, but locally destructive, radiolucent mass in bone (usually the jaws). It may represent a reactive process rather than a neoplasm. It is composed of a non-encapsulated mass of multinucleated giant cells in a fibrovascular stroma (Fig. 7.22). It may be found in combination with an Aneurysmal Bone Cyst, and they may represent different presentations of the same condition. Because CGCG is histologically indistinguishable from the **Brown Tumor of Hyperparathyroidism**, patients with CGCG need to be evaluated for the risk of hyperparathyroidism. The CGCG is also histologically identical to the Peripheral Giant Cell Granuloma (PGCG), a localized reactive gingival mass that is not associated with hyperparathyroidism. Treatment is usually surgical. Although newer non-surgical therapies exist, randomized clinical trials of these methods are rare. PGCG will be discussed in a separate chapter. The true benign neoplasm, Giant Cell Tumor of Bone, also called **Osteoclastoma,** rarely occurs in the head and neck, but can be aggressive [72, 73].

Fibrous Dysplasia (**FD**), a member of the group of bone diseases known as **Benign Fibro-Osseous Lesions**, is not a neoplastic disease. However, patients with fibrous dysplasia are considered to be at increased risk for the development of Osteosarcoma and some other malignancies. Fibrous Dysplasia is caused by a mutation in the gene on Chromosome 20 for a stimulatory G protein. Because of this mutation, osteoblasts create fibrous tissue instead of bone, and the affected bone is weakened. FD usually affects only one bone (Monostotic FD), but it may occasionally affect multiple bones (Polyostotic FD). When it affects multiple

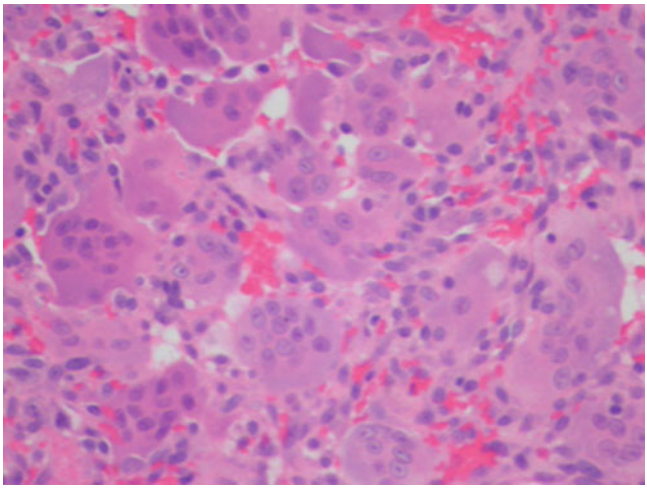

Fig. 7.22 Giant Cell Granuloma. Masses of giant cells in bone form the Central Giant Cell Granuloma and the brown tumor of Hyperparathyroidism. In gingiva, grant cells characterize the Peripheral Giant Cell Granuloma (H&E, 40×)

bones of the facial region, it is termed Craniofacial FD, which is considered a special type of Monostotic FD, not polyostotic despite the involvement of several adjacent bones. FD is a disease of youth, and it can cause cosmetic disfigurement. Affected areas are enlarged, and radiographically exhibit a diffuse radiolucency/radiopacity that often has a "ground glass" appearance. Adjacent normal structures such as teeth may be displaced, and pressure on anatomic structures may cause headache, proptosis, and nasal obstruction. In the case of such symptoms, or of disfigurement, the lesions may be surgically reduced, but disease activity usually ceases at the time of skeletal maturity. Radiation treatment is contraindicated as it makes malignant transformation more likely. Biopsy shows that there is a fibrous stroma in the bone, with irregular slender trabeculae of bone that have been described in the past as "Chinese characters" by observers who had little knowledge of written Chinese. Polyostotic FD can be a component of **McCune Albright Syndrome**, in which there are also endocrine disturbances such as precocious puberty, and café au lait spots on the skin [74, 75].

Paget Disease Of Bone, also known as **Osteitis Deformans**, is another Benign Fibro-Osseous Lesion. Its name must be differentiated from Paget Disease of Breast. It is an unusual systemic condition of abnormal bone remodeling, and like Fibrous Dysplasia, it is not a neoplasm but raises the risk of osteosarcoma. Its etiology is unknown, but viruses have been suggested, genetic and geographic clusters occur. In contrast to FD, Paget Disease is a disease of older patients. It often affects the bones of the skull, and is usually asymptomatic. However, in some patients, the expansion of affected bone can compress nerves, causing pain, deafness, and arthritis. Patients may notice an increase in their head size, or that

dentures are no longer large enough – which should not be expected in an adult patient. The non-symmetry of bone increase should differentiate this from pituitary adenomas secreting somatostatin, which cause symmetrical enlargement. The teeth may become spaced and the roots of teeth may develop excessive cementum [76]. The affected bone is weakened, and may be hypervascular. Radiographs of affected bone show cotton-wool radiopacities. Serum alkaline phosphatase levels are elevated. Biopsy shows that the bone remodeling is askew: the early osteolytic phase is marked by osteoclast-rimmed bone; the middle phase has a combination of bone resorption and production; and the osteoblastic phase is marked by irregular masses of new bone with reversal lines that give the bone the appearance of a mosaic. Treatment is medical, and many patients use bisphosphonates to suppress bone remodeling [77–79].

7.2.10 Immune Cells

Langerhans Cell Histiocytosis (**LCH**) is a group of disorders caused by monoclonal proliferation of dendritic cells that histologically resemble, and are likely closely related to, Langerhans cells of the skin. Other immune cells, especially eosinophils, are also present. It remains unclear whether LCH represents a neoplasm or a reactive lesion, although disease progression in many cases suggests a neoplastic process. Acute Disseminated LCH (Letterer-Siwe Disease), Chronic Disseminated LCH (Hand-Schüller-Christian Disease), and Chronic Localized LCH are recognized forms of the disease. Before the cell of origin was determined, Chronic Localized LCH was called Histiocytosis X or Eosinophilic Granuloma. The most common form of LCH, it usually presents as a well-circumscribed osteolytic bone lesion in a young person. The lesion may sometimes be painful, and soft tissue involvement can occur. In the oral cavity, LCH can destroy the bone around a tooth, resulting in the appearance of a "floating tooth". Such lesions are usually treated surgically or with localized chemotherapy or radiotherapy, and prognosis is good. Acute Disseminated LCH, which has a leukemia-like presentation, has a high mortality rate. Chronic Disseminated LCH is multifocal and can result in death. Both these more aggressive forms tend to affect young children [80, 81].

Plasmacytoma is a localized monoclonal neoplasm of plasma cells. Plasmacytomas may occur in soft tissue (Extramedullary Plasmacytoma) or in bone marrow, and is usually seen in patients of at least middle age. These are considered different conditions. The diagnosis of a Plasmacytoma in either location necessitates a careful evaluation for the presence of Multiple Myeloma (Plasma Cell Myeloma), the disseminated plasma cell malignancy. In bone marrow, Plasmacytoma proceeds to Multiple Myeloma in over half of cases. The Extramedullary Plasmacytoma carries a lower, but still significant, risk of the development of Multiple Myeloma. Discussion of Multiple Myeloma is outside the scope of this chapter [82, 83].

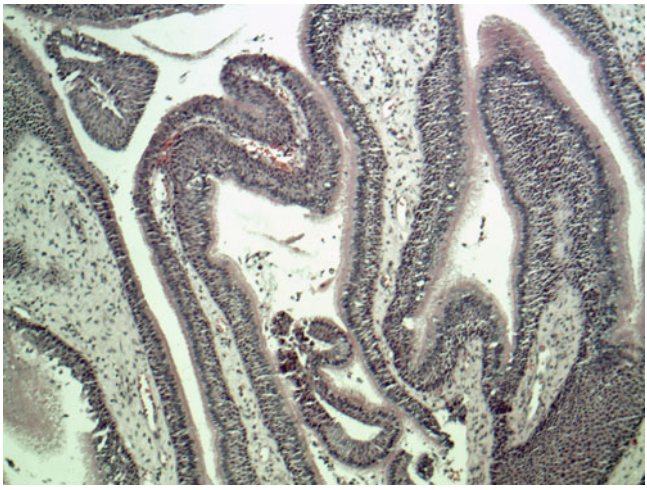

Fig. 7.23 Inverted Sinonasal Papilloma. This Inverted Papilloma exhibits invaginations of hyperplastic respiratory epithelium (H&E, 10×)

7.3 Benign Sinonasal and Nasopharyngeal Neoplasms

The ectodermally derived Schneiderian membrane lines the sinonasal cavity, and it can give rise to **Sinonasal (Schneiderian) Papillomas.** These are generally benign and relatively uncommon papillary growths, but they are less common than inflammatory nasal polyps and common warts (verruca vulgaris) in this region. The WHO classifies Sinonasal Papillomas into several different categories that differ in their neoplastic potential: Inverted Papillomas, Oncocytic Papillomas, and Fungiform Papillomas. They occur most commonly on the lateral nasal wall, but also in other sites such as the sinuses, the turbinates, and the nasal septum. Patients may complain of various symptoms including nosebleeds, congestion, headache, and loss of their sense of smell. Sinonasal Papillomas may be incidental findings on radiographs, including dental panoramic radiographs. CT and MRI can aid nasal endoscopy in the assessment and diagnosis of these lesions, and management is chiefly surgical. Recurrences are common [84–87].

Inverted Papillomas are the most common type of Sinonasal Papilloma, accounting for 60–70%. They are not always associated with a chronic viral infection, but may be associated with HPV types 6, 11, 16, 18, and occasionally 57. Some investigators also associate these lesions with Epstein-Barr Virus. These lesions are capable of locally aggressive behavior, and they may destroy surrounding bone. Inverted Papillomas earn their name from their microscopic appearance; they exhibit hyperplastic squamous or respiratory epithelium that invaginates into the underlying connective tissue (Fig. 7.23). They occasionally appear dysplastic,

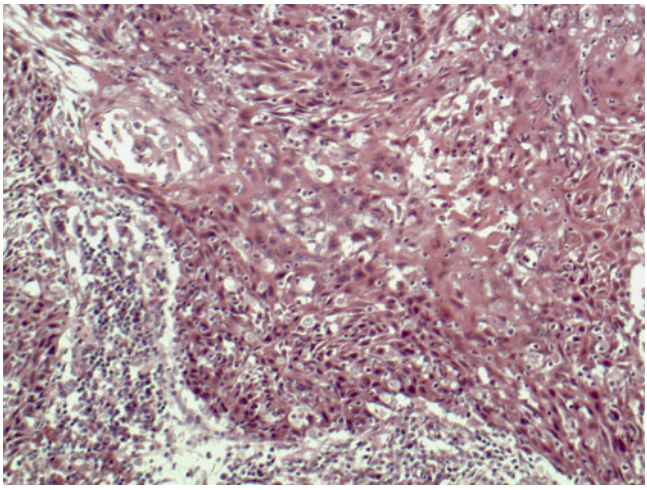

Fig. 7.24 Squamous Cell Carcinoma Arising from an Inverted Sinonasal Papilloma. This Squamous Cell Carcinoma arose in an Inverted Papilloma of the maxillary sinus (H&E, 20×)

and overall the Inverted Papilloma has a significant (11%) association with transformation into Squamous Cell Carcinoma or Adenocarcinoma, especially if it harbors "high risk" HPV 16 and 18 (Fig. 7.24) [88–92].

The **Inverted Papilloma of the Middle Ear** is similar to the Inverted Sinonasal Papilloma. However, there are some important differences regarding this lesion's pathogenesis and clinical behavior. It is quite rare, and has a much higher risk of malignant transformation, estimated at about 40%. It may not be associated with HPV [93–95].

About one-third of Sinonasal Papillomas are **Fungiform Papillomas,** which are associated with HPV 6 and 11 and most frequently arise on the nasal septum. These are warty-looking benign lesions with no malignant potential.

Oncocytic (Cylindrical Cell) Papillomas are the least common type, and have only a weak association with HPV. They are characterized by tall, columnar oncocytes that contain large numbers of mitochondria (Fig. 7.25). Malignant transformation has been reported in 4–17%.

Nasopharyngeal Angiofibroma is a rare, highly vascular proliferation in the nasopharynx that occurs almost exclusively in young males. This gender predilection appears to be due to the character of its cell-surface receptors for steroid hormones [96]. It may represent a vascular malformation rather than a neoplasm, although its behavior is aggressive and locally destructive. Nasopharyngeal Angiofibroma can invade vital intracranial structures, and can cause heavy bleeding that occasionally leads to exsanguinations (bleeding to death). Treatment is chiefly surgical; due to the high vascularity of the tumor, preoperative embolization may be performed to block blood flow to the lesion. Chemotherapy and radiation therapy

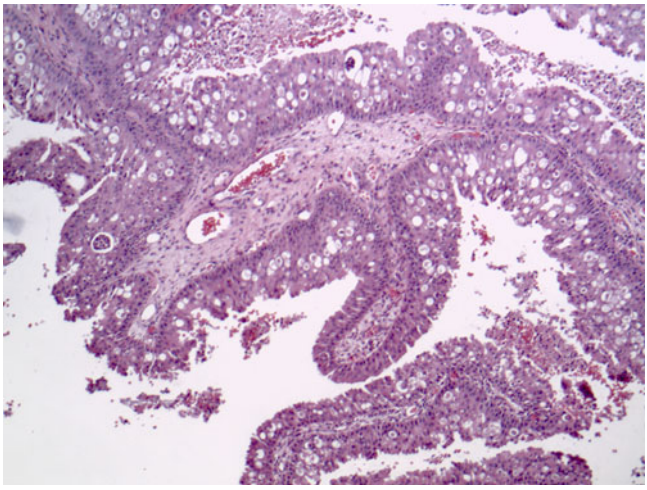

Fig. 7.25 Oncocytic (Cylindrical Cell) Sinonasal Papilloma. This Oncocytic Papilloma of the left nasal cavity exhibits pink columnar oncocytes (H&E, 10×)

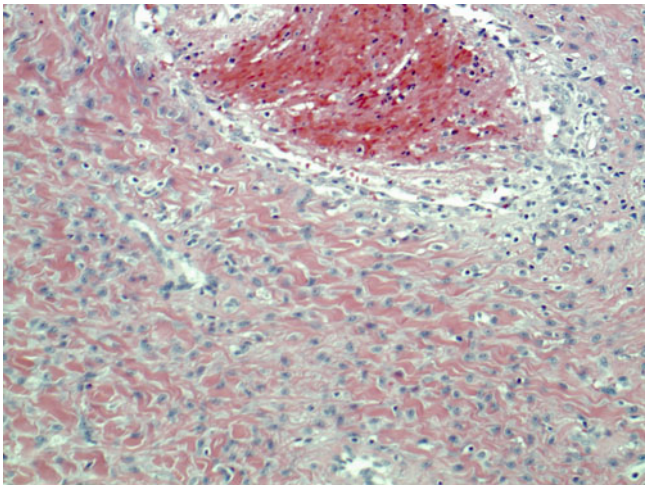

Fig. 7.26 Nasopharyngeal Angiofibroma. This mass of blood vessels and fibrous tissue arose in the nasal cavity of a 13-year-old boy (H&E, 20×)

are sometimes employed as adjunct therapies, despite the small potential for post irradiation malignant transformation. The recurrence rate is about 20%, and the death rate is about 1% (Fig. 7.26) [97].

7.4 Benign Neoplasms of the Jaws

Odontogenic tumors only originate in a potentially tooth-bearing region of the jaws. The enamel of teeth is a product of ameloblasts, which are epithelial. Dentin is created by odontoblasts, which are ectomesenchymal. Thus, odontogenic neoplasms may arise from odontogenic epithelium, odontogenic ectomesenchyme, or a mixture of the two. The World Health Organization classifies benign odontogenic tumors as those of:

- odontogenic epithelium with mature, fibrous stroma without odontogenic ectomesenchyme;
- odontogenic epithelium with odontogenic ectomesenchyme, with or without hard tissue formation; and
- mesenchyme and/or odontogenic ectomesenchyme with or without odontogenic epithelium [98].

7.4.1 Odontogenic Epithelium

The **Ameloblastoma** is an aggressive, unencapsulated, but benign odontogenic epithelial neoplasm of young adults. Although it is less common than Odontoma or Keratocystic Odontogenic Tumor in North America, Europe, and China, it is reported as the most frequent odontogenic tumors in many areas of the world [99–103]. It may form around the crown of a developing tooth, or in an area of the jaw where no tooth is present. It usually presents as an expansile multilocular radiolucency of the jaw, and can cause considerable destruction of surrounding tissues, including teeth. The Unicystic Ameloblastoma presents as a single cystic radiolucency, usually around the crown of an impacted tooth. Biopsy of Ameloblastoma reveals non-encapsulated islands of odontogenic epithelium with lining up (palisading) of the basal epithelial cell layer. The nuclei of the basal cells are pushed away from the basement membrane (reverse polarization), as shown in Fig. 7.27. These two features are often called the Vickers and Gorlin criteria. The epithelial islands may be cystic at their centers, and the suprabasal cells often resemble stellate reticulum of odontogenesis, although pathologists recognize various microscopic subtypes of Ameloblastoma. The Ameloblastoma has a substantial risk of recurrence, so excision with follow-up is the treatment of choice. The Unicystic variety has a lower risk of recurrence, and may represent an earlier phase of disease development. Peripheral Ameloblastoma occurs solely in the soft tissues of the gingiva [104, 105].

The most common tumor of odontogenic epithelium in North America and Europe is the **Keratocystic Odontogenic Tumor** (KOT), which was previously called the **Odontogenic Keratocyst** (OKC) [106]. This benign yet aggressive tumor makes up between 3 and 11% of odontogenic cysts in North America, although some reports state a higher rate above 20%. In other regions of the world, it is the

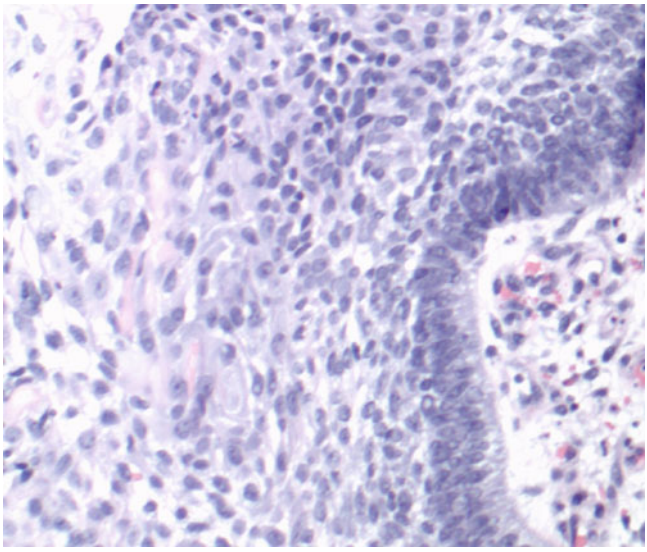

Fig. 7.27 Ameloblastoma. This epithelial proliferation of the mandible exhibits palisading of the basal epithelial layer and reverse polarization of basal cell nuclei (*right*). The cells to the left of the basal layer are more loosely arrayed, resembling the stellate reticulum seen in enamel formation (H&E, 40×)

second or third most common odontogenic tumor. It is most common in young adults. Radiographically, it presents as a well-defined corticated radiolucency that may be small or large, non-expansile or expansile, unilocular or multilocular. It may be located around the crown of an impacted tooth, or develop independently in a tooth-bearing region. Biopsy is necessary to establish the diagnosis, as it shares some clinical and radiographic features with other lesions such as the Ameloblastoma. The KOT has a distinctive histologic appearance with a thin lining, palisading of the basal epithelial layer, and a corrugated layer of parakeratin on the surface (Fig. 7.28). Treatment is surgical, and KOTs have a recurrence rate of up to 30% [101, 105, 107, 108]. Multiple KOTs are often associated with the autosomal dominant **Nevoid Basal Cell Carcinoma Syndrome (Gorlin-Goltz Syndrome),** caused by a mutation in the tumor suppressor gene PTCH1, which participates in the Hedgehog signaling pathway. Patients with this syndrome can experience hundreds of Basal Cell Carcinomas on skin, beginning a young age. Other potential problems include ovarian or cardiac Fibromas, Medulloblastoma of the brain, pits on the palms and soles, calcification of the falx cerebri, skeletal malformations, and other findings [109].

Other less common epithelial odontogenic neoplasms include **Calcifying Epithelial Odontogenic Tumor** (**Pindborg Tumor**) (Fig. 7.29)**,** which can arise over a wide age range and is less aggressive than the Ameloblastoma; **Adenomatoid Odontogenic Tumor,** an encapsulated non-aggressive tumor of youth; and the rare **Squamous Odontogenic Tumor** (Fig. 7.30).

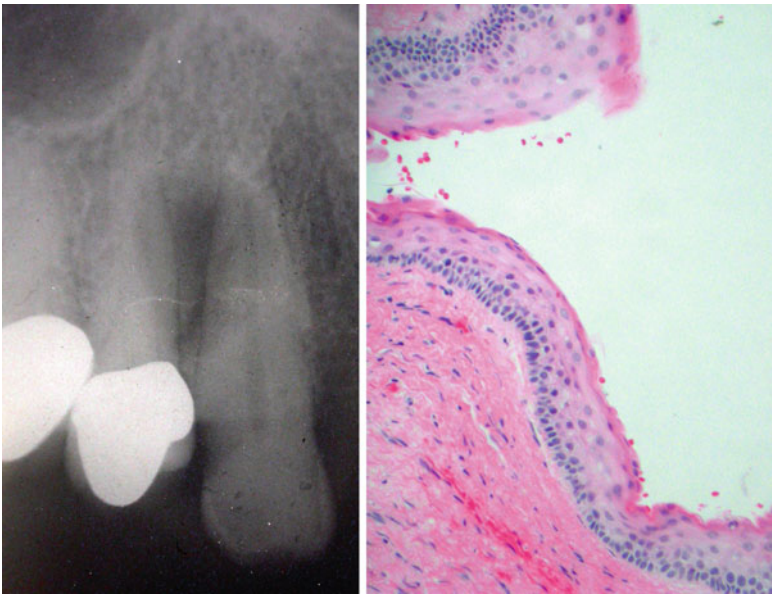

Fig. 7.28 Keratocystic Odontogenic Tumor (Odontogenic Keratocyst). The well-defined radiolucency (*left*) between the roots of the maxillary right cuspid and first bicuspid was biopsied. Biopsy (*right*) revealed a thin uniform cystic lining with a hyperchromatic palisaded basal layer and a layer of parakeratin, so the diagnosis was Keratocystic Odontogenic Tumor

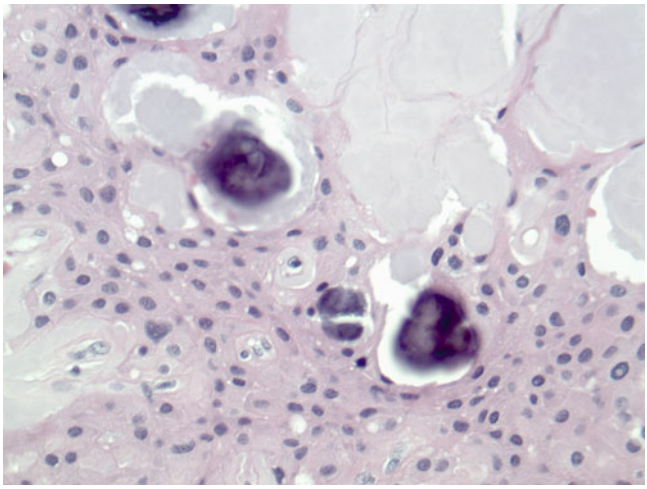

Fig. 7.29 Calcifying Epithelial Odontogenic Tumor. This tumor of the left maxilla exhibits focal calcifications and masses of somewhat pleomorphic eosinophilic epithelial cells (H&E, 40×)

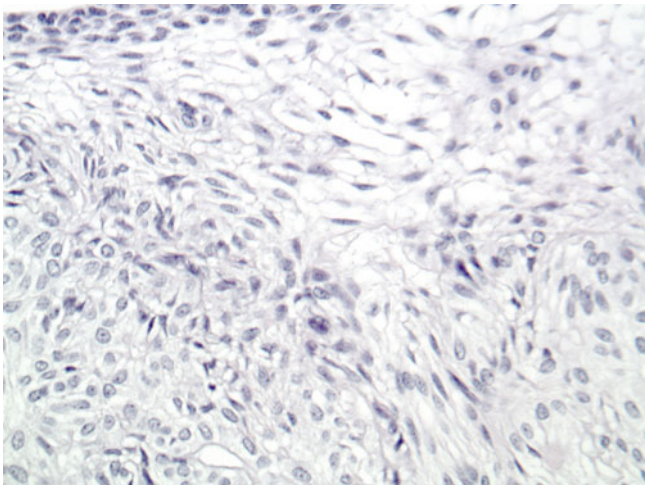

Fig. 7.30 Adenomatoid Odontogenic Tumor. This tumor of the anterior mandible in a 17 year-old was encapsulated. It exhibits aggregates of spindle-shaped epithelial cells, and occasional duct-like structures lined by cuboidal cells (H&E, 40×)

7.4.2 Odontogenic Epithelium and Odontogenic Ectomesenchyme

The **Odontoma** [110] is a non-aggressive tooth-like formation. Some classify it as an odontogenic tumor, while others consider it a hamartoma. Worldwide, it is in the top three most common odontogenic tumors. In the anterior maxilla, the most common type of Odontoma is the Compound Odontoma, essentially an aggregation of miniature teeth, while in the posterior mandible the Complex Odontoma is more common, representing a poorly formed discrete mass of dental hard tissues. Odontomas are most common in youth, and are uncommon in the primary dentition. They are not aggressive and do not recur after excision [111].

Examples of less common odontogenic tumors that arise from a mixture of odontogenic epithelium and ectomesenchyme include the **Ameloblastic Fibroma**, an encapsulated tumor of childhood, the **Ameloblastic Fibro-Odontoma**, an Ameloblastic Fibroma with an Odontoma component, and the **Calcifying Cystic Odontogenic Tumor (Gorlin Cyst)**, which is more common in an older population.

7.4.3 Odontogenic Ectomesenchyme

The **Central Odontogenic Fibroma** (COF) is a fibroblastic proliferation that may or may not contain a scattered inactive population of clustered odontogenic epithelial

cells, and focal calcifications. A COF without the epithelial population is referred to as a Simple COF, while a COF with the epithelial clusters is termed a WHO-type COF. COF is more common in younger patients, and some have reported a female predilection. The COF is a slow-growing neoplasm that can sometimes be seen in combination with a central giant cell lesion [112].

The **Odontogenic Myxoma** is an infiltrative paucicellular neoplasm of connective tissue. It produces large amounts of hyaluronic acid and chondroitin sulphate, which impart a distinctive mucinous appearance and texture. It is most common in early adulthood, and may recur after excision [113].

The **Cementoblastoma** is a benign tumor of cementum. In many respects, it is very similar clinically and histologically to the Osteoblastoma. However, it can be differentiated from the Osteoblastoma by its unique location; it grows attached to the root of a tooth, usually a mandibular molar. After resection, which usually necessitates extraction of the involved tooth, the Cementoblastoma does not recur [66].

7.4.4 Bone-Related and Tumor-Like Jaw Lesions

Osseous Dysplasias are benign fibro-osseous lesions that may represent hamartomas. They only occur in the tooth-bearing regions of the jaws, and they are sometimes known as Cemento-Osseous Dysplasias. Osseous dysplasias are quite common in middle-aged African American women, but they occur less frequently in other populations. These lesions begin as asymptomatic radiolucencies, which gradually develop cotton-wool radiopacities centrally as the lesions mature. They do not usually cause bone expansion or disturb adjacent teeth. Biopsy is not usually necessary, as the radiographic presentation is distinctive. The lesions are composed of fibrous tissue admixed with trabeculae of bone, and dense ovoid pieces of cementum-like hard tissue. The proportion of hard tissue increases as the lesion matures. The lesions are asymptomatic and do not expand the bone. Periapical, Focal, and Florid forms all have identical microscopic appearance and similar radiographic features. **Periapical Osseous Dysplasia** occurs only around the roots of anterior mandibular teeth, although it may involve multiple teeth in this specific site. The periapical radiolucencies of the early stage of this condition may be mistaken for periapical radiolucencies due to dental pulp necrosis, but tooth vitality testing usually indicates that the adjacent teeth have live pulps. **Focal Osseous Dysplasia** affects one site only, but not the anterior mandible. **Florid Osseous Dysplasia** occurs in multiple jaw sites, but like other forms of osseous dysplasia is strictly confined to tooth-bearing areas. It may bear some superficial resemblance to the cotton-wool radiopacities of Paget Disease of Bone, but the anatomic distribution of lesions is different. These sites in which these conditions occur are depicted in Fig. 7.31. The high density of the lesional bone makes it susceptible to osteonecrosis, for example under an ill-fitting denture, and such a case is shown in Fig. 7.32. Otherwise, Osseous Dysplasias need no treatment [114, 115].

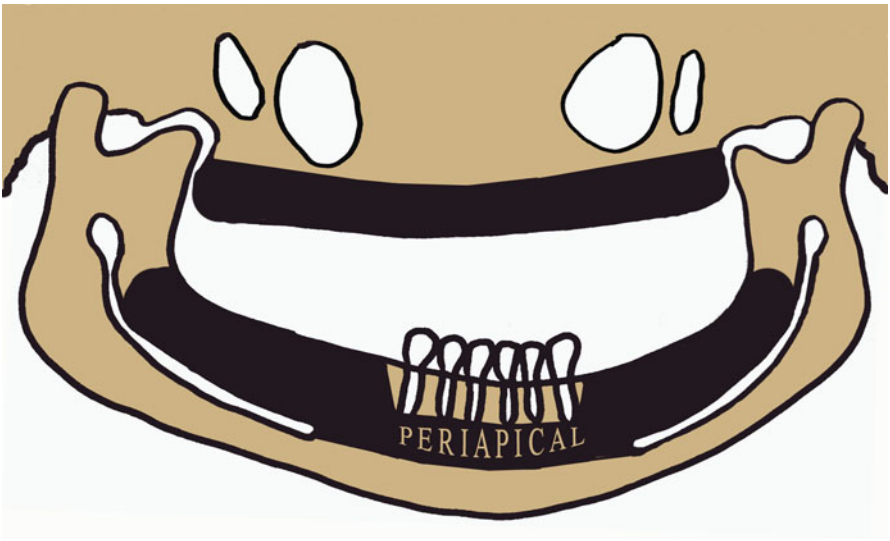

Fig. 7.31 Osseous Dysplasias. The areas where Osseous Dysplasias can occur are shown in *black*, in this depiction of partially edentulous jaws as they would be seen on panoramic radiograph. The cotton wool mixed radiolucent/radiopaque lesions of OD are found only in tooth bearing regions. If OD occurs around the roots of one or more anterior mandibular teeth (see area labeled PERIAPICAL above), it is termed Periapical Osseous Dysplasia. If OD occurs in only one site, excluding the anterior mandible, it is termed Focal Osseous Dysplasia. If OD occurs in multiple areas, it is called Florid Osseous Dysplasia. Note that lesions do not extend inferior to the inferior alveolar nerve canal, nor into the mandibular ramus

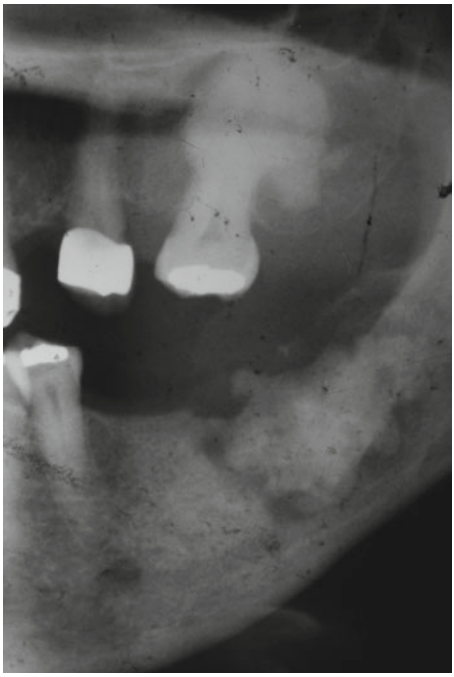

Fig. 7.32 Sequestrum in Florid Cemento-Osseous Dysplasia. This radiograph shows a sequestrum of necrotic bone that developed under the denture of a 69-year-old female with Florid Cemento-Osseous Dysplasia

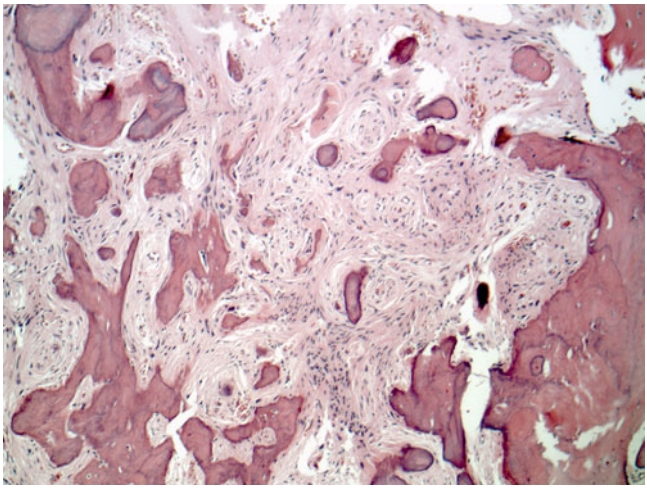

Fig. 7.33 Ossifying Fibroma. As a Benign Fibro-Osseous Lesion, this lesion is in some ways microscopically similar to Fibrous Dysplasia and other members of the group. It is composed of a mixture of fibrous and mineralized tissue with some round psammomatoid calcifications. It was a slow growing encapsulated mass in the left maxilla of a 55-year-old woman (H&E, 20×)

Ossifying Fibroma is also unique to the maxilla and mandible. A true benign neoplasm, it is a mass of fibrous and mineralized tissue. A member of the group of Benign Fibro-Osseous Lesions, it is a slow-growing, painless mass that may bear some radiographic similarity to Osseous Dysplasia. Unlike Osseous Dysplasia, Ossifying Fibroma can cause bone expansion and move adjacent teeth. It is initially a well-defined radiolucency (fibro-osseous tissue), but eventually develops a central area of radiopacity (mineralized tissue). When it is explored surgically, an encapsulated mass is discovered. The microscopic appearance of a case is shown in Fig. 7.33. Treatment is surgical excision [116].

7.5 Benign Salivary Gland Neoplasms

Pleomorphic Adenoma (PA) (Benign Mixed Tumor) is the most common benign salivary gland neoplasm, and can occur in any salivary gland, minor or major, including glands of the larynx and the paranasal sinus/nose. Its cutaneous counterpart is called the **Chondroid Syringoma** [117]. It presents as a slow growing painless mass, usually in a middle-aged patient. Tumors can attain a large size, and frequently will develop a multinodular character. The PA is characteristically encapsulated, although lesions on the hard palate may lose their capsule. In that specific site, lack of encapsulation is not a cause for alarm. Biopsy (Fig. 7.34) will reveal that the tumor is composed of a mixture of epithelial,

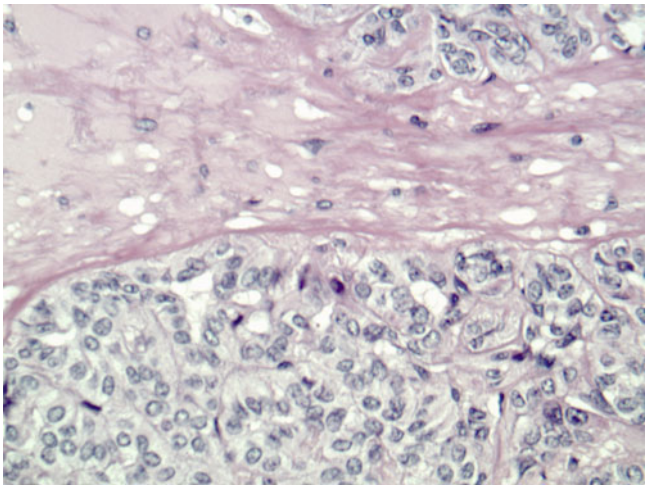

Fig. 7.34 Pleomorphic Adenoma. This Pleomorphic Adenoma occurred in an 89-year-old woman. Typically but not always encapsulated, PAs can have a confusing variety of microscopic appearances, even within the same specimen. A relatively unique feature of these tumors is the ability of the tumor cells, epithelial in origin, to mimic connective tissue cells and produce connective tissue elements such as fat, bone, cartilage, fibrous tissue, and hyalinized areas as seen in this specimen (H&E, 40×)

myoepithelial, and stomal components. Myoepithelial cells are interesting cells; although they are epithelial in origin, they function to squeeze saliva out of salivary acini. They contain contractile elements such as smooth muscle actin, smooth muscle myosin, and calponin [118]. When myoepithelial cells become neoplastic, they can begin to act in ways that are normally associated with connective tissue, not epithelium. Thus, Pleomorphic Adenomas can produce fat, bone, cartilage, hyaline, and myxoid areas. This tendency caused early pathologists to erroneously believe that PAs were tumors of both connective tissue and epithelium. The stromal tissue is mixed with myoepithelioid cells, which most commonly have a plasmacytoid or spindle appearance, and epithelial cells that are normally cuboidal. Ducts and tubules are often seen. Although excision is usually curative, the lesion may recur, particularly if the capsule has been broached. If a PA persists for many years, it may undergo malignant transformation into **Carcinoma Ex Pleomorphic Adenoma** [119–121]. A tumor that lacks ducts, tubules, and obvious epithelial elements is called a **Myoepithelioma,** and it may behave in a more aggressive manner [122].

"**Monomorphic Adenoma"** is an obsolete term for benign salivary gland tumors that are not Pleomorphic Adenomas. Warthin Tumor and Oncocytoma were removed from the umbrella term because they contain oncocytes; eventually the category included just the Canalicular Adenoma (CA) and the Basal Cell Adenoma (BCA). As understanding grew that CA and BCA were different tumors with differences in demographics and presentation, Monomorphic

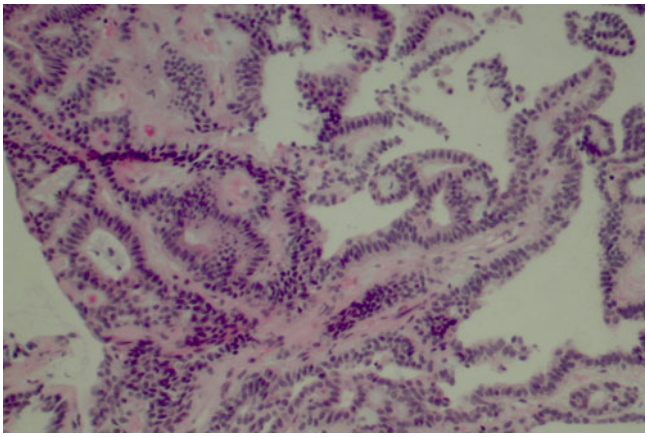

Fig. 7.35 Canalicular Adenoma. This Canalicular Adenoma of the buccal mucosa near the upper lip shows the characteristic bilaminar strands of cells with periodic kinking (H&E, 40×)

Adenoma was abandoned as a diagnosis [123, 124]. It may be used simply as an umbrella term.

Warthin Tumor, also known by the tongue-twisting yet pathologically descriptive name **Papillary Cystadenoma Lymphomatosum**, is a benign cystic neoplasm (cystadenoma) that contains papillary epithelial intraluminal projections. The cystadenoma is surrounded by a stroma that is rich in lymphocytes. Most often found in the parotid gland, this is an encapsulated tumor and may occasionally be bilateral [125]. It is the second most common benign neoplasm of the parotid gland, and more frequent in middle age. It is strongly associated with smoking, the only benign salivary gland neoplasm to show this association. Treatment is surgical, and recurrence is not expected [126–128].

Canalicular Adenoma usually occurs as a slow-growing mass in the minor salivary glands of the upper lip, where it is the most common salivary gland neoplasm. It occurs most often in older patients. Multiple synchronous and metachronous tumors may develop. Pathologically, it is encapsulated and displays bilaminar double-celled ribbons ("canals") of epithelial cells which can undergo kinking, the so-called "beading" phenomenon (Fig. 7.35). Treatment is surgical [129].

Basal Cell Adenoma also presents as a slow-growing mass, but it usually occurs in the major salivary glands, especially the parotid glands. It is a solitary encapsulated neoplasm. Composed of basaloid cells, it may display solid, membranous, tubular, and tubulo-trabecular forms. The membranous subtype may be part of an autosomal dominant syndrome that includes benign scalp tumors and potentially malignant Trichoepitheliomas [130].

Numerous other benign minor salivary gland neoplasms are less common; these include **Oncocytoma**, **Cystadenoma**, and **Ductal Papilloma**.

7.6 Benign Hypopharyngeal and Laryngeal Neoplasms

Laryngeal Papillomatosis (Recurrent Respiratory Papillomatosis) is a chronic recurrent condition of the larynx found mostly in children under the age of 5, although it can also occur in adults. It presents with multiple papillary growths, caused by HPV 6 and 11; these warts may occur at multiple sites in the upper airway but are most common in the larynx. They may appear as multiple discrete warts, or as a carpet-like proliferation. Patients may be hoarse, or complain of cough or choking. Juvenile-onset Laryngeal Papillomatosis is linked to transmission of genital HPV infection during childbirth, although maternal warts are not always transmitted to infants. Juvenile forms of the disease may be particularly aggressive. The treatment includes surgical excision and medical interventions. Aggressive cases may require repeated surgeries, but in some cases, the condition resolves spontaneously [131–138].

7.7 Benign Thyroid and Parathyroid Neoplasms

Most thyroid nodules are the result of hyperplasia, not neoplasia. However, up to 20% represent thyroid neoplasms. Thyroid Adenomas, solitary encapsulated masses, may be follicular or papillary. The **Follicular Adenoma** is the more common of the two, and is present in 2–3% of the population. Most Follicular Adenomas are clinically silent; patients do not typically present with hyperthyroidism. They may present with symptoms due to the size of the mass, such as hoarseness or difficulty swallowing. Diagnosis is usually by means of ultrasound and fine needle aspiration biopsy, but distinction between Follicular Adenoma and Follicular Carcinoma may be difficult. Follicular Adenomas are subclassified histologically as fetal, colloid, embryonal, and Hürthle cell types; only the colloid subtype is not capable of microinvasion. They are often surgically excised because of the diagnostic difficulties and because some progress to Follicular Carcinoma. However, after excision, a Follicular Adenoma is not expected to recur [139, 140].

Parathyroid Adenoma is the most common cause of primary hyperparathyroidism. High levels of parathyroid hormone take calcium out of the bones and put it into the bloodstream, causing hypercalcemia. Symptoms of full-blown hyperparathyroidism, which is rare today, include *stones* (metastatic calcifications such as renal stones; hypercalcemia can progress to renal insufficiency), *bones* (diffuse bone loss, loss of lamina dura on dental radiographs, and central giant cell granulomas), *moans* (malaise, confusion, nervousness, psychosis), and *groans* (stomach hyperacidity, nausea, constipation, and abdominal pains). Parathyroid Adenoma is the most common feature of **Multiple Endocrine Neoplasia Type 1** (MEN1, Wermer Syndrome), a heritable syndrome caused by mutation of the MEN1 tumor suppressor gene. MEN1 can also feature various benign and malignant tumors. Besides parathyroid, the other glands that are most commonly affected in MEN1 are the pituitary (Prolactinomas and Somatotrophic Adenomas are the most common) and pancreas (Gastrinomas

and Insulinomas are the most common benign tumors, but malignancy may develop). Other findings can include Carcinoid tumors, cutaneous Lipomas, Collagenomas, and Angiofibromas, as well as gingival papules [141–144].

7.8 Conclusions

The head and neck includes a number of specialized tissues such as salivary glands and teeth, which leads to the development of an array of benign tumors not found elsewhere in the body. The orifices of the face are the body's portals to the world, so a number of environmental influences have a particularly strong effect – for example, carcinogens, and other compounds carried in air and food. The human body is also encountering relatively new chemical challenges, such as tobacco, ethanol, pollutants, and electromagnetic radiation that will continue to exert pathologic influences. Infections are frequent in the head and neck because of its role as the body's gateway, and some of these infections such as HPV can lead to the development of unique lesions. The teeth and periodontium are sites to some of the most common infections in the human body: gingivitis, periodontitis, and dental caries. The complex oral biofilm and the resulting microenvironment interact with oropharyngeal tissues in ways that are just beginning to be explored. The intensity of infectious challenges to the oropharynx and nasopharynx has lead to the development of highly specialized immunologic defenses, so it is unsurprising that a variety of immunologic diseases occur in this region. The development of the head and neck follows a special embryologic pathway, which can lead to tumors and tumor-like lesions that are not found elsewhere. Finally, metabolic diseases may have highly visible consequences in the head and neck. All of these influences may play a role in the development of head and neck neoplasms, and they can also give rise to developmental, allergic/immune, metabolic, and infectious conditions, as will be explored in the next chapter.

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Chapter 8
Benign Non-neoplastic Lesions of the Head and Neck

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Contents

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Abstract This chapter continues the previous chapter's discussion of the DAMIEN mnemonic concept for formulating a differential diagnosis of pathology of the head and neck. The categories to be discussed are Developmental, Allergy or immunologic, Metabolic or systemic, Infectious, and Environmental. Neoplastic benign conditions were discussed in the prior chapter, and malignant neoplastic conditions are discussed elsewhere in this book. In each category, pathologic entities or conditions common to multiple sites in the head and neck are discussed, followed by discussion of examples of pathology characteristic to several different locations in the head and neck.

Keywords Benign pathology • Head and neck • Developmental • Immunologic • Metabolic • Infectious • Environmental • Non-neoplastic

Abbreviations

ANCA	Anti-neutrophil cytoplasmic antibodies
BMG	Benign Migratory Glossitis
CMV	Cytomegalovirus
COC	Calcifying Odontogenic Cyst
DAMIEN	**D**evelopmental **A**llergic/immunologic, **M**etabolic/systemic, **I**nfectious, **E**nvironmental, or **N**eoplastic
EAF	Eosinophilic Angiocentric Fibrosis
EBER	In-situ hybridization for EBV-encoded RNA
EBV	Epstein Barr Virus
GERD	Gastroesophageal Reflux Disorder
GOC	Glandular Odontogenic Cyst
H&E	Hematoxylin and Eosin stain

HHV-1	Human Herpesvirus Type 1 (aka HSV type 1)
HHV-2	Human Herpesvirus Type 2 (aka HSV type 2)
HHV-3	Human Herpesvirus Type 3 (aka VZV)
HHV-4	Human Herpesvirus Type 4 (aka EBV)
HHV-5	Human Herpesvirus Type 5 (aka CMV)
HHV-8	Human Herpesvirus Type 8 (aka Kaposi Sarcoma Associated Virus)
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HSV	Herpes Simplex Virus
LPC	Lateral Periodontal Cyst
MAGIC	Mouth And Genital Ulcers with Inflamed Cartilage
NSAID	Non-steroidal anti-inflammatory drug
PCR	Polymerase Chain Reaction
RAS	Recurrent Aphthous Stomatitis
REAH	Respiratory Epithelial Adenomatoid Hamartoma
SLE	Systemic Lupus Erythematosus
VZV	Varicella Zoster Virus
WG	Wegener's Granulomatosis
WHO	World Health Organization

8.1 Introduction

The head and neck region encompasses a great variety of tissue types and accordingly, there are a multitude of benign lesions that occur in the head and neck. Since a comprehensive discussion of all benign entities of the head and neck is beyond the scope of this chapter, one way to view these lesions is based on disease process. As mentioned in the previous chapter, a helpful differential diagnosis tool for pathologic lesions is the DAMIEN system, based on several broad groups of etiologic processes: Developmental, Allergic/Immune, Metabolic/Systemic, Infectious, Environmental, and Neoplastic. General geographic regions of the head and neck include sinus/nose/nasopharynx, oral cavity/oropharynx, hypopharynx/larynx, ears, neck, salivary glands, and thyroid/parathyroid glands. Many disorders are common to multiple locations in the head and neck but some are unique or characteristic for one location. This chapter will discuss each disease process, first in terms of diseases that share several locations in the head and neck, and then in terms of diseases that are characteristic for specific locations.

8.2 Developmental Conditions

8.2.1 General Considerations for Developmental Conditions

In general, developmental lesions of the head and neck often occur in younger patients than other pathologic entities. Lesions that are common to several locations

in the head and neck include Hamartomas, Teratomas, Choristomas, and Heterotopias. These lesions often are present in early life. Many of these are asymptomatic and found incidentally. Developmental lesions are usually treated by observation, medical management, or surgical management in some cases [1].

Hamartomas are proliferations of tissue that is native to a given area and can be either mesenchymal (connective tissue) or epithelial (surface tissue) [1]. Hamartomas of many different tissue types can be found in multiple locations in the head and neck: in the sinonasal/nasopharyngeal, oropharyngeal/oral cavity, ear, and laryngeal areas [2, 3]. Nasal hamartomas have an incidence of 1 in 20,000–40,000 individuals [4]. Most sinonasal hamartomas are mesenchymal. Blood vessel proliferations are the most common, but hamartomas can also be composed of fat, cartilage, chondromesenchymal tissue (connective tissue with a cartilage-like appearance), epithelial, or glandular tissue [5]. In the oral cavity, hamartomas can be composed of mesenchymal tissue (such as smooth muscle) or odontogenic epithelium, which functions to produce teeth in normal development [6, 7]. Multiple hamartomas of the oral cavity can be associated with syndromes such as Oro-Facial-Digital Syndrome, Tuberous Sclerosis, Cowden Syndrome, and Cleft Palate [2, 8, 9]. Hamartomas of the ear and larynx are very rare but reported [10, 11].

A **Teratoma** is composed of tissues from all three germ cell layers: endoderm, mesoderm, and ectoderm. These can be solid or cystic [12]. Teratomas are the most common tumor-like lesions in infants, and are usually found at the midline of the body [13]. After the sacrococcygeal region, the head and neck is the second most common area of involvement; locations here include the neck, thyroid, neck, palate, and nasopharynx [13, 14]. One common type of cystic teratoid lesion is the **Dermoid Cyst,** which has a cyst lining similar to the skin, with appendages such as hair and sometimes cartilage and muscle in the wall [15, 16]. The dermoid cyst is most commonly found in the neck; it comprises one quarter of masses found on the midline [17]. Other locations for dermoid cysts include the floor of the mouth, nasopharynx, periorbital, and larynx [14, 18]. The **Hairy Polyp** is a teratoma that occurs in the nasopharynx, oropharynx, or middle ear [18]. In the nasopharynx, it is the most common congenital growth [16]. The **Epidermoid Cyst** is very similar to a dermoid cyst; it may occur on the skin of the face or back and typically arises from a hair follicle [19]. It is similar to the dermoid cyst histologically, except that it lacks dermal appendages in the cyst wall (Fig. 8.1) [19].

Choristomas are composed of proliferations of tissues that are non-native to the location [20]. **Heterotopias** are similar to choristomas; they consist of normal-looking tissue in an abnormal location [20]. Choristomas of the head and neck occur in the oral cavity (tongue, floor of mouth), pharynx, and hypopharynx [21]. In the oral cavity, most of the lesions of the anterior tongue or floor of the mouth are composed of cystic respiratory or gastrointestinal epithelium, known as **Anterior Median Lingual Cysts** [21]. Other choristomas in the oral cavity can be composed of osseous (bone) or cartilaginous tissue, for example, osseous choristomas of the tongue (Fig. 8.2) [22]. Choristomas and heterotopias are also reported in the middle ear where the most common tissue type is salivary [23]. Heterotopias may contain glial (central nervous system) tissue; these are usually present at birth but may not be detected until later [24].

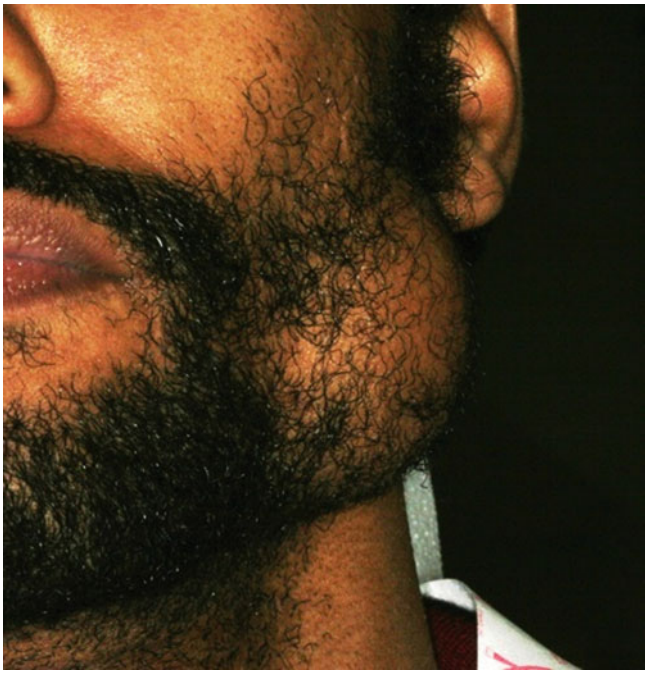

Fig. 8.1 Epidermoid cyst. A fluctuant subepidermoid mass in the left masseter area had been present for several years. The clinical impression was Epidermoid Cyst. A CT scan was performed which confirmed the clinical impression; however, the patient was lost to follow-up prior to biopsy

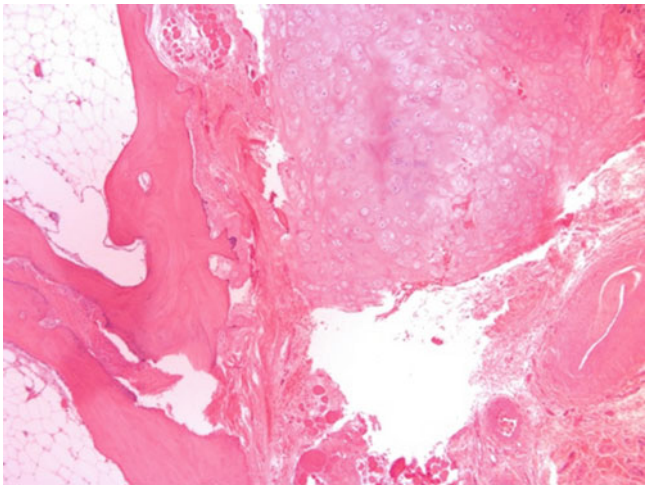

Fig. 8.2 Osseous and cartilaginous choristoma in the upper lip of a 58 year-old male patient. Histological examination revealed mature bone and cartilage tissue with supporting connective and adipose tissues (H&E, 5×)

An **Encephalocele**, by contrast, is a lesion in which brain tissue herniates into an abnormal location [24]. There are also histological differences between the two [24]. Glial heterotopias are most common in the sinonasal area but have also been reported in the nasopharynx and parapharynx, soft palate, tongue, lip, and scalp, and rarely in the middle ear, orbit, and other locations [25]. Heterotopia of the salivary glands can also be found in multiple locations [26].

Developmental lesions characteristic of specific locations in the head and neck are discussed in the following sections.

8.2.2 Sinonasal/Nasopharyngeal Developmental Conditions

Glial Heterotopias (also called Nasal Gliomas) are most specific to the sinonasal region. An extranasal glial heterotopia (60% of the cases) presents as a mass in the nasal dorsum or glabella, An intranasal glial heterotopia (30% of cases) most often occurs in the lateral nasal wall, middle turbinate, or nasal septum; 10% occur both extranasally and intranasally [27, 28]. They are usually detected in the first year of life but have been reported as "acquired" in older patients, possibly as an encephalocele whose connection to the brain has been lost over time [28, 29]. Nasal gliomas are histologically characterized by neural tissue mixed into supporting connective tissue [29]. **Encephaloceles,** defined above, are most often found in the occipital region but about 10% are located in the nasal sinuses [28, 30]. Most are treated by surgical intervention [30].

The **Respiratory Epithelial Adenomatoid Hamartoma (REAH)** is composed of lining epithelium of the type found in the respiratory tract, forming seromucous glands. It is usually found in the posterior nasal septum and rarely in the nasal cavity [31, 32]. It is the most common hamartoma in the sinonasal tract, yet it is rare [33]. It is significantly more common in males and is usually found in adults [31, 33]. A less common but likely related hamartoma of the sinonasal tract is the **Seromucous Hamartoma**, which is composed of similar glandular structures forming small tube-like patterns [31]. This is found most often in the posterior nasal septum and rarely in the nasopharynx; it is slightly more common in males [31, 33]. Most seromucous hamartomas also contain focal areas of REAH [31]. These glandular hamartomas generally behave in a benign manner [31]. They are generally treated by excision with low rate of recurrence [34].

8.2.3 Oral/Oropharyngeal Developmental Conditions

The oral cavity is home to a wide variety of conditions considered developmental in origin including both soft tissue and gnathic entities. These include ectopic sebaceous glands (termed **Fordyce Granules**), which have been reported in over 80% of patients, and **Leukoedema**, a mucosal condition of unknown etiology. Leukoedema

gives a gelatinous whitish appearance to the intraoral mucosa, most often buccal mucosa, but disappears when stretched [19, 35]. It can vary greatly by ethnicity but is seen in up to 60% of patients in a given cohort [36, 37]. Leukoedema is especially common in patients of African ancestry. These entities require no treatment.

Perhaps the group of developmental lesions with the most diversity is the vast group of odontogenic cysts that may be found in the tooth-bearing areas of the jawbones. Some of these cysts are currently regarded as cystic tumors, and were discussed in the previous chapter. The best known is the Odontogenic Keratocyst, which was recently re-named the Keratocystic Odontogenic Tumor in recognition of its classification as a benign neoplasm.

However, most odontogenic cysts are considered developmental, rather than neoplastic. By far, the most common entity in this category is the **Dentigerous** or **Follicular Cyst**, an epithelial lined cyst surrounding the crown of an unerupted or impacted tooth. It comprises 20% of all jaw cysts [6]. Dentigerous cysts are generally treated via enucleation at the time of removal of the impacted tooth [6].

Other odontogenic cysts include the **Lateral Periodontal Cyst (LPC), Glandular Odontogenic Cyst (GOC),** and **Calcifying Odontogenic Cyst (COC)**. The LPC is rare, accounting for approximately 1% of jaw cysts [38]. It is generally asymptomatic and often found incidentally as radiolucency at the lateral aspect or side of a tooth, favoring the canine and premolar regions [39]. The LPC has a distinctive histological appearance; it is lined by epithelium showing focal thickenings along with clear cells [39]. LPC is treated with conservative excision [39]. The GOC can be an aggressive cyst and occurs more commonly in the anterior of the jaws, usually in the mandible [40]. It may appear as a unilocular or multilocular radiolucent lesion [40]. Numerous histological features have been attributed to GOC but a recent publication found the most important to be the presence of small "microcysts" in the epithelial lining, focal thickenings in the cyst lining similar to the LPC, and the presence of clear cells (Fig. 8.3) [40]. They are usually treated with conservative excision [40]. The Calcifying odontogenic cyst is a rare but sometimes aggressive cyst that occurs most commonly in the maxillary anterior regions of the jaws and appears as a mixed radiolucent and radiopaque lesion [41]. It is lined with epithelium containing ghost cells, or squamous cells which have lost their nuclei [41]. It is also treated with conservative excision [6].

The most common non-odontogenic cyst of the oral cavity is the **Nasopalatine Duct Cyst** or **Incisive Canal Cyst**. It occurs in about 1% of the population and composes 40–70% of non-odontogenic oral cysts [19, 42–44]. This cyst arises between the maxillary central incisors from the remnants of the nasopalatine duct and is most common in adults in the 4th to 6th decades [45]. It may have a variety of different epithelial lining types but most commonly is composed of respiratory or stratified squamous epithelium or a combination of both. A distinctive histological feature is that the cyst wall usually contains neurovascular bundles consistent with the contents of the nasopalatine duct [19, 45]. Recurrence is rare, and treatment consists of surgical enucleation [45].

Tori (singular: Torus) and **Exostoses** are very common in the oral cavity. These are protuberances of normal cortical bone and fibro-fatty marrow. They are named according to location. The **Torus Palatinus** is located at the midline of the hard palate, and

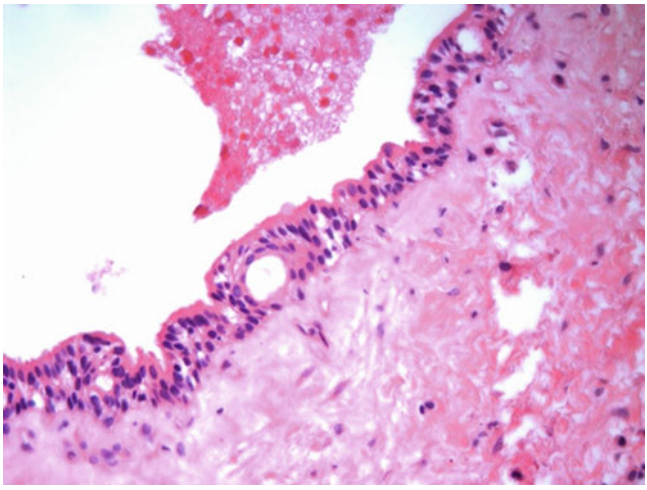

Fig. 8.3 Glandular odontogenic cyst. Features shown include formation of microcystic spaces in the epithelial linings, clear cell change, and apocrine appearance of epithelial cells (H&E, 40×)

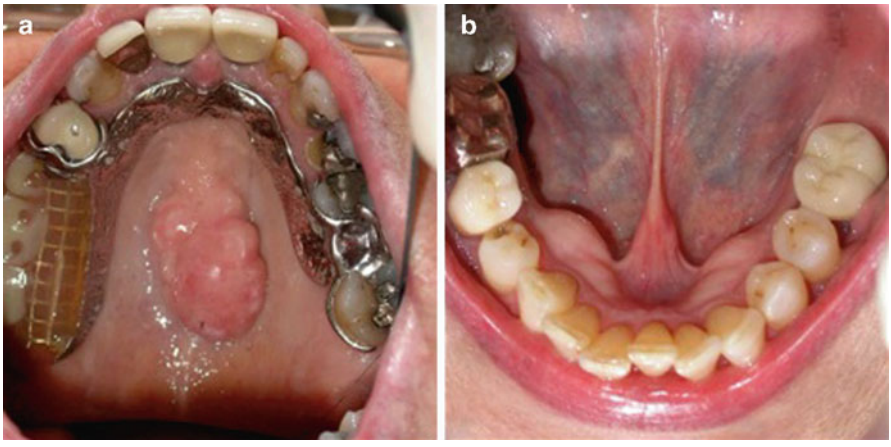

Fig. 8.4 Tori. (**a**) Multilobated palatal torus at the *midline* of the hard palate. (**b**) Bilateral tori on the lingual aspect of the mandible appearing as smooth submucosal bony protuberances in the canine and premolar areas

the **Torus Mandibularis** is generally bilateral on the lingual aspect of the mandible (Fig. 8.4). About 9–60% of the population has torus palatinus, and torus mandibularis has been reported in 5–40% [19]. Exostoses often refer to bony outgrowths on the buccal surface of the jaws. They are most likely due to a combination of genetic and environmental factors. Exostoses are less common than tori [46]. These lesions rarely cause a problem unless they obstruct the fit of a denture or partial denture.

8.2.4 Hypopharyngeal/Laryngeal Developmental Conditions

Laryngomalacia is the most common congenital laryngeal abnormality (60–75%) and the most common cause of infant breathing difficulty [47, 48]. Laryngomalacia occurs when the supraglottic tissue collapses onto the glottis during inspiration due to an abnormality of the epiglottis or surrounding tissues [47, 48]. It is rare but can be life threatening [47]. Most childhood cases resolve early, but surgery is needed in 15–20% of cases [48, 49]. There is also a late-onset form in adults [48]. The pathogenesis is poorly understood but it may be syndromic (most often associated with Down syndrome) or familial [48, 50]. In some cases, it has been linked to gastro-esophageal reflux disorder (GERD) and may respond to treatment of the GERD [47, 49, 51].

Laryngeal cysts are often developmental in origin. The **Laryngocele** and **Saccular Cyst** compose a spectrum of lesions, which differ in that Laryngoceles are dilated areas of the laryngeal saccule that cause symptoms or can be visualized on endoscopic exam [52]. The saccular cyst is similar to a laryngocele but maintains a connection to the inner aspect of the larynx [52]. Laryngoceles are usually filled with air but if they become filled with mucus, they are termed "Laryngomucocele", and if filled with pus are termed "Laryngopyocele" [52]. Laryngoceles may be located internally to the thyrohyoid membranes, externally, or in a combined location [52]. Laryngoceles may be congenital or acquired [53]. They are characterized histologically by respiratory type epithelium and a thin basement membrane [53]. Treatment consists of excision, with antibiotics if secondary infection is present [54]. Laryngoceles are sometimes associated with cancer of the larynx [54].

8.2.5 Auricular Developmental Conditions

Auricular lesions can be classified according to their location: external, middle, or inner ear. In the external ear, a common developmental lesion is the **Accessory Tragus**. The tragus is the cartilaginous fold on the anterior aspect of the ear canal. Accessory tragus is usually an isolated developmental defect but can be familial or associated with syndromes such as Goldenhar Syndrome and others (Fig. 8.5) [20, 55]. It is an aberration of the first branchial arch and the incidence has been reported as less than 1% consistently in multiple different geographic locations [55–57]. It usually presents as a skin-colored nodule anterior to the tragus but can be in other locations [55]. It is bilateral in 6% of cases [55]. Excision is generally curative [20].

8.2.6 Neck Developmental Conditions

The **Branchial Cleft Cyst** is the second most common congenital lesion of the head and neck, second only to the Thyroglossal Duct Cyst, which will be discussed later in this chapter [58, 59]. It comprises 20% of cervical masses in children [58].

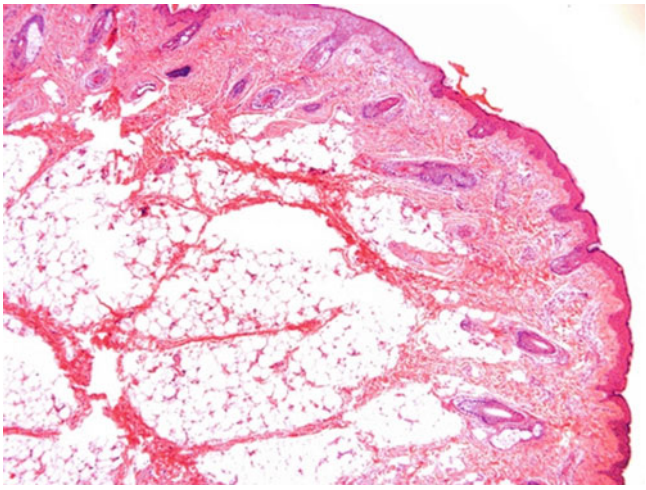

Fig. 8.5 Accessory tragus. These preauricular developmental lesions show normal surface epidermis and adnexal structures with underlying fibro-fatty tissue and sometimes a cartilage core (H&E, 5×)

The most accepted theory is that it arises from a failure of the disappearance of the embryonal branchial clefts and pouches during development [58]. Almost all (95%) are associated with the second branchial arch [58]. Cysts associated with the first branchial arch usually arise in the external auditory canal and rarely in the inner ear. Those of the second branchial arch usually occur in the supratonsillar fossa, and those of the third and fourth arches are found in the pharyngopyriform sinus [59]. They are composed of respiratory or squamous epithelial lining with variable amounts of lymphoid tissue, sebaceous tissue, or salivary tissue in the stroma (Fig. 8.6) [59]. Rare malignant forms have been reported, but many of these may actually represent metastatic cystic Squamous Cell Carcinoma [59]. Treatment consists of surgical excision [60].

Rare cysts of the neck include the **Cervical Thymic Cyst, Bronchial** or **Bronchogenic Cyst, Parathyroid Cyst,** and **Thoracic Duct Cyst**. Most of these cysts are named for the tissue components that they recapitulate or consist of. The cervical thymic cyst usually occurs in the lateral neck of a child [61]. On biopsy, it has thymic tissue in the cyst wall [61]. The bronchial/bronchogenic cyst contains elements that would be found in the respiratory structures [62]. It is most often found in children as an asymptomatic neck mass, usually above the sternal notch [62], composed of respiratory-type epithelium; it sometimes may contain cartilage and smooth muscle in the cyst wall [62]. The parathyroid cyst is usually found in adults and may cause hyperparathyroidism [63]. It is usually a lateral neck cyst and may be asymptomatic or a palpable mass. It is composed of a single layered cuboidal epithelial cyst with parathyroid tissue in the cyst wall [64]. Thoracic duct cysts

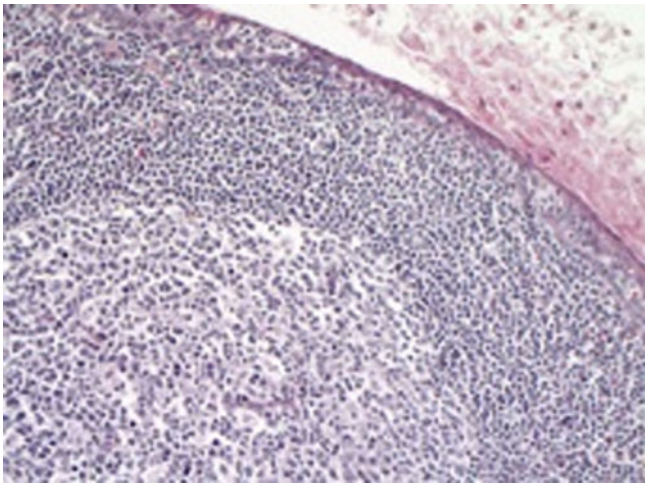

Fig. 8.6 Brachial cleft cyst. Histological examination reveals a stratified squamous epithelial lining with florid lymphoid aggregates in the cyst wall. A germinal center is noted at the *bottom left* (H&E, 40×)

are rare in the neck, and are more often found in the abdominal or thoracic areas. They are thought to be due to either a congenital weakness of the thoracic duct or an acquired disease [65]. Treatment for most of these cysts consists of surgical excision [66, 67].

8.2.7 Salivary Gland Developmental Conditions

One example of a salivary gland developmental lesion is **Salivary Heterotopia**. Salivary tissue is considered ectopic or heterotopic if it is found outside of the major (parotid, submandibular, sublingual) or minor salivary glands (on the palate, buccal and labial mucosa, or tongue). Heterotopic salivary tissue is most often found in the neck, and less frequently in the mandible, middle ear, pituitary, or parathyroid glands [26]. Rarely it may be found in far distant sites such as the mediastinum or rectum [26]. Most cases are evident early in life. Neck lesions tend to occur close to the sternocleidomastoid muscle [26], and the right side of the neck is most often affected than the left. They can be serous or mucous, or a mixture of the two [26]. They are generally cured by excision [26].

Polycystic Disease Of The Salivary Glands is a rare developmental condition [68, 69]. It is usually found bilaterally in females early in life [68, 69]. It is usually an asymptomatic bilateral swelling [69]. Histologically, it contains multiple cysts composed of salivary duct tissue [69]. Treatment is usually not indicated except in cosmetic incidences [68].

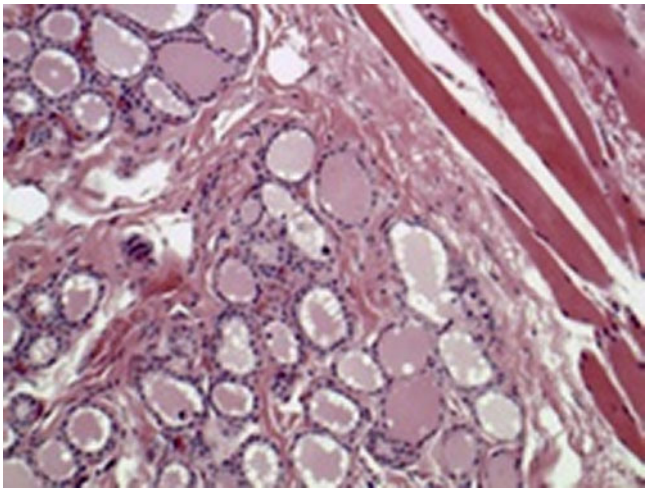

Fig. 8.7 Thyroglossal duct cyst. Thyroid follicles are present in the cyst wall (H&E, 40×)

8.2.8 Thyroid/Parathyroid Developmental Conditions

The most common congenital head and neck lesion is the **Thyroglossal Duct Cyst**, which is up to three times more common as the branchial cleft cyst [59, 70]. It may appear anywhere along the pathway along which the thyroid gland descends during development, from an area termed the foramen cecum, on the posterior midline of the tongue, to the lower neck at the midline. It most often presents in the hyoid area [17]. This cyst may occur over a broad age range [71]. Clinically, it consists of a mass whose movement corresponds with swallowing and tongue protrusion [17]. A significant complication of this cyst is the tendency to secondary infection, thus it may also present as a draining sinus at the midline [17]. Histologically, it is a cyst formed by ductal-type epithelium that may or may not contain thyroid tissue in the cyst wall [17] (Fig. 8.7). It is generally excised via the sistrunk procedure [18]. Carcinoma arising from a thyroglossal duct cyst is rare, but when it occurs most consist of **Papillary Thyroid Carcinoma** [70].

Up to 90% of ectopic thyroid tissue occurs at the base of the tongue in the foramen cecum area, where it is termed a **Lingual Thyroid**. It may arise anywhere else on the path of thyroid descent; it may occur in the mediastinum, or rarely below the diaphragm (Fig. 8.8) [72]. The **Lateral Ectopic Thyroid** usually occurs in a submandibular location, usually on the right side [73]. It can also be found rarely in intratracheal, intrathoracic, or intracardial locations [73]. Clinically significant ectopic or lingual thyroid is rare; however, at autopsy up to 10% of patients have ectopic thyroid tissue [73, 74]. In 70–90%, this tissue is the patient's only functioning thyroid tissue [73]. It is more common in females, and approximately 33% present with hypothyroidism [75]. Biopsy must be performed with caution due to the

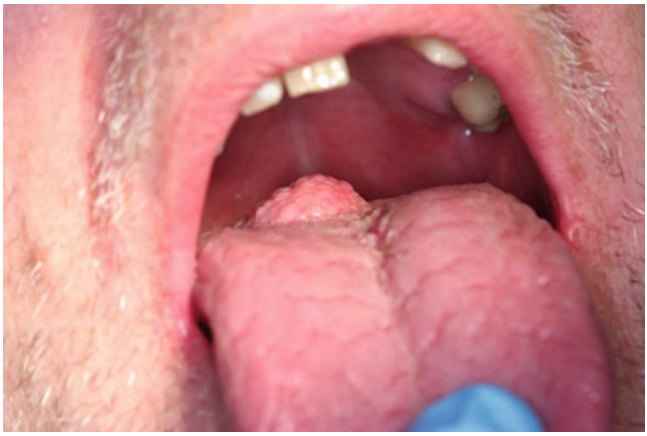

Fig. 8.8 Ectopic thyroid. This *pink* sessile mass on the posterior dorsal tongue in a 58-year-old male had been present since childhood. The patient had a long history of thyroid dysfunction. The clinical diagnosis was Lingual Thyroid (Ectopic Thyroid). The patient refused further follow-up

possibility of the tissue being the only functioning thyroid tissue for the patient [19]. Malignant transformation is rare but reported in approximately 1% [19].

8.3 Allergic/Immunologic Conditions

8.3.1 General Considerations for Allergic/Immunologic Conditions

Systemic disorders that manifest in multiple locations of the head and neck include, among others, Wegener's Granulomatosis, Sarcoidosis, Systemic Lupus Erythematosus, and various vesiculobullous disorders.

Wegener's Granulomatosis (WG) is an idiopathic systemic disease causing inflammation of the blood vessels and granulomatous inflammation. It mainly affects the upper respiratory tract, lungs, and kidneys, although forms limited to the head and neck have been reported [76]. According to some reports, the head and neck is involved in nearly all Wegener's cases [77]. Sinonasal areas are the most frequently affected sites in the head and neck [78]. Chronic sinusitis is common. A perforated nasal septum or saddle nose deformity may result [78]. Ocular lesions may also be noted over time in almost half of patients, and may present in diverse ways [76]. The ear is also a common site, and by far the most common ear location is the middle ear; most cases manifest as otitis media with effusion [78]. The external and inner ear are rarely involved [78]. Inner ear lesions may result in sensorineural hearing loss [76]. Laryngeal or tracheal lesions, though not common, may result

in subglottic stenosis [76]. The oral cavity is rarely affected, but WG of the oral cavity may present as a deep ulcer or as "strawberry gingivitis", a deep red diffuse nodular gingival hyperplasia [76, 78]. The salivary glands can rarely develop WG-associated sialadenitis [76, 78]. Facial palsy can be an initial manifestation [20]. Cutaneous lesions occur in many patients [78]. Histopathologically, Wegener's granulomatosis consists of granulomatous inflammation and vasculitis along with necrosis [79]. Laboratory diagnosis measures anti-neutrophil cytoplasmic antibodies (ANCA) proteins, especially ANCAs reacting with the neutrophilic enzyme proteinase 3 (cANCA) [20]. The progression of the disease is variable, and treatment most often consists of corticosteroids and immunosuppressive therapy [20].

Sarcoidosis is another multi-organ disease of unknown etiology. It affects patients of African ancestry in a disproportionate manner. It is thought to be related to an abnormal antigen-triggered and cell-mediated immune response. Genetic and environmental factors appear to play a role in its development, but they are incompletely understood [80]. In some cases, it causes no symptoms, and in others, it causes nonspecific symptoms such as fever, weight loss, fatigue, and organ specific disease [80]. Pulmonary involvement occurs in 90% of cases, although it may be subclinical as only 30–50% of patients may show lung symptoms [80, 81]. Lymph node involvement, usually thoracic, is present in many cases as well; affected hilar nodes are often described as "potato nodes" and their appearance on routine lung radiographs may lead to the detection of an asymptomatic case [80]. Cutaneous manifestations are fairly common [80]. The head and neck is involved in 10–15% of cases of Sarcoidosis, usually in the form of cervical lymphadenopathy [82]. The next most common head and neck location involved is the parotid gland, where facial palsy can occur because of facial nerve compression [80]. The other salivary glands are rarely involved by sarcoidosis [83]. Dry mouth sometimes occurs with salivary involvement, and the combination of xerostomia and gland enlargement may lead to a differential diagnosis of Sjögren Syndrome which is discussed later in this chapter. **Heerfordt's Syndrome** is characterized by sarcoidosis with parotitis (parotid inflammation), uveitis (inflammation of the uvea of the eye), facial paralysis, and fever [80]. Other rare head and neck locations include the nose and sinuses; external, middle, and temporal bone regions of the ear; larynx and trachea; lacrimal glands and eye; oral mucosa; and tonsils [78, 81, 83, 84]. Sarcoidosis is generally diagnosed by clinical presentation along with chest x-ray findings, and biopsy demonstrating noncaseating chronic granulomatous inflammation (Fig. 8.9). Blood tests may also aid diagnosis; these may include elevated Angiotensin Converting Enzyme (ACE) and serum calcium levels. Other diseases that may present with similar clinical and histological findings often need to be ruled out [80]. The disease has a variable course; most cases are mild and resolve, but others are severe and potentially fatal, especially with pulmonary involvement. Treatment generally consists of systemic corticosteroids or sometimes topical or inhaled corticosteroids for mucosal or skin disease [80].

Systemic Lupus Erythematosus (SLE) is a systemic autoimmune condition that disproportionately affects women and patients of African ancestry. It is more common in young and middle adulthood [85]. Clinical features include skin rashes, joint pain, fever, kidney disease, and lung disease [85]. The characteristic "butterfly

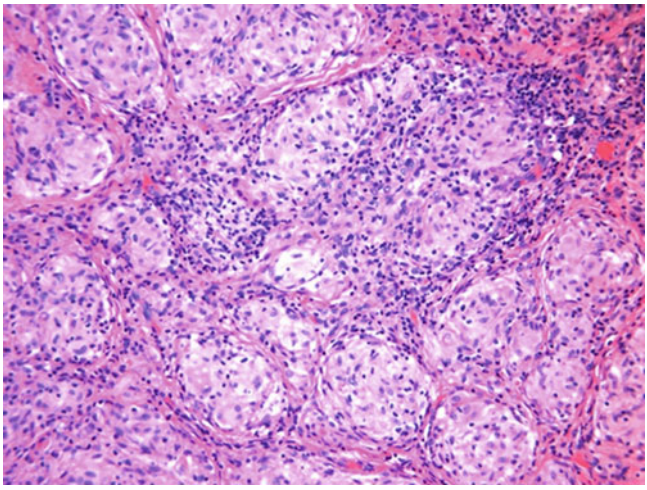

Fig. 8.9 Sarcoidosis presenting as a mass of the gingiva in a 60 year-old female patient. Histological features include the formation of multiple non-necrotizing granulomas consisting of epithelioid histiocytes and giant cells, rimmed by lymphocytes (H&E, 20×)

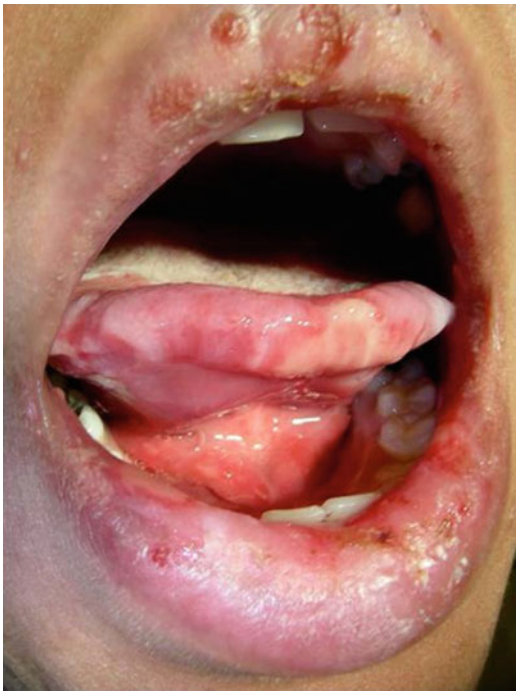

Fig. 8.10 Erythema multiforme presenting in a patient with Systemic Lupus Erythematosus. Generalized ulcerations intraorally along with crusting of the lips are shown

rash" across the malar process of the nose appears to be heightened by sun exposure. Forms include cutaneous, systemic, or mixed [85]. SLE may affect the oral cavity in 15–40% of cases, usually as ulceration (Fig. 8.10) [86]. Many SLE cases show

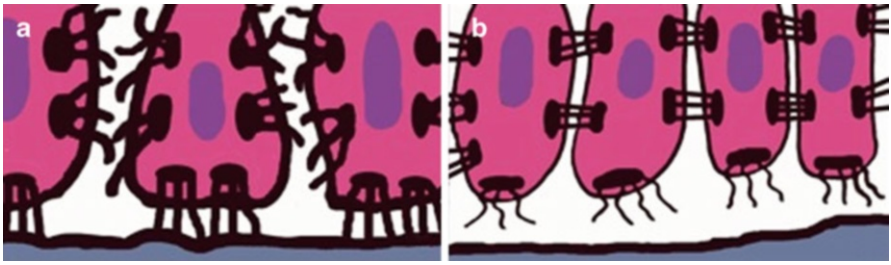

Fig. 8.11 Loss of attachments in pemphigus and pemphigoid. (**a**) In Pemphigus, the keratinocytes lose their attachment to each other because of the immune attack on desmosomes, so the keratinocytes become more rounded and may float freely. (**b**) In Pemphigoid, the desmosomes are not attacked, so the keratinocytes retain their cell-to-cell attachments. However, the attachment of the basal keratinocytes to the basement membrane is weakened by immune attack, so the entire epithelium separates from the underlying connective tissue

laryngeal involvement [87]. Rarely, SLE may affect the ear, nose, or salivary glands [86, 88]. Diagnostic modalities may include biopsy, immunofluorescence, and blood/urinary workup. The clinical course is variable; mortality and morbidity are often related to renal failure, infection, or central nervous system symptoms. Medical management includes steroids, immunosuppressants, and nonsteroidal anti-inflammatory medications (NSAIDS) [85].

Vesiculobullous diseases of autoimmune etiology can affect multiple sites in the head and neck. Of these, the most common are **Mucous Membrane Pemphigoid (MMP)** and **Pemphigus Vulgaris (PV)** (Figs. 8.11 and 8.12). In general, both affect an older population. PV has an equal gender predilection, but MMP is more common in women [85].

Pemphigoid encompasses a family of skin and mucosal lesions that cause chronic blistering and ulceration. The disease is caused by autoantibodies that attack components of the basement membrane, most commonly BPAG2, BP180 but also BPAG1, laminin 5 (epiligrin), and others [89]. These antibodies cause the epithelium to detach cleanly from the underlying tissues, as shown in Figs. 8.12 and 8.13. The epithelium forms a bulla that disintegrates, leaving an ulcer. MMP only rarely causes skin lesions but most often affects the oral mucosa, then the ocular mucosa, and rarely the nose, larynx, esophagus, bronchial tissues, or genital mucosa [90–92]. One study of patients with oral lesions showed that 30% were also affected by ocular disease [91]. Laryngeal involvement is rare but may be life threatening, and is most often due to cases associated with laminin 5 autoantibodies. These have also been linked to adenocarcinoma of the lung, colon, stomach, and uterus [93]. The disease has a variable course, but may cause significant blindness if eye disease is uncontrolled [90, 94]. Treatment is based on symptoms, and includes topical steroids or sometimes immunosuppressants in refractive cases [94].

PV has a similar clinical presentation, although it affects the skin to a much greater degree than MMP does. Within the head and neck, it nearly always affects the oral cavity, followed by the pharynx/larynx, sinuses, nose, and ear [95]. Clinicians

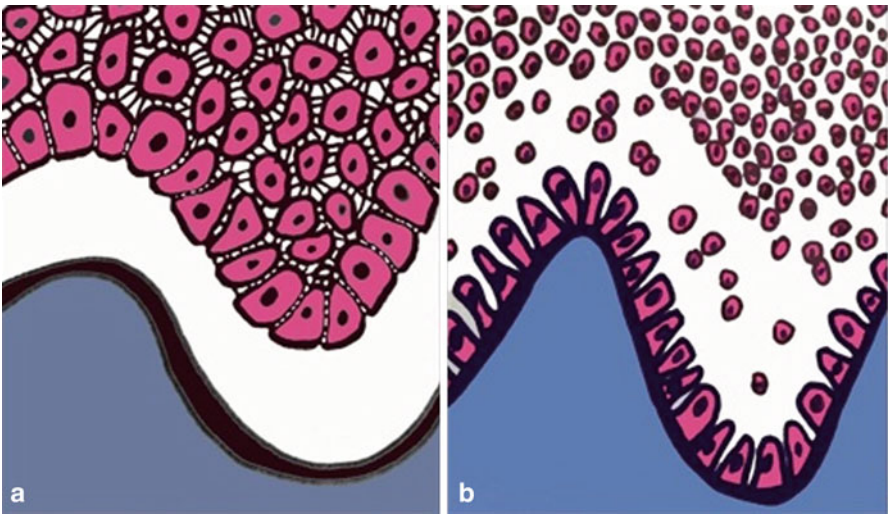

Fig. 8.12 Pemphigoid and Pemphigus. (**a**) Subepithelial separation typical of Mucous Membrane Pemphigoid (MMP). In MMP, the desmosomes are not attacked, so the keratinocytes retain their cell-to-cell attachments. However, the hemidesmosomes that attach the basal keratinocytes to the basement membrane are weakened by immune attack, so the entire epithelium separates cleanly from the underlying connective tissue. This often results in a bulla, characteristically located below the basal layer (sub-basal separation). In MMP, the bulla may remain intact for hours because of the intercellular attachments, unlike the more fragile bulla found in Pemphigus. (**b**) Suprabasilar separation typical of Pemphigus Vulgaris (PV). In PV, there is an immune attack on desmosomes. The keratinocytes lose their attachment to each other because of this attack, so they become more rounded and may float freely. However, the basal keratinocytes remain anchored to the basement membrane by hemidesmosomes, which are not affected in PV. This results in a suprabasal bulla, i.e. located above the basal layer. The bulla has a fragile roof because of the loss or weakening of the attachments between epithelial cells (acantholysis). Microscopically these basal cells look like tiny tombstones, giving rise to the term "tombstone layer"

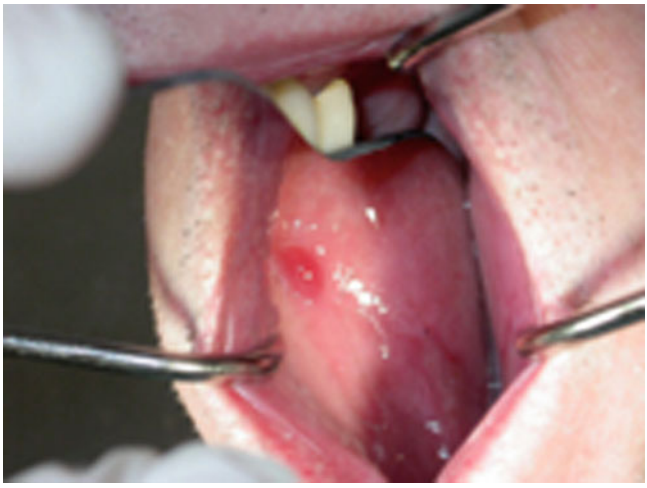

Fig. 8.13 Mucous Membrane Pemphigoid. Intact blood blister on the right buccal mucosa in Mucous Membrane Pemphigoid. Unlike Pemphigus Vulgaris, in which bullae rupture quickly and are rarely seen upon clinical exam, the bullae in Mucous Membrane Pemphigoid may remain intact for several days

sometimes remark that in PV, the oral cavity is the "first to show, and last to go". In PV, bullae and vesicles quickly disintegrate to leave ulcers. It is caused by autoantibodies to desmosomes, which attach epithelial cells to each other. The keratinocytes lose their attachment to each other because of the immune attack on the desmosomes, as shown in Fig. 8.11. Because the epithelial cells cannot adhere to each other well, biopsy shows ragged bulla and a separation within the epithelium. The basal keratinocytes remain attached to the connective tissue, because the hemidesmosomes that anchor them to the basement membrane are not attacked [85]. This line of basal keratinocytes is sometimes called the "tombstone layer", because of its appearance. This is shown in Fig. 8.12. PV is generally treated with systemic steroids, and if it affects a large portion of the body and cannot be controlled, it can be fatal [95]. Direct immunofluorescence is often a useful tool in distinguishing between PV and MMP, as test antibodies directed towards the pathologic antibodies in PV will glow in the spaces between keratinocytes, forming a fish-net pattern, whereas the pathologic antibodies in MMP will glow in a line along the basement membrane [85].

Another autoimmune disorder that may affect several different areas of the head and neck is **Relapsing Polychondritis**, a recurring inflammation of hyaline and elastic cartilage [96]. This chondritis most commonly affects the ear, especially the pinna but also the middle and inner ear. Ear involvement is usually bilateral. Nasal chondritis is present in half of cases, and it can destroy the nasal bridge, causing a saddle-nose deformity. The cartilage of the larynx and trachea is also frequently affected, as well as the joints, so patients often also have joint pain and respiratory symptoms [96–99]. It can also affect the vertebrae, eye, heart, and blood vessels [98]. About a third of patients have other autoimmune, rheumatoid, or hematological disorders [98]. It most often is seen in middle-aged adults, although a large age range is found [96, 99]. Histologically, there is a dense mixed inflammatory infiltrate and ulceration [96]. It has an intermittent but progressive course, and treatment is often directed simply towards suppressing symptoms. Treatment can involve nonsteroidal anti-inflammatory agents, corticosteroids, or immunosuppressants [98].

8.3.2 Sinonasal/Nasopharyngeal Allergic/Immunologic Conditions

Rhinosinusitis, or inflammation of the sinonasal tract, affects 10–25% of Western populations and may have many different causes; however, an allergic source is the most common [100]. Other types are non-allergic or idiopathic, infectious (viral, bacterial, or fungal), hormonal, and occupational [100, 101]. Acute bacterial sinusitis often develops as a complication after viral infection [34]. Chronic sinusitis can develop after persistent or repeat bouts of sinusitis [34]. Clinical features of rhinosinusitis include sneezing, rhinorrhea, and congestion [100]. Histologically, there is a mixed inflammatory infiltrate including eosinophils, lymphocytes, histiocytes, and neutrophils. The lamina propria is edematous or fibrotic, and the respiratory epithelium has a thickened basement membrane [34]. Rarely, extension may occur into

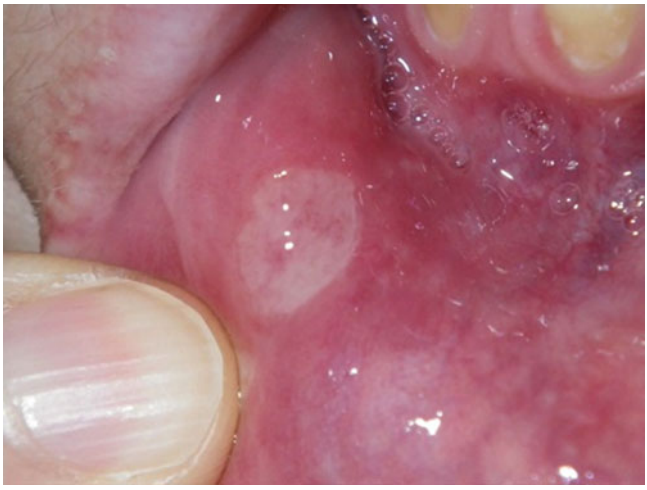

Fig. 8.14 Aphthous ulcer. Recurrent Aphthous Stomatitis manifesting with an ulcer on the labial mucosa. Ulcers typically last less than 1 week and are painful, with a necrotic center and erythematous halo

nearby bone, brain, or ocular spaces [34]. Treatment is usually based on etiology, but can include medical and surgical treatment [34].

Eosinophilic Angiocentric Fibrosis (EAF) is a rare disorder affecting the sinonasal region. Its etiology is unknown, but it has been proposed that it is linked to an allergic response. EAF results in slowly progressive fibrosis, or the replacement of tissue with a thick collagenous connective tissue, and it shares features with the dermatologic lesion **Granuloma Faciale** [102, 103]. In 75% of cases, it involves the upper airways, and results in obstruction of the nasal cavity along with pain, swelling, or epistaxis (nosebleed). Secondarily involved sites are rare but can include the subglottis, orbit, or oropharynx [102]. It is usually seen in middle-aged patients, and many of the patients also report allergy [102]. It is generally treated with surgery, but recurrence is common [34].

8.3.3 Oral/Oropharyngeal Allergic/Immunologic Conditions

Recurrent Aphthous Stomatitis (RAS) is the most commonly seen disease of the oral mucosa [104]. Commonly termed "canker sores", it is characterized by recurring painful ulcerations. The peak age for this disorder is between 10 and 19 years of age but it has a wide age range [104, 105]. There are several distinct forms of RAS. **Aphthous Minor**, which is most common, presents as small non-scarring ulcers on non-keratinized oral mucosa that heal within 7–10 days (Fig. 8.14). Non-keratinized mucosa includes the lip mucosa, buccal mucosa, tonsillar pillars, lateral and ventral tongue, and the floor of the mouth. **Aphthous Major** has larger and deeper ulcers that take longer to heal, may scar, and may present anywhere in the oral cavity.

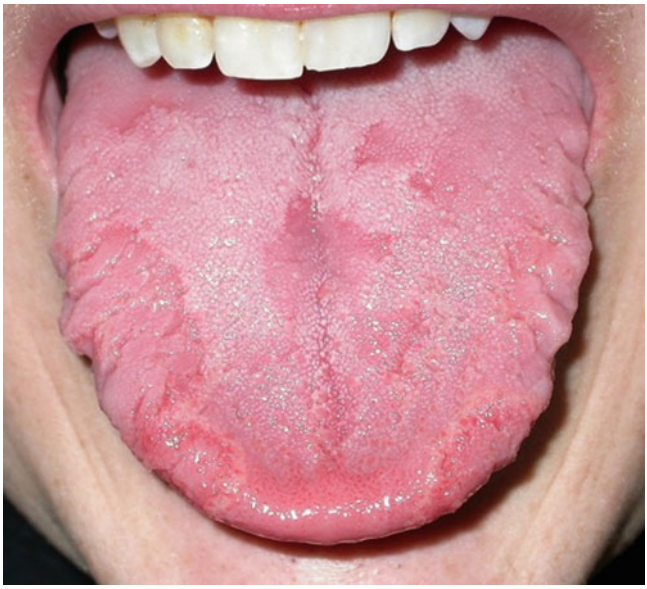

Fig. 8.15 Benign migratory glossitis (geographic tongue) exhibiting zones of depapillation of the dorsal and lateral tongue surrounded by raised *white-yellow* borders. This patient also has a Fissured Tongue, which frequently co-exists with Geographic Tongue. Neither condition requires treatment

Herpetiform Aphthous Stomatitis, the least common form, presents as multiple small lesions that may have frequent recurrences [106]. RAS is thought to be primarily an immunologic disorder but has strong familial tendencies. Clinically indistinguishable lesions may be a manifestation of many systemic disorders including Behçet's Disease, Cyclic Neutropenia, MAGIC Syndrome (Mouth And Genital ulcers with Inflamed Cartilage), various nutritional deficiencies, HIV, Crohn Disease, Ulcerative Colitis, and Celiac Disease [104]. Care should be taken to rule out a systemic cause of aphthous ulceration. The disorder is mainly self-limiting and is generally treated symptomatically. However, lesions cause pain disproportionate to their size, and aphthous major is particularly painful. It is sometimes treated with topical analgesics and corticosteroids; a complete search for underlying disease should be performed as well, but may be frustrating and inconclusive [106].

Benign Migratory Glossitis (BMG), also known as **Geographic Tongue** or **Oral Erythema Migrans**, is a benign condition that affects approximately 1–2.5% of the population [107]. It is similar histologically to psoriasis of the skin, but most people with BMG do not have psoriasis. It is more common in females, and presence of concurrent allergy is common. Other potential etiologic factors may be genetic or hormonal [107]. It is characterized by erythematous curved areas formed by the loss of filiform papilla, outlined by a creamy yellow rim containing large numbers of neutrophils (Fig. 8.15). These are most often found on the dorsal and

lateral tongue. The lesions may move about, appear, and disappear over a matter of days within these areas [9]. Rarely, oral mucosa other than the dorsal and lateral tongue may be involved, in which case the term oral erythema migrans or ectopic geographic tongue is used. A fissured tongue is associated with geographic tongue in approximately half of cases [107]. The lesions generally cause no problems so treatment is rarely indicated, but a minority of patients experience sensitivity to spicy foods, fruits, or cigarette smoke, [108]. Reassurance to the patient of the benign nature of the lesion is often important.

Lichenoid lesions of the oral cavity are common in the general population, affecting up to approximately 2% [109, 110]. They can be referred to by the umbrella term, **Lichenoid Mucositis**; the lesions in this category share many common clinical and histological features, but have diverse immunologic or allergic etiologies. They are characterized by a cytotoxic T-lymphocyte attack on the epithelium.

Lichen Planus, the best known member of the group, is an autoimmune disease of the skin that may also affect mucosa including the oral cavity, although in many cases only oral lesions are present [111]. Rarely, locations other than skin and oral cavity can be involved including the fingernails, eye, larynx, esophagus, and genitals [110, 112]. **Lichenoid Contact Mucositis** may be caused by a contact allergy to a dental restorative material such as amalgam, or a flavoring agent, particularly cinnamon. A **Lichenoid Drug Reaction** may be an allergic response to a systemically administered medication, or other systemic factors. Lichenoid drug reactions, unlike oral lichen planus, are often single lesions, and lichenoid contact allergies are found in sites in specific contact with the allergen [111]. In **Graft Versus Host Disease** after a bone marrow transplant, the transplanted immune system recognizes the epithelium as foreign and attacks it. Lupus Erythematosus may also appear clinically similar to lichenoid mucositis.

Whatever the cause, lichenoid mucositis features areas of epithelial atrophy (red) and hyperkeratosis (white), and may be ulcerated. The reticular form has a lacy white non-ulcerated pattern (called Wickham's Striae) on a red background; it is usually seen bilaterally on the buccal mucosa and lateral tongue (Fig. 8.16). In the erythematous form, the mucosa is red and atrophic, but not actually ulcerated. In the erosive form, there are ulcers with erythema and surrounding white striated mucosa [9, 111].

Lichenoid lesions have a distinct histological appearance with a degraded epithelial basal layer, spiky so-called "saw-tooth" rete ridge formation, development of colloid or civatte bodies from degenerating keratinocytes, and most importantly, a band-like collection of lymphocytes close to and within the epithelium, called an interface stomatitis [9]. Direct immunofluorescence can also be useful in differentiating lichenoid mucositis from other diseases such as SLE, PV, and MMP, as lichenoid mucositis is cell-mediated so antibodies are not detected [9].

Malignant transformation has been estimated at up to 3% of cases, usually in the erosive form of oral lichen planus [113]. Care must be taken to distinguish oral lichenoid lesions from oral dysplasia, however, because T-cells may attack dysplastic epithelium, causing a clinical and histological appearance that mimics lichenoid conditions [111].

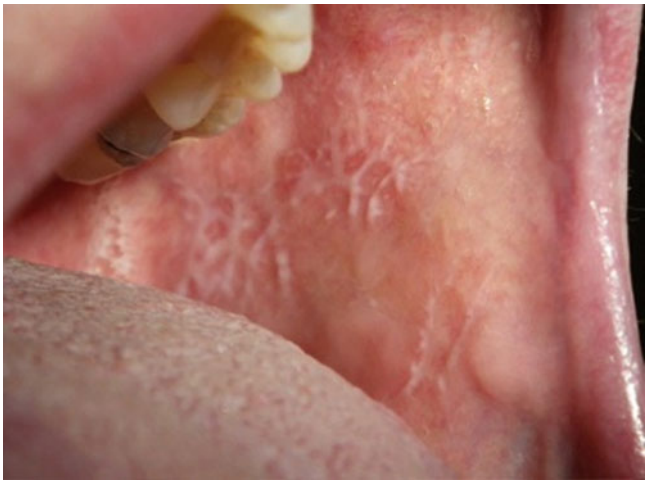

Fig. 8.16 Lichen planus/lichenoid mucositis. Reticulated white lacy lesion on the left buccal mucosa is typical of oral reticular Lichenoid Mucositis

Treatment of symptomatic lichenoid mucositis usually consists of elimination of any triggering factors if possible, or topical steroids and other immune modulating medications [9].

8.3.4 Hypopharyngeal/Laryngeal Allergic/Immunologic Conditions

One systemic chronic autoimmune disease that causes lesions involving the larynx is **Rheumatoid Arthritis** [114]. Laryngeal rheumatoid nodules can be found in some series in 26–53% of cases, although in post-mortem series, the estimates may reach the 80% [115]. They may also be seen in the trachea, nose, ear, cervical spine, and temporomandibular joints [115]. Clinical manifestations include hoarse voice, difficulty breathing or swallowing, and wheezing [114]. Laryngeal rheumatoid nodules may be dangerous due to limitation of air flow [115]. Other laryngeal manifestations of rheumatoid arthritis can include cricoarytenoid joint arthritis, and amyloidosis [116]. Biopsy usually shows a fibrin center with surrounding histiocytes, giant cells, and lymphocytes [114]. Treatment is usually medical and includes NSAIDS, immunosuppressants, and corticosteroids [3].

8.3.5 Auricular Allergic/Immunologic Conditions

Allergy-related disease of the middle ear often manifests as **Otitis Media with Effusion**, characterized by fluid retention in the ear without an infective source and with an intact tympanic membrane [117]. Allergic patients have increased risk of

otitis media with effusion that is 2–4 times higher than in non-allergic patients [117]. It may cause hearing loss or delayed speech [117]. Treatment of the underlying allergy may resolve chronic otitis media with effusion [117].

The inner ear is affected by a significant number of immune disorders that may be due to an underlying systemic disorder, or considered idiopathic. **Autoimmune Inner Ear Disease** is characterized by rapidly progressive hearing loss. It is most common in women in early to middle adulthood but can be seen in children [118, 119]. Severe irreversible hearing damage can develop if it is not treated promptly [118]. Systemic disorders leading to autoimmune inner ear disease include Cogan Syndrome and Vogt-Koyanagi-Harada Syndrome [118]. In addition, many other autoimmune diseases may affect hearing including Relapsing Polychondritis, SLE, Rheumatoid Arthritis, Sjögren Syndrome, Systemic Sclerosis, Myasthenia Gravis, Goodpasture Syndrome, Hashimoto Thyroiditis, Sarcoidosis, and Wegener's Granulomatosis [120].

Meniere's Disease is believed to have an autoimmune component. It affects the inner ear, causing dizziness, hearing loss, and tinnitus (ringing of the ears) [121]. It is generally seen later in life but has a wide age range [20]. It is characterized by the damage to the labyrinth of the ear due to over-accumulation of endolymph [20]. Medical management includes dietary changes, diuretics, antivertigo medications, or steroids [20].

8.3.6 Salivary Allergic/Immunologic Conditions

Sjögren Syndrome (SS) affects up to 0.5–4.8% of the population and is one of most common systemic autoimmune diseases after Systemic Lupus Erythematosus and Progressive Systemic Sclerosis (Scleroderma) [122–124]. It affects women nine times more often than men and generally is seen in the 4th–7th decades of life [68, 123]. Symptoms include dry eyes (xerophthalmia) and dry mouth (xerostomia) along with variable expression of other symptoms including salivary gland enlargement [125]. SS can be present without any other autoimmune disease (Primary SS), or secondary to another autoimmune disease such as Rheumatoid Arthritis or SLE (Secondary SS) [125]. Diagnosis is made by a combination of clinical symptoms, measurement of salivary and lacrimal flow rates, measurement of serum markers such as anti-SSA, anti-SSB, Rheumatoid Factor (RF), and salivary duct antibody, and salivary gland biopsy. Biopsy reveals chronic salivary gland inflammation (sialadenitis) with dense collections of lymphocytes. Pathologists look for one focus or more of at least 50 lymphocytes per 4 mm^2 of tissue (Fig. 8.17) [68, 125]. A related lesion is **Lymphoepithelial Sialadenitis**, which is usually associated with SS. This most often presents clinically as bilateral swelling of the parotid glands and histologically appears as a lymphocytic infiltrate with preservation of the general structure of the salivary glands [68]. Caution must be taken to differentiate this lesion from an early low-grade lymphoma, as it may be histologically similar. Patients with SS have a markedly increased risk of lymphoma [68]. Treatment of SS is generally supportive [125].

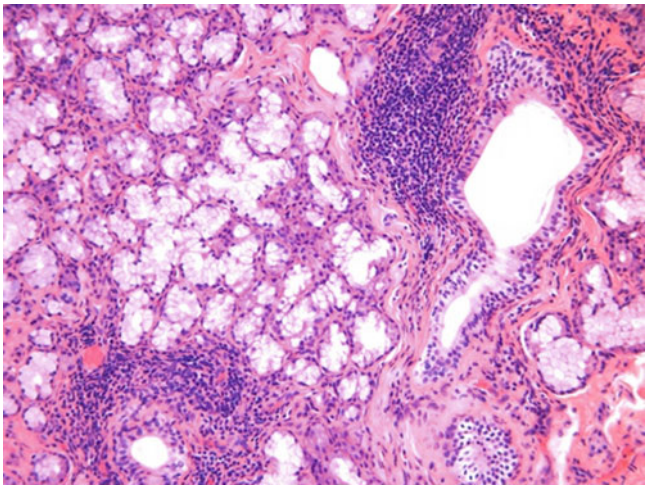

Fig. 8.17 Sjögren syndrome. Histological features include large aggregates of lymphocytes within the salivary gland lobules (H&E, 20×)

8.3.7 Thyroid/Parathyroid Allergic/Immunologic Conditions

The thyroid gland is especially vulnerable to autoimmune disorders, mainly **Graves Disease**, causing hyperthyroidism, and **Hashimoto's Thyroiditis**, which causes hypothyroidism [126].

Graves Disease is the most common cause of hyperthyroidism and often causes ocular symptoms [127]. It is caused by autoantibodies that attach to and activate the receptor for Thyroid Stimulating Hormone (TSH), causing the gland to overproduce thyroid hormones. It is most common in younger women [127]. Clinically it presents as a goiter (enlarged thyroid gland) and exophthalmos (protrusion of the eyeballs) caused by infiltrative ophthalmophathy [128]. There are also clinical symptoms of hyperthyroidism, which increases the basal metabolic rate thus leading to increased pulse rate, blood pressure, and body temperature, unexpected weight loss, and causes changes in many other systems. Histologically, there is an infiltrate of lymphocytes with enlargement of follicles; small papillary projections form in the lumen of the thyroid follicles [127]. Treatment may include anti-thyroid medications such as thioamides, which inhibit the thyroid's processing of iodine. In radioactive iodine treatment, the patient is given radioactive iodine, and the radiation selectively destroys thyroid tissue, where its uptake is greatest. In severe cases, thyrectomy (removal of the thyroid gland) is necessary [127].

Hashimoto's thyroiditis is the most common cause of adult hypothyroidism in populations with adequate iodine intake, and affects 2% of the population [129]. It affects ten times as many women than men, and presents as gradual onset of goiter and hypothyroidism [129, 130]. Like Graves disease, it is caused by anti-thyroid

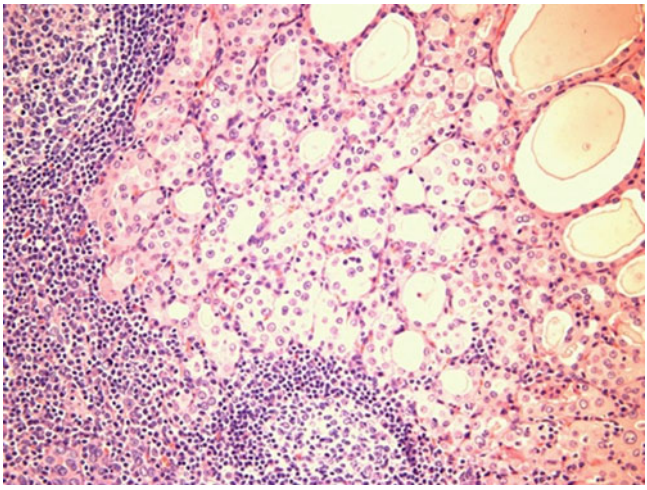

Fig. 8.18 Hashimoto's thyroiditis. A diffuse lymphocytic infiltration is noted along with a decrease in the size of the thyroid follicles (H&E, 20×)

antibodies, but in this case, they shut down production of TSH. A genetic component is suspected in some cases [129]. An asymptomatic goiter (thyroid mass) is the most common manifestation, and patients are usually hypothyroid [127]. Low levels of thyroid hormones cause a lowering of the basic metabolic rate, with subsequent fatigue, cold intolerance, weight gain, and many other symptoms. Biopsy reveals an infiltration rich with lymphocytes and plasma cells and a decreased number and size of thyroid follicles (Fig. 8.18) [127]. Treatment consists of thyroid hormone replacement [127].

8.4 Metabolic/Systemic Conditions

8.4.1 General Considerations for Metabolic/Systemic Conditions

Many diseases affect the head and neck that are systemic in scope or metabolic in origin. One disorder that can be found in many locations in the head and neck is **Amyloidosis**. Amyloidosis occurs when fibrillary protein is deposited extracellularly in tissue [131]. Amyloidosis can occur as a localized or systemic disorder. It is classified according to the type of protein that is deposited. In AL type amyloidosis, the protein consists of the light chains of immunoglobulins; the name AL stands for Amyloidosis, Light Chains. This type is usually associated with plasma cell dyscrasias such as **Multiple Myeloma**; all cells in the neoplastic clone of plasma cells secrete identical immunoglobin, which is referred to as a monoclonal gammopathy.

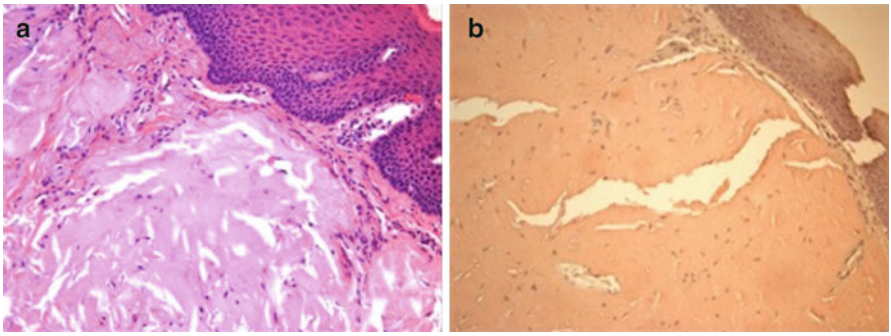

Fig. 8.19 Amyloid. Amyloid deposits from a biopsy of the lower lip in a 78 year-old male patient. (**a**) Deposition of eosinophilic material in a submucosal location (H&E, 20×). (**b**) Congo red positive staining of the amyloid deposits (Congo Red, 20×)

AA type amyloidosis is caused by accumulation of an acute-phase protein; it is most often associated with chronic infection and chronic inflammatory diseases, [132]. Many other types of amyloidosis also exist, with correspondingly different types of amyloid deposits. Amyloid depositions are not rare in the head and neck, and the most common location is the larynx [132, 133]. Other locations are the oropharynx, especially in the tongue, the trachea, orbit, nasopharynx, and rarely in the salivary glands, sinonasal areas, or lymph nodes [132, 133]. Most head and neck amyloid is of the localized AL type [134]. Clinically, it usually forms a yellowish submucosal mass that is generally not ulcerated [135]. Histologically, amyloid appears as amorphous eosinophilic fibrillar material deposited extracellularly in the tissue or around blood vessels or salivary ducts, and stains red with Congo Red stain. Under polarized light, the red of amyloid changes to green; this is called apple green birefringence (Fig. 8.19) [136]. A search for systemically associated disease should be performed in the setting of no previously known disease, and treatment usually consists of conservative excision and observation [134].

Another systemic disease that sometimes affects the head and neck is **Gout**. Gout is caused by the deposition of urate crystals in the tissues secondary to hyperuremia (high levels of uric acid in the blood) [137]. It most often affects the small joints in the feet, especially the great toe. The urate crystals trigger inflammation, causing painful, hot, swollen arthritis of only one or two joints [137]. A gouty tophus is a longstanding lesion of gout. Some population groups are more prone to developing gouty tophi, including the elderly, women, patients with renal insufficiency, and patients using medications such as cyclosporine or nonsteroidal anti-inflammatory drugs [137]. In the head and neck, the most common location is the ear, especially the auricle [137]. Other areas of involvement include the arytenoid, true vocal cord, hyoid, thyroid cartilage, cricoarytenoid joint, soft tissue of the nasal dorsum, nasal septum, temporomandibular joint, soft palate, cervical spine, middle ear, and glossoepiglottic ligament [137,

138]. In the superficial areas of the head and neck, a gouty tophus appears chalky white or yellow and may have an ulcerated surface [137]. In the ear, it may mimic cancer [137]. Histologically uric acid forms thin crystals that are not polarizable but can be dissolved in formalin [137]. Treatment generally consists of dietary modification or medications such as allopurinol or probenecid [137]. **Pseudogout** is clinically similar, but caused by calcium pyrophosphate crystals; it usually affects larger joints, and may be associated with trauma, surgery, or heart disease [138].

Inflammatory Bowel Disease (IBD), including **Crohn Disease** and **Ulcerative Colitis,** can also have head and neck manifestations. IBD most often presents in patients before age 30, but a second age peak occurs after age 60 [139]. Up to one third of patients with IBD develop extra-intestinal manifestations involving the joints, skin, mouth, or eyes, and rarely, the larynx, esophagus, or nose [140–142]. In the joints, arthritis is the most common symptom. The skin may develop **Erythema Nodosum**, tender red nodules, or **Pyoderma Gangrenosum**, deep necrotic ulcers. In the head and neck, the mouth is the most commonly affected area [139]. Aphthous-like ulcerations are not specific to these disorders, as discussed earlier in the chapter, but are the most common oral manifestations of IBD [140].

In patients with Crohn Disease, oral lesions often occur before the intestinal symptoms [142]. Oral Crohn disease may appear as non-specific recurrent aphthous-like ulcerations, or non-caseating chronic granulomatous inflammation that is histologically similar to the bowel lesions [140, 142]. Granulomatous inflammation in Crohn disease may take many forms: swelling of the lips, swelling or cobblestone lesions of the buccal mucosa or vestibules, mucogingivitis, linear ulcerations, or mucosal tags (Fig. 8.20) [143, 144].

Pyostomatitis Vegetans is a characteristic oral presentation that is more strongly associated with ulcerative colitis [143]. This lesion has a characteristic "snail-track" pattern and usually appears bilaterally on the buccal mucosa [145]. Ocular lesions may be varied in presentation and may include inflammation of the sclera (scleritis), the covering of the sclera (episcleritis), and the uvea (uveitis) [140, 142]. Sensorineural hearing loss has rarely been reported in ulcerative colitis patients [146, 147].

Patients with oral manifestations of bowel disease tend to be male and younger than the other bowel disease patients, and have more widespread and more severe lesions [141, 142]. Treatment of the extraintestinal manifestations usually involves treatment of the underlying bowel disease; when the bowel disease is controlled, the other manifestations usually subside [140].

8.4.2 Sinonasal/Nasopharyngeal Metabolic/Systemic Conditions

Cystic fibrosis is an autosomal recessive disease caused by a mutation on chromosome 7q31 that results in a faulty sodium-chloride cell transport, leading to thicker exocrine gland secretions [148]. It occurs most often in Caucasian populations.

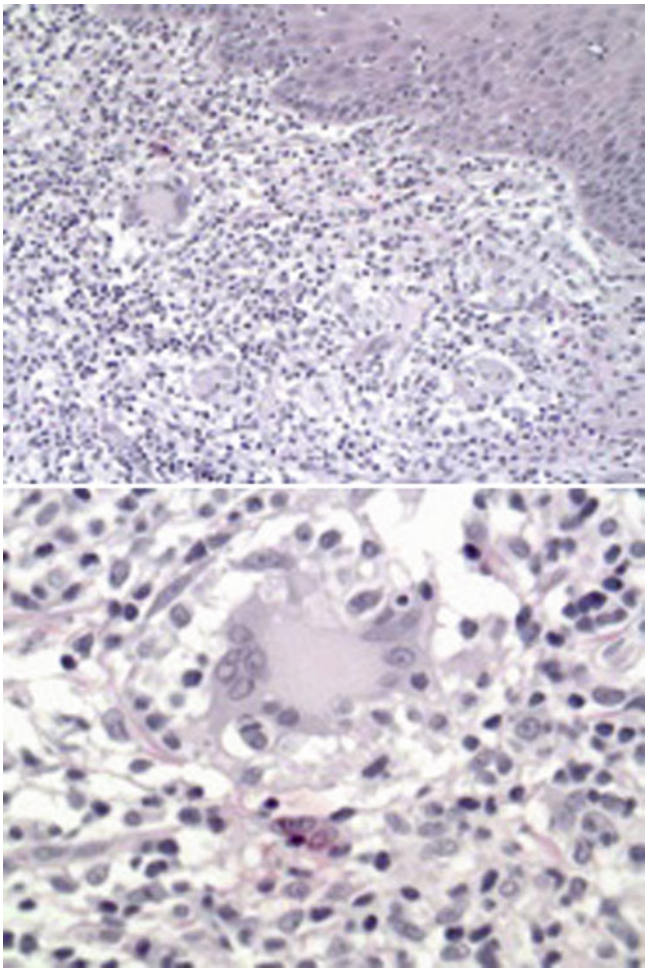

Fig. 8.20 Crohn mucositis demonstrating chronic granulomatous inflammation (*top*) (H&E, 20×). A large multinucleated giant cell is featured (*bottom*) (H&E, 40×)

Severe chronic pulmonary disease is a prominent clinical feature of this disease and a major cause of death. Respiratory manifestations include infections, respiratory difficulty, and respiratory failure [148]. Patients also suffer from gastrointestinal, pancreatic, and hepatobiliary disease [148]. Thick secretions block pancreatic ducts, leading to pancreatic failure, malabsorption of nutrients, and potentially to diabetes mellitus. Head and neck manifestations include chronic sinusitis and chronic nasal obstruction with nasal polyps in a significant percentage of patients [148]. Within the nasal polyps of cystic fibrosis, the inflammatory infiltrate contains high numbers of neutrophils, eosinophils, and a conspicuous absence of

plasma cells [148]. Treatment of the nasal symptoms includes intranasal corticosteroids for the nasal polyps, antihistamines if the sinusitis has an allergic component and antibiotics for acute exacerbations [148]. Otitis media with effusion has also been reported in adult patients with cystic fibrosis at a higher rate than the non-affected population, although in children the rate is the same as patients without cystic fibrosis [148]. Salivary glands may rarely be involved. Significant advances in treatment have been made; however, early mortality by age 30 is still the norm [34].

8.4.3 Oral/Oropharyngeal Metabolic/Systemic Conditions

One of the most common systemic diseases to show oral manifestations is **Diabetes Mellitus**. Diabetes affects 346 million people worldwide [149]. Oral problems reported with diabetes include xerostomia (dry mouth), increased incidence of periodontal disease, and increased susceptibility to fungal diseases (especially in uncontrolled diabetics) [150, 151]. Increased susceptibility to other infectious agents from bacterial and viral sources has also been reported in uncontrolled diabetics [151]. Other manifestations such as burning sensation, erythema, ulceration, angular cheilitis (cracking at the angles of the mouth), sialosis (non-inflammatory enlargement of the salivary glands), and lichenoid mucositis have also sometimes been reported in diabetics, although these remain unproven [151]. Lichenoid disease in diabetics appears to be a lichenoid drug reaction. Xerostomia is believed to be secondary side effects from medication or direct damage to the salivary glands by the disease [150]. Premature attachment loss from periodontal disease can also be a complication of diabetes [145]. The most common fungal infection seen is candidiasis, which may present in several forms including pseudomembraneous, erythematous, or hyperplastic forms and is often complicated by oral prosthetic use such as complete dentures [145]. Uncontrolled diabetics are also more prone to developing certain forms of deep fungal infections, such as zygomycosis, which generally presents in the sinonasal or palatal regions [145].

Another group of systemic disorders with multiple manifestations in the oral cavity are anemias. Anemias such as **Iron Deficiency Anemia, Pernicious Anemia, Vitamin B-complex deficiency anemias**, and nonspecific anemias may all present with a pale color of the oral mucosa, atrophy of the papillae of the tongue leaving a smooth surface (atrophic glossitis), candidiasis, and angular chelitis [152]. Other symptoms also reported are burning sensation, pain or tenderness, and redness [152]. **Sickle Cell Anemia**, which is most prevalent in areas of the world where malaria is found, has also been reported to have oral manifestations such as osteomyelitis, particularly in the mandible [153]. There may be coarsening of the bone trabeculae on dental radiographs, because of increased erythropoeisis. Other oral manifestations of sickle cell anemia include anesthesia of the mandibular nerve (V3) and asymptomatic pulpal necrosis [153].

8.4.4 Hypopharyngeal/Laryngeal Metabolic/Systemic Conditions

The hypopharynx and larynx may be affected by **Gastroesophageal Reflux Disorder** (GERD), or laryngopharyngeal reflux, which is defined as the backflow of gastric contents into the laryngeal or pharyngeal regions [154]. GERD is very common and asymptomatic; it may be present undetected in up to 75% of clinically normal patients [154]. It can cause erosion of teeth. Most symptoms of laryngopharyngeal reflux are nonspecific but it can cause dysphonia or other vocal changes [154]. Extraesophageal reflux has also been linked to otitis media in children, usually less than 1 year old [155].

8.4.5 Auricular Metabolic/Systemic Conditions

Nearly 400 syndromes have been associated with hearing loss [156]. Syndromes associated with a metabolic dysfunction causing hearing loss include Pendred Syndrome, Alstrom Syndrome, Laurence-Moon-Biedl Syndrome, Mucopolysaccharidosis (Hunter, Hurler, Sanfilippo, and Morquio Syndromes), Diabetes Mellitus, Hermann Syndrome, Perrant Syndrome, and DiGeorge Syndrome [156]. For example, Diabetes Mellitus Type 1 is associated with hearing loss in children [157]. It is generally bilateral sensorineural hearing loss and is related in severity to the length of time and level of control of the disease.

8.4.6 Salivary Metabolic/Systemic Conditions

The salivary glands are affected by many systemic disorders. One manifestation that is linked to multiple different forms of disease is **Sialadenosis (also called Sialosis)**. Sialadenosis usually presents as bilateral enlargement of the parotid glands. These enlargements are asymptomatic and not due to any inflammatory or neoplastic source [68]. The condition most commonly linked to this pathology is liver disease, either alcohol or non-alcohol related; this has been reported in between 30 and 80% of patients [158]. Other disorders associated with sialadenosis include diabetes mellitus, nutritional deficiencies, bulemia and anorexia, pregnancy, obesity, medications, and chemotherapy [159] (Fig. 8.21). Advanced liver disease generally leads to some form of nutritional deficiency, which may be a common link between some of these diverse underlying disease forms [160]. Biopsy shows enlarged acinar structures with accumulation of secretary granules [68]. Treatment is usually directed to the underlying disease [68].

8.4.7 Thyroid/Parathyroid Metabolic/Systemic Conditions

Reidel's Disease is a rare fibrosclerosing disorder affecting the thyroid gland, usually in middle aged or older women. It has been linked to other fibrosclerosing

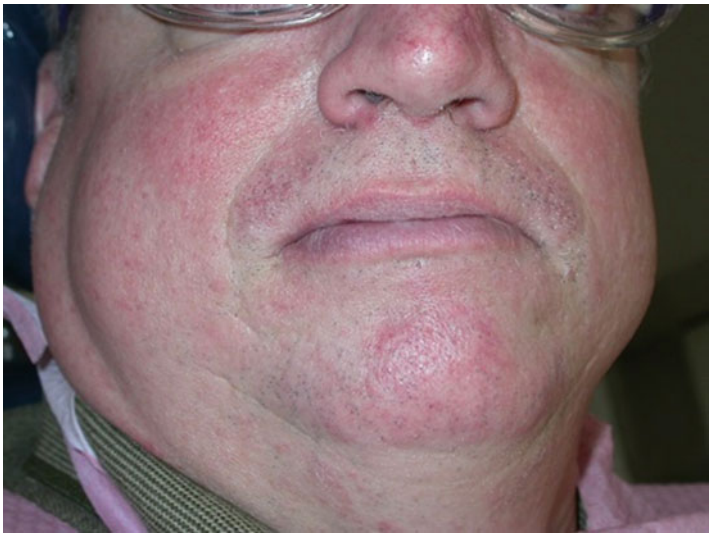

Fig. 8.21 Diabetic sialadenosis. Diffuse enlargement of the parotid glands is seen in this patient with poorly controlled Type 2 Diabetes Mellitus

disorders of the retroperitoneal and mediastinal regions [161]. Reidel's Disease usually presents as a hard goiter exhibiting local compression of adjacent structures and may lead to hypocalcemia (low serum calcium levels) and hypothyroidism [162]. It has been related to IgG4 linked systemic disease [162]. Up to 38% of cases may be associated with other fibrosclerosing diseases [162]. Other theories have linked Reidel's Disease to Hashimoto thyroiditis and other autoimmune disease [162]. It has been rarely associated with follicular carcinoma of the thyroid [161]. The histological features of Reidel's Disease include dense fibrous connective tissue that replaces normal thyroid tissues, accompanied by a mixed inflammatory infiltrate including lymphocytes, plasma cells, and eosinophils [162]. Treatment generally consists of surgery if needed for decompression, and long-term anti-inflammatory medications [161, 162]. The clinical course is variable [162].

8.5 Infections

8.5.1 General Considerations for Infections

Infectious organisms including bacteria, fungi, viruses, and others, may infect multiple areas of the head and neck with varying degrees of involvement. Many bacterial diseases which were formerly widespread became much less common in developed nations after the advent of antibiotic therapy. However, the HIV epidemic

led to resurgence in immunocompromised patients. Many of these diseases are also still not uncommon in developing and undeveloped nations. For example, **Tuberculosis** is a systemic granulomatous disease primarily involving the lungs, and caused by bacteria. It is found worldwide with especially high rates in India [163]. Transmission is generally through airborne spread [164]. It may affect the oral cavity or oropharynx, larynx, salivary glands, middle ear and mastoid process, sinonasal area, vertebrae of the neck, thyroid, neck spaces, lymph nodes, or soft tissues [163]. In most of these locations, primary disease is rare and manifestations are more often seen with secondary disease, with the exception of the middle ear where primary disease is most common [163]. The cervical lymph nodes are the most common location for tuberculosis in the head and neck [163], especially nodes in the posterior triangle, supraclavicular, and internal jugular chains. Bilateral involvement is common [163]. Secondary lesions in mucosal sites are often chronic painless ulcers or nodular lesions that mimic carcinoma [163, 164]. In the middle ear, it may manifest as chronic otitis media [165]. Histopathologic examination of fully developed lesions reveals necrotizing granulomas containing Mycobacterium tuberculosis organisms, which can be highlighted with special stains such as the Ziehl-Neelsen [165]. The treatment for tuberculosis includes long-term multi-agent antibiotic use [164].

Syphilis, caused by the spirochete Treponema pallidum, is another bacterial infection that has multiple manifestations in the head and neck. Previously declining in incidence after antibiotic treatment began in the middle of the last century, cyclic epidemics continue to occur [164, 166]. It is most often spread via sexual contact, but can be congenitally passed from mother to child [166]. Primary disease results in a chancre, or ulcer, at the site of infection. It is most commonly found in the anogenital area but can be found in the oropharynx including the lips, tongue, and tonsils [166]. Secondary syphilis occurs 4–10 weeks later and leads to systemic symptoms such as a cutaneous rash of the palms and soles, lymphadenopathy, sore throat, and malaise [164]. Mucosal surfaces of the upper aero-digestive tract may develop mucous patches or superficial ulcerations [166]. Condyloma lata, papillary lesions at the site of original inoculation, may also occur in secondary syphilis [166]. Tertiary syphilis can occur after multiple years and may result in destructive granulomatous lesions termed gumma, central nervous system involvement, and cardiovascular disease [166]. Gummae can occasionally cause palatal perforation. Congenital syphilis may lead to tooth abnormalities (Hutchinsons Incisors and Mulberry Molars), ocular interstitial keratitis, and hearing loss [164, 166]. Otosyphilis may affect the ear in either congenital or acquired disease and leads to sensorineural hearing loss [166]. The sinonasal areas may be affected rarely, but tertiary disease may produce a saddle nose deformity as it destroys the cartilage [166]. Laryngeal manifestations are also reported in all stages of the disease [3, 166]. Histopathologic presentation depends on the stage of disease but there may be lymphoplasmacytic inflammation and granulomatous inflammation in late disease [3]. The spirochetes may be identified by special stains such as Warthin-Starry or Dieterle's stain [3]. Treatment generally consists of systemic antibiotics [3, 166].

Leprosy, or **Hansen disease** is still found with frequency in several countries such as Brazil and India although antibiotic therapy has significantly reduced this

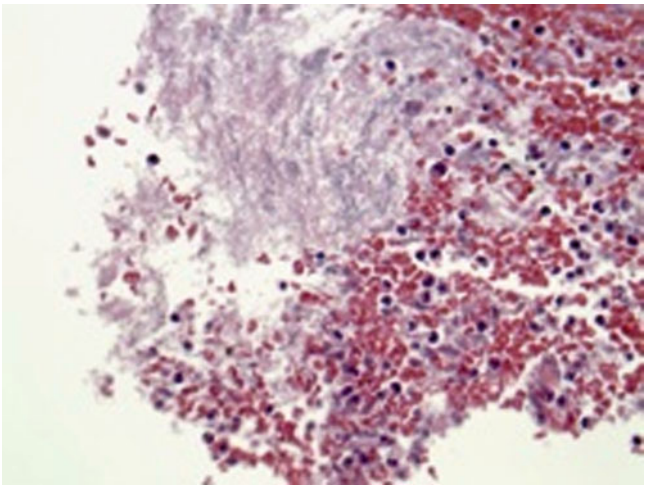

Fig. 8.22 Allergic fungal sinusitis. Pools of mucous material with a mixture of inflammatory cells rich with eosinophils are present (H&E, 40×)

disease in countries with more uniform access to medical care [167]. It is caused by the bacterium Mycobacterium leprae and is one of the leading causes of infectious disease related disability [167]. Transmission is thought to be through aerosol droplets but is not proven [164, 167]. The disease causes chronic granulomatous inflammation of the skin and peripheral nerves and can cause significant nerve damage and disability [167]. The sinonasal areas can be involved sometimes leading to significant destruction of tissue and a resulting saddle nose deformity [80, 164]. Oral cavity and facial skin lesions have been reported [164]. Oral cavity lesions are most often found on the hard palate or soft palate but have also been reported on the gingiva, tongue, lips, and buccal mucosa [164]. The skin of the ears is also a common site of involvement [3]. Laryngeal lesions may be seen usually through extension from the nasal regions [3]. Histopathologic examination shows granulomatous inflammation with organisms identified via Fite-Faraco stain [80]. Treatment consists of long-term multidrug antibiotic therapy [164, 167].

Fungal disease in the head and neck may be caused by many different species of fungi, and has a variety of manifestations. In the sinonasal region, **fungal related rhinosinusitis** may occur as acute fulminant invasive, chronic invasive, granulomatous invasive, mycetoma or fungus ball, or allergic fungal rhinosinusitis [168, 169]. Invasive fungal species include Zygomycetes (Zygomycosis), most commonly found in uncontrolled diabetics, and Aspergillus, which also may affect immunocompromised hosts [79, 168]. Zygomycosis may cause significant tissue damage by invading blood vessels and causing large zones of necrosis [170]. Aspergillus and other species can also cause non-invasive disease [79]. Allergic fungal sinusitis usually occurs with immunocompetent patients with a history of allergy [79, 169] (Fig. 8.22). The oral cavity/oropharynx and larynx are most often affected by

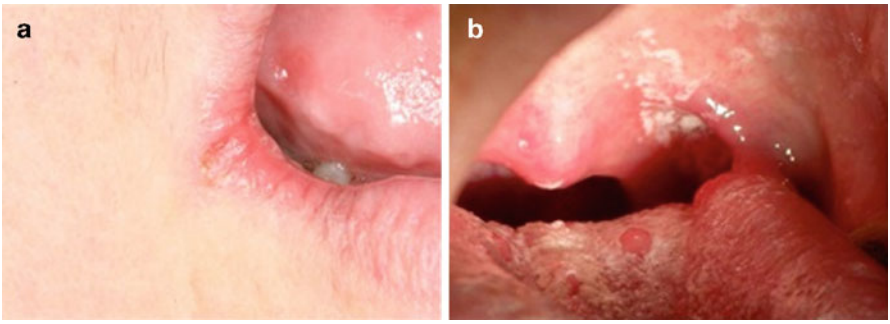

Fig. 8.23 Candidiasis. (**a**) Angular Cheilitis manifesting as cracked and fissured areas at the commissures of the mouth. (**b**) Pseudomembranous Candidiasis of the soft palate

Candidiasis (in the oral cavity most commonly Candida albicans) but may also develop **deep fungal infections** such as blastomycosis, histoplasmosis, paracoccidioidomycosis, coccidioidomycosis, and cryptococcus [168]. Oral cavity infections due to candidiasis are common and may present in pseudomembraneous (white clumps covering ulcerations), erythematous (red non-ulcerated lesions), or hyperplastic forms (white lesions that do not rub off). Candidiasis can cause distinct presentations such as angular chelitis (ulcers at the commissures of the lips), denture stomatitis, or median rhomboid glossitis (a red lesion on the mid-dorsal tongue) [171] (Fig. 8.23). Infection is often related to underlying immunocompromise combined with local factors such as denture use [171]. Within the larynx, candidiasis is often secondary to immunosuppression or the use of inhaled steroids or long-term antibiotics [172]. Deep fungal infections usually present as chronic non-healing ulcerations and are often are a part of disseminated disease or found in an immunocompromised host [171]. **Otomycosis**, or fungal infection involving the ear, will be discussed later in the section. Treatment of fungal disease in the head and neck is dependent on the degree of invasiveness and specific form.

Viral diseases of the head and neck are also extremely varied. Human Herpesviruses (HHV) are common culprits, including **HHV-1**, also known as **Herpes Simplex Virus (HSV), HHV-3**, also known as **Varicella Zoster Virus (VZV), HHV-5**, also known as **Cytomegalovirus (CMV),** and **HHV-8 (Kaposi Sarcoma Associated Virus). Human Papillomavirus (HPV)**, Coxsackiervirus infections, and manifestations relating to infection by **Human Immunodeficiency Virus (HIV)** are also frequently found [173].

HHV-1, or Herpes Simplex, affects most people; exposure increases with age. Like most HHV infections, it has a primary and recurrent form. **Acute Herpetic Gingivostomatitis (Primary Herpes)** is the disease pattern that occurs when the patient first acquires the viral infection. Primary herpes usually occurs in young children who develop painful irregular vesicles that coalesce into ulcers throughout the oral cavity [174] (Fig. 8.24). However, primary herpes can be sub-clinical. In many patients, the virus then becomes latent in sensory ganglia, often the trigeminal

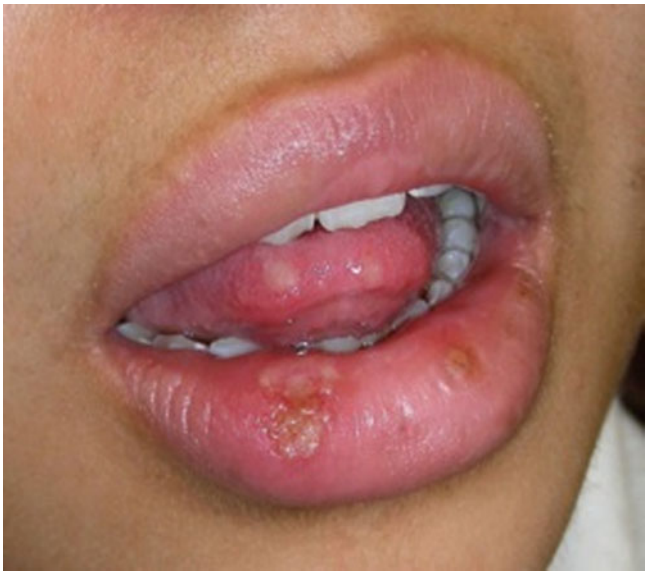

Fig. 8.24 Primary herpetic gingivostomatitis. In this 15-year-old girl, lesions appear as single and coalescing ulcers on the lower lip and tongue. There had been vesicles earlier in the course of the illness. Vesicular lesions were also present on the gingiva

nerve [173]. **Recurrent Herpes** is very common, and occurs when the latent virus reactivates later in life and re-emerges in the area innervated by the affected nerve. The patient develops multiple small vesicular lesions clustered in one spot; characteristically, the same site is involved with every outbreak. These are most commonly found on the vermilion border of the lip where they are called **Herpes Labialis**, although they can occur on other areas of the skin and on keratinized areas of the oral mucosa [174]. In immunocompromised patients, the virus may cause lesions in atypical locations such as the larynx, or lesions that last longer and are more extensive [3]. HHV-2 (Genital Herpes) occasionally occurs orally and is usually clinically indistinguishable from HHV-1 infection. The pattern of HHV-3 or Varicella Zoster Virus infection is similar; it causes a primary childhood infection, Chickenpox, and then the virus often becomes dormant in the dorsal root ganglia. Recurrent disease usually occurs later in life and is known as **Shingles**. In the head and neck as elsewhere in the body, shingles is a painful condition in which vesicles form along the distribution of the host nerve [173]. HHV-5 or CMV is a similar virus, which may remain latent and become reactivated especially in immunocompromised patients, especially those with HIV, and may involve the head and neck including the oral cavity, the larynx, and the salivary glands [3, 174].

HIV-related diseases of the head and neck are diverse, but often cause opportunistic infections such as candidiasis, mycobacterial infections, and deep fungal infections such as cryptococcus [174]. In addition, pathology related to secondary

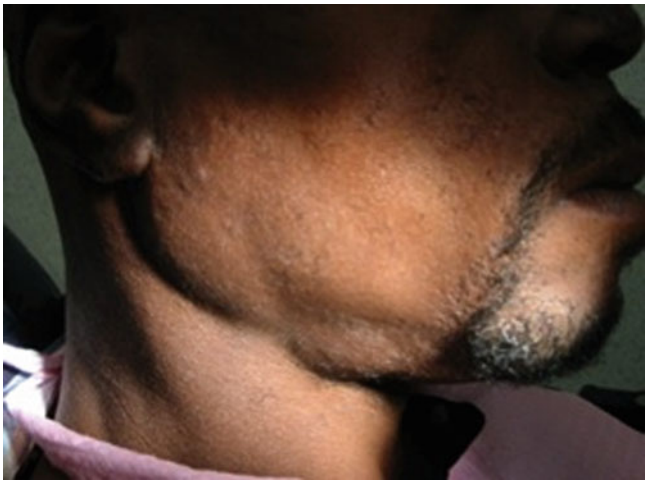

Fig. 8.25 HIV salivary gland disease. Salivary gland enlargement of the parotid glands and submandibular glands is seen in this HIV+ patient

viral infection may be characteristic. Epstein Barr Virus (EBV) (HHV-4) may cause **Hairy Leukoplakia**, linear white benign striations on the lateral tongue that are discussed later in this chapter, and HHV-8 can cause **Kaposi Sarcoma** [173]. Other manifestations of HIV in the head and neck include persistent lymphadenopathy, cystic salivary gland enlargement, and periodontal disease [174] (Fig. 8.25).

One of the most quickly evolving areas of research in head and neck pathology is that of the relationship between HPV infection and squamous cell carcinoma of the head and neck, as discussed in the previous chapter and also elsewhere in this book. More than 100 different subtypes of HPV exist and cause many different lesions such as Verruca Vulgaris or common wart and Condyloma Acuminatum or venereal wart, a sexually transmitted form of the disease [175]. Benign lesions in the head and neck area related to HPV infection include some forms of sinonasal papillomas, oral cavity lesions such as squamous papilloma, and laryngeal papillomatosis. These were discussed in the previous chapter.

8.5.2 Sinonasal/Nasopharyngeal Infections

In the sinonasal region, **Rhinoscleroma** results from chronic progressive granulomatous inflammation caused by infection with Klebsiella rhinoscleromatis. The disease is found worldwide, but is most common in lower socio-economic, rural settings and iron-deficient young adult women are particularly susceptible [176]. Upper airway disease presents in the nose in 95–100% of cases, and in the nasopharynx in up to 50% of cases [176]. Other rare locations that may be affected include

the Eustachian tubes, oral cavity, larynx, orbit, or skin [176]. The disease may progress through three stages: catarrhal-atrophic, granulomatous, and sclerotic [176]. Most cases are diagnosed in the granulomatous stage where the presenting symptoms include nosebleed and nasal deformity [176]. The histopathology is dependent upon the stage but in later stages show granulomatous inflammation with numerous large macrophages called Mikulicz cells with the microorganisms identifiable by Warthin-Starry, Giemsa, or Gram stains [79]. Treatment consists of prolonged antibiotic courses and surgery; a high relapse rate is common [176].

A rare disease caused by waterborne Rhinosporidium seeberi is **Rhinosporidiosis**. Endemic to southern India and Sri Lanka, it is found less often in South America and Africa [177]. It causes chronic granulomatous disease most often affecting the mucous membranes of the sinonasal and nasopharyngeal areas but has also been reported to cause disease of the conjunctiva, oral cavity, tonsils, epiglottis, larynx, and trachea [177]. In the sinonasal region, nasal blockage, nosebleed, and discharge are often noted [177]. Histopathologically, the organisms appear as very large sporangia with numerous endospores [79]. Treatment consists of surgical excision, sometimes with adjunct medical management [177].

8.5.3 Oral/Oropharyngeal Infections

Within the oral cavity, clinically significant bacterial infections are common. In adults, the most frequent is dental caries, but others include periodontal disease (loss of the bone supporting the teeth) pericoronitis (inflamed tissue around a partially impacted tooth), and infection developing in an extraction socket [178–180]. The most commonly affected teeth are lower posterior molars; infection in this area may lead to deep space infections of the head and neck, airway compromise, or other complications [178, 179]. In children, infection often occurs from tonsillar or lymphatic abscess [179]. The bacteria that cause deep space infections of the head and neck are mixed species, including aerobic forms such as Streptococcus and anaerobic forms such as Peptostreptococcus, Actinomyces, Bacterioides, and Fusobacterium nucleatum [179]. Treatment generally consists of resolution of the source of infection with appropriate antibiotic therapy [181].

One example of a virally mediated disease characteristic to the oral cavity is **Oral Hairy Leukoplakia (OHL)**. Most often associated with HHV-4 (Epstein Barr Virus, EBV) reactivation in the setting of underlying HIV infection, oral hairy leukoplakia usually presents as an asymptomatic white plaque on the lateral border of the tongue with a corrugated or "hairy" appearance [174, 182]. Unlike pseudomembraneous oral candidiasis, oral hairy leukoplakia lesions cannot be wiped off with gauze. Histopathologically, oral hairy leukoplakia is characterized by a thickened parakeratin layer, often with superficial secondary Candida colonization, with acantholytic underlying epithelium exhibiting nuclear clearing and peripheral marginalized chromatin [174] (Fig. 8.26). EBV can be demonstrated within the cells via immunohistochemical staining, in situ

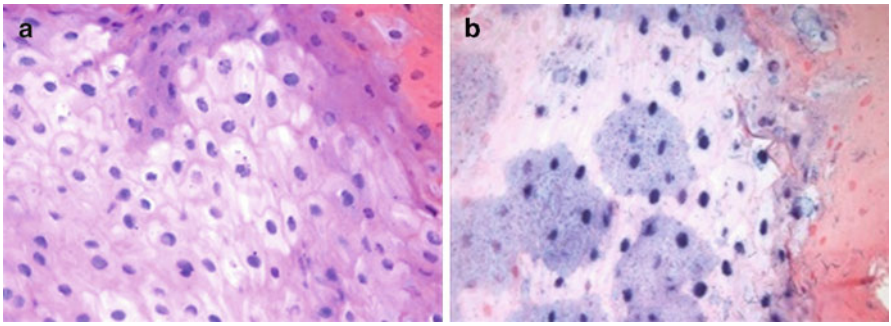

Fig. 8.26 Oral hairy leukoplakia on the lateral tongue of an HIV+ patient. (**a**) Paranuclear condensation of chromatin in the upper spinous layer (H&E, 40×). (**b**) In-situ hybridization for EBV-encoded RNA (EBER) reveals EBV+ lesional cells (EBER, 40×)

hybridization, polymerase chain reaction (PCR), or Southern Blot method [174]. Diagnosis of OHL does not guarantee a diagnosis of HIV, as occasionally, OHL can be due to other immunocompromising conditions such as solid organ transplant. However, if a patient has OHL, HIV testing should be carried out. Treatment should be directed at correcting the underlying immunocompromise, if possible; for example, response of the underlying HIV to antiretroviral therapy usually resolves the oral lesions. The lesions themselves are not painful or destructive, but a signal of an underlying problem so treatment of the OHL itself is not usually required. If necessary, OHL lesions may be treated with antiherpesviral medication or topical preparations [173, 174].

8.5.4 Hypopharyngeal/Laryngeal Infections

Within the larynx and hypopharynx, infectious disorders include **Croup** and **Epiglottitis**. Croup, or laryngotracheobronchitis, is most commonly seen in young children between the ages of 6 months and 3 years and is usually related to a parainfluenza virus, although other viruses have been reported [183]. It presents with a gradual onset of viral symptoms, including low-grade fever and sore throat, for several days before the development of a "barking" cough, stridor, and respiratory distress [183]. Treatment includes airway support and medical management in some cases [183]. Epiglottitis, on the other hand, presents abruptly with sore throat and fever along with the "3 D's": drooling, dysphagia, and respiratory distress [183]. Previously it was most commonly associated with Haemophilis influenza B but since the development of an effective vaccine, it is more often seen in adults and may be caused by a variety of bacterial, viral, or fungal causes. The epiglottis is bright red, with edema and redness of the surrounding structures [172]. Treatment consists of emergency airway management, antibiotics, and steroids [183]. Other rare forms of infectious disease in the larynx include diphtheria, pertussis, tuberculosis, syphilis, leprosy, Actinomyces bacteria, and deep fungal

infections [172]. Rare infections of the larynx by protozoa such as Trichinella and Schistosoma are also reported [3].

8.5.5 *Auricular Infections*

In the external auditory canal, infections may occur from fungal or bacterial sources. **Otomycosis** can be caused by fungal sources, mainly Aspergillus and Candida species, and is more commonly found in swimmers who have chronically wet ear canals ("swimmers ear") [165, 184]. Symptoms can include itching, pain, ringing in the ears, loss of hearing, or discharge [168]. **Malignant Otitis Externa** is an aggressive invasive infection found mainly in diabetic patients but can be associated with other immunocompromising conditions. It is most commonly caused by the bacterium Pseudomonas aeruginosa but may also be involved with fungal Aspergillus sources [185]. The external auditory canal develops severe ear pain, discharge, granulation tissue, or exposed bone and infection may spread to the skull base and brain. Treatment consists of long-term antibiotic therapy [185].

Otitis Media may be caused by bacterial infection in the middle ear. It is most common in childhood and usually accompanies an upper respiratory infection [20]. Fever, ear pain, and diminished hearing may be noted [20]. The most common etiologic organisms are Streptococcus pneumoniae and Haemophilis influenza [20]. It is generally a clinical diagnosis. Treatment consists of antibiotic therapy [186].

HIV infection results in a significant amount of pathology of the ear, with up to 75% of adult HIV patients showing auditory disorder [187]. HIV may affect the outer ear, middle ear, cochlea, or central nervous system [187]. Opportunistic infections such as Pneumocystic carinii may involve the middle and external ear. Other opportunistic infections reported in HIV patients include Cryptococcocus, CMV, adenovirus type 6, HHV-1 [165]. HIV patients who develop neurosyphilis may experience hearing loss [165, 187].

8.5.6 *Salivary Infections*

Acute Suppurative Sialadenitis is an acute bacterial infection of the salivary glands, usually the major glands. Infection can be caused by contamination of the salivary ducts from the oral cavity or obstruction of the ducts due to local factors such as sialolith (salivary stone) formation [188]. Predisposing factors include dehydration, recent surgical procedure, compromised immune function, and medications that lead to dehydration [188]. The parotid gland is most often involved, and the condition is usually unilateral [188]. The incidence of bacterial sialadenitis has decreased since the advent of perioperative antibiotic therapy during abdominal surgery [189]. Staphylococcus aureus is the most common pathogen, though other

organisms can be involved [189]. Symptoms include pain, swelling, exacerbation with meals, and purulence [188, 189]. Treatment is generally rehydration along with antimicrobial therapy [188, 189].

The most common cause of viral sialadenitis is **Mumps**, most often caused by a paramyxovirus [174, 184]. Mumps can also be caused by Coxsackieviruses, parainfluenza, CMV, and others [174]. Mumps is most commonly found in patients under age 15, though due to the advent of vaccination it is not commonly seen in developed countries [188, 190]. A prodrome is often present, with constitutional symptoms such as headache, myalgia, malaise, arthralgia, and anorexia [188]. Unlike bacterial sialadenitis, bilateral involvement is common [188, 190]. The parotid glands are usually firmly swollen, and a fever is common as well [188, 190]. Mumps can be confirmed by viral serology and treatment is usually supportive [188]. Complications from the systemic disease may include inflammation of the testes, ovaries, or breasts; aseptic meningitis; pancreatitis; or hearing loss [188].

8.5.7 Thyroid/Parathyroid Infections

The thyroid may develop bacterial infection in rare cases, which can be caused by both Gram-positive and Gram-negative bacteria [191]. Other rare causes of thyroid infection include fungi, parasites, viruses, and opportunistic infections such as Pneumocystic carinii [127]. Patients generally present with swelling, pain, and fever [191]. Patients are usually euthyroid [127]. Treatment consists of antibiotic therapy and surgical drainage. There is a good long-term prognosis [191].

Viruses have been implicated in several forms of thyroid disease. **Subacute Thyroiditis** or **DeQuervain's Disease** classically occurs following an upper respiratory infection, usually in women [192]. Implicated viruses include those in the enterovirus family including echovirus, Coxsackievirus A and B, and paramyxovirus [192]. It presents with sudden neck pain and thyrotoxicosis (high levels of thyroid hormones) [192]. Biopsy shows granulomatous inflammation, and the condition is generally treated supportively with anti-inflammatory drugs, although surgery may be needed in persistent cases [127]. Many different viruses have also been found associated with autoimmune thyroid disorders such as Graves's disease and Hashimoto's thyroiditis; however, no direct evidence of causation has been demonstrated [192].

8.6 Environmental Conditions

8.6.1 General Considerations for Environmental Conditions

A number of reactive pathologic processes can occur in the head and neck. While they may differ slightly from area to area in nomenclature, presentation, and histology,

they may represent the same basic process. For example, reactive granulation tissue can form in multiple sites, though in different areas it may be called different names such as the pyogenic granuloma of the oral cavity and the contact ulcer or vocal process granuloma in the larynx. Both of these entities will be discussed later in the section in further detail. Many different environmental triggers can cause head and neck disease, such as chronic sinusitis and reactive otitis. In addition, common medical and dental procedures in the head and neck may lead to the introduction of foreign material causing inflammatory conditions.

Myospherulosis is a reaction to lipids, usually lipid-based antibiotic ointments [193]. It may occur following surgical packing of these ointments in the nasal cavity or paranasal sinuses, middle ear, or oral cavity [79, 165, 193, 194]. However, other cases may have no history of possible introduction of foreign material and are believed to be inflammatory in nature. Myospherulosis is generally treated by excision of the affected tissue, and addressing any known underlying disease [165, 195].

Certain idiopathic diseases may also affect the head and neck in a disproportionate manner. For example, **Rosai-Dorfman Disease**, or sinus histiocytosis with massive lymphadenopathy, is a rare histiocytic disorder found mainly in young patients, which most often manifests as massive cervical lymphadenopathy [196]. About half of all cases occur extranodally, and three quarters of these occur in the head and neck, often multifocally [197]. The most commonly affected head and neck location is the upper respiratory tract, particularly the sinonasal areas but it can also be seen commonly in the orbit, ear, and salivary glands and rarely in the oral cavity, oropharynx, thyroid, trachea [196, 198, 199]. The skin, soft tissues, and bone can also be affected in the head and neck [196, 199]. Patients may have a febrile episode at onset, and subsequent lymphadenopathy can reach impressive size [196]. Histopathologically, the lesions show effacement of the lymphoid follicles with proliferation of sinus histiocytes showing emperipolesis or entrapment of lymphocytes [196] (Fig. 8.27). It is generally a self-resolving entity [198].

8.6.2 Sinonasal/Nasopharyngeal Environmental Conditions

In the sinonasal region, **Inflammatory Polyps** are common; 1–4% of the population has been found to exhibit signs of these at autopsy. However, fewer patients actually exhibit symptoms of the disease [200]. Men are more commonly affected than women, and the condition is most common in adults [79, 201]. They generally present bilaterally [79] and most are associated with chronic rhinosinusitis. Inflammatory polyps can be associated with aspirin associated respiratory disease, cystic fibrosis, and allergic fungal sinusitis [201]. Diabetes has also been linked to nasal polyposis [79]. Inflammatory polyps show a broad clinical presentation but most symptoms relate either to nasal obstruction or rhinosinusitis [201]. The polyps can be locally invasive in nature [79]. Inflammatory polyps have a respiratory type lining with a prominent basement membrane, and the underlying polypoid connective tissue

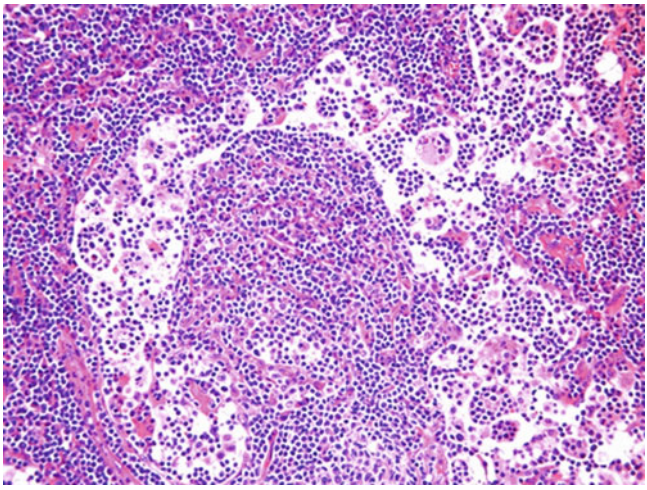

Fig. 8.27 Rosai-Dorfman lymphadenopathy. Histological features include emperipolesis or engulfing of lymphocytes by histiocytic cells (H&E, 20×)

is generally edematous with a mixed inflammatory infiltrate [79]. Treatment of inflammatory polyps can be surgical or medical (steroids or other medications) [79, 201].

One subset of sinonasal polyps is **Antrochoanal Polyps**, which are mostly seen in children or young adults. These arise from the maxillary antrum and involve the choana of the nasal cavity [79, 202]. They are generally unilateral [202]. The etiology of antrochoanal polyps is unknown but may relate to chronic sinusitis or allergy [202]. Antrochoanal polyps are similar to inflammatory polyps but generally have a longer stalk and do not show a thickened basement membrane [79, 202]. Antrochoanal polyps are generally treated by surgical excision [202].

Paranasal Sinus Mucoceles are cystic lesions that arise secondary to obstruction, usually secondary to inflammation or allergy [79]. These may be more aggressive than nasal polyps and cause extensive local damage, mimicking a neoplasm. They are lined by respiratory epithelium with mucoid material internally [79]. These lesions are usually treated with marsupialization [203].

8.6.3 Oral/Oropharyngeal Environmental Conditions

Within the oral cavity, reactive lesions comprise the majority of biopsies submitted to pathology services. These lesions often consist of apical intrabony lesions secondary to chronic or acute inflammation from carious or periodontally involved teeth, and gingival lesions secondary to irritating local conditions such as the

accumulation of plaque or calculus on teeth. **Periapical inflammatory lesions** consist of acute or chronically inflamed granulation tissue in the majority of cases (70–75% of cases) [181, 204]. In some instances, a periapical cyst can develop from various epithelial sources within the gingiva such as residual developmental epithelium, the epithelial lining that surfaces the periodontal pocket around the tooth, or fistula tract linings [181]. The lesions generally present as radiolucency at the apex of the tooth on a dental radiograph and often are asymptomatic or only mildly painful. Significant pain and swelling can occur with the formation of a periapical abscess, however. In most cases, resolution of the infected tooth source either through root canal therapy or extraction will resolve the lesion.

Reactive lesions of the gingiva are often secondary to local irritants such as plaque or calculus, occasionally exacerbated by hormones or medications. The most common reactive lesions of the gingiva are **Focal Fibrous Hyperplasia (FFH), Pyogenic Granuloma (PG), Peripheral Ossifying Fibroma (POF),** and **Peripheral Giant Cell Granuloma (PGCG)** [205]. These lesions are clinically similar: a localized pink-red nodule or growth on the gingiva. The surface may be ulcerated and the lesion may bleed easily. Such a lesion is sometimes clinically referred to as an epulis. POF and PGCG are unique to the gingiva, but PG and FFH can occur in many other sites. FFH (often called **Irritation Fibroma**) is a very common oral finding on the gingiva, labial, lingual, or buccal mucosa, and is thought to result from trauma such as biting [206]. Histopathologically, it consists of dense fibrous connective tissue forming a submucosal nodule. The oral PG is sometimes called a "pregnancy tumor" due to its predilection for pregnant females [207] (Fig. 8.28). It is a highly vascular lesion that is often ulcerated. [206, 207]. The peripheral ossifying fibroma exhibits reactive bone formation within the fibrous stroma. Finally, the PGCG is a vascular lesion that shows collections of multinucleated giant cells and hemosiderin [206, 207]. The treatment for all of these lesions is excision, though recurrence can be common in some, especially the POF.

8.6.4 Hypopharyngeal/Laryngeal Environmental Conditions

In the larynx, **Vocal Cord Nodules** and **Polyps** represent a reactive spectrum. They are believed to be related to mechanical stress such as voice abuse [208]. Other factors include smoking, gastroesophageal reflux disease (GERD), atmospheric pollutants, and hypothyroidism [54]. Vocal cord nodules arise in Reinke's space in the vocal fold and tend to be bilateral with a female predisposition [3, 208]. They occur over a broad age range [209]. Vocal cord polyps, on the other hand, arise on the anterior third of the vocal fold, are usually unilateral, and have a male predisposition [208]. Both present with hoarseness and can be visualized as masses via endoscopy [208]. Histopathologically both appear similar and consist of a stratified squamous epithelial covered mass with stromal change, which may be myxoid, fibrous, or vascular [3]. Vocal cord polyps are usually larger than nodules, generally over 3 mm

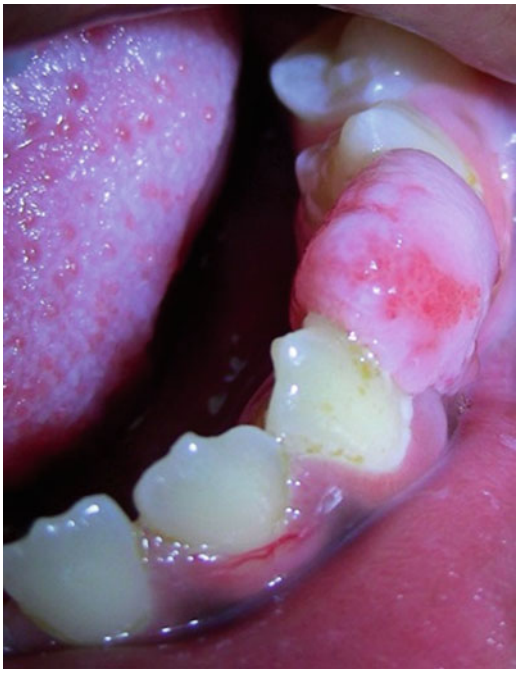

Fig. 8.28 Pyogenic granuloma, or so-called "pregnancy tumor", manifesting as a pedunculated *red* and *pink* growth in the interproximal papilla between the mandibular left premolar teeth in a 27 year-old female patient. The patient had recently been pregnant

in size [3]. Vocal nodules are usually treated with behavioral intervention to eliminate the vocal trauma and vocal cord polyps are often treated with excision [3, 208].

A rare inflammatory lesion in the larynx is the **Vocal Process Granuloma** or **Contact Ulcer**. In addition to hyperfunction or vocal misuse (similar to vocal fold nodules) contact ulcers have also been linked to GERD and intubation [210]. These usually occur on the vocal process of the arytenoid fold and may result in sore throat and voice change [3, 210]. Histopathologically, they consist of polypoid granulation tissue, often with an ulcerated surface [3]. Treatment is directed towards the source and includes voice therapy, treatment for GERD, or resection [210].

8.6.5 Auricular Environmental Conditions

The ear is home to a variety of inflammatory diseases, most commonly in the external and middle sections. One entity that affects the external ear is **Chondrodermatitis Nodularis Chronica Helicis**. This chronic inflammatory condition is thought to be caused by a combination of factors including sun damage, trauma, and vascular compromise [211]. It manifests as a small painful scaly or ulcerated nodule usually on the helix or antihelix of the ear [211, 212]. It usually affects men of older

age [211, 212]. Biopsy may show surface hyperplasia with underling collagen degeneration and necrosis; there may or may not be cartilage degeneration [212]. Treatments include steroid injections, excision, or laser eradication, and recurrence is common [165].

The external ear is also damaged by chronic exposure to a cold and humid environment, a condition termed **Pernio** [165]. It is usually seen in young to middle age [213]. Several systemic conditions may make patients more susceptible to pernio-like damage to the external ear. It manifests as painful erythematous nodules and histologically presents as inflammation around blood vessels, edema of the connective tissue, and lymphocyte rich inflammation of the rete ridges and sweat glands [165]. Treatment stresses prevention of cold exposure and treatment of any underlying systemic disease. Most cases resolve within 2–3 weeks [213].

The external ear canal can be affected by **Keratosis Obturans**, a disease of unknown etiology that is similar to a cholesteatoma, an inflammatory condition more common in the middle ear [214]. Keratosis obturans is usually seen in younger patients. Often associated with chronic sinusitis or bronchitis, it may cause severe pain and hearing loss [214]. Histologically it appears as desquamated cerumen and squamous keratin [165]. It is treated by removal of the keratin plug but may need regular debridement to prevent re-accumulation [214].

Exostoses and **Osteomas** are common in the external canal [165, 215]. They are more common in patients with frequent exposure to cold water such as swimmers [20]. Other potential causes include trauma, irritation, hormones, inflammation, or infection [215]. Exostoses, like those arising in other locations in the head and neck including the oral cavity, are often bilateral and symmetric, and osteomas are usually unilateral [165]. Biopsy may be necessary to rule out neoplasia. Exostoses and osteomas appear similar histopathologically with dense benign bone proliferation [20]. Surgery is sometimes necessary in some patients to relieve obstruction of the canal [165].

In the middle ear, **Cholesteatoma** is often related to chronic otitis media. It may be congenital or acquired [216]. Though rarely found in the external canal, it is most common in the middle ear [165, 214]. It may be destructive to the adjacent structures [214]. Clinically it presents often as painless discharge of the ear with hearing loss [217]. Histologically, it consists of layers of keratin in a cystic cavity lined by stratified squamous epithelium [214]. It is treated primarily by excisional curettage [165].

8.6.6 Salivary Environmental Conditions

The salivary glands are a common place for inflammatory pathology. The salivary **Mucocele** is a common lesion found in the oral cavity, often found in children or young adults [218]. It is caused by mucous spillage into the surrounding tissue after the rupture of a salivary gland duct, and often follows trauma [68,

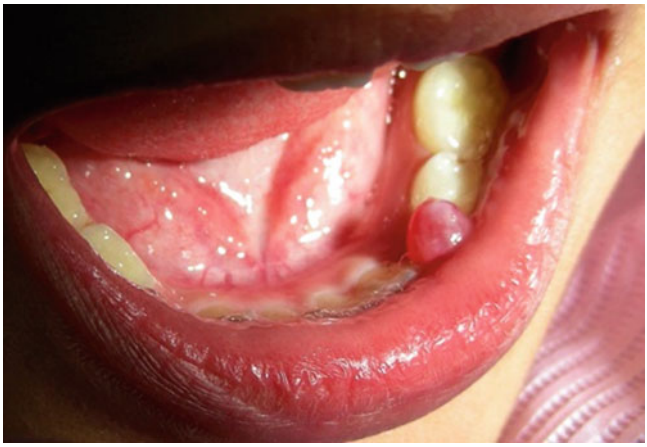

Fig. 8.29 Mucocele. A dome shaped mass on the lower labial mucosa is typical of a minor salivary gland Mucocele. Mucous spillage occurs generally following minor trauma and an inflammatory reaction follows

218]. They are most often found in the lower lip mucosa, although they may be also found in other areas including the floor of the mouth, buccal mucosa, palate, and rarely the salivary glands of Blandin-Nuhn on the ventral tongue [68, 218, 219]. Clinically, a mucucele appears as a bluish, dome shaped, translucent submucosal mass that may fluctuate in size [68] (Fig. 8.29). Histologically mucoceles consist of a pseudocystic mucous pool surrounded by inflamed granulation tissue [218]. They are generally treated via excision including the minor feeder salivary gland [68]. A **Ranula** is a mucocele in the floor of the mouth, and it can extend into the soft tissue of the neck (**Plunging Ranula**) [220]. These are most common in young adult populations and may have a higher frequency in patients with abnormalities of the mylohyoid muscle [220]. Asian populations have been identified to have a higher rate of involvement [220]. Treatment includes marsupialization or removal of the feeder gland [125].

Necrotizing Sialometaplasia is most likely caused by vascular ischemia [221]. The ischemic insult may be caused by a surgical procedure, dental injection, trauma, denture wear, radiation therapy, alcohol or tobacco use, or intubation [221]. Bulemia has also been associated with necrotizing sialometaplasia [221]. It is a self-limiting disease but may mimic carcinoma clinically and histologically. The most common site is the hard palate and other minor salivary glands, but it may occasionally be seen in the major glands [222]. Other rare sites include the sinonasal region, trachea, larynx, buccal mucosa, and tonsil [221]. Clinically, it presents as a slow-healing deep ulceration [68]. Histopathologically, there is exuberant hyperplasia of the surface epithelium, which may mimic carcinoma, along with necrosis of the minor salivary glands and transformation of the salivary ductal epithelium into surface-like stratified squamous epithelium [68, 221]. Most heal spontaneously within 2–3 months and usually do not recur [221].

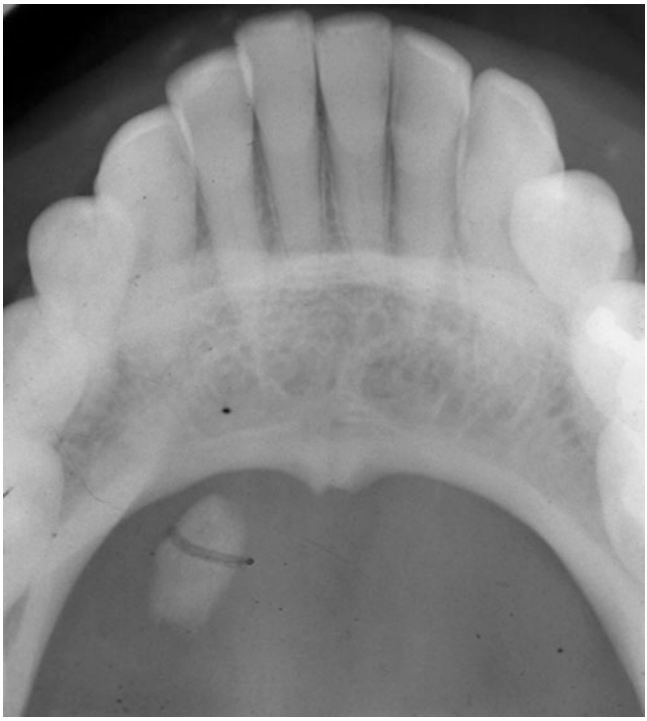

Fig. 8.30 Sialolith, or Salivary Duct Stone, is present in the floor of the mouth and viewed by occlusal radiograph

Chronic Sclerosing Sialadenitis is commonly associated with ductal blockage. This is a tumor-like condition that may be termed the Kuttner tumor of the submandibular gland [68]. Ductal blockage is usually attributed to **Sialolithiasis** (salivary stone formation) [223] (Fig. 8.30). Other causes of duct blockage include stenosis, inflammation of the duct, mucous plug, or foreign material [223]. It is most common in middle age with only a slight female predilection [68, 224]. Salivary gland swelling is usually present, and patients may report a painful increase in swelling prior to eating, especially when sialoliths are involved [68]. Histologically, there is chronic inflammation and fibrosis adjacent to the salivary ducts along with ductal dilatation [68]. If sialoliths are present, they may be noted on radiographs [68]. Treatment includes excision, endoscopy, and lithotripsy for sialoliths [68].

8.6.7 Thyroid/Parathyroid Environmental Conditions

Any enlargement of the thyroid gland is termed a **Goiter** (Fig. 8.31). Goiters can be normal (nontoxic), overactive (toxic), or underactive (hypothyroid) [225].

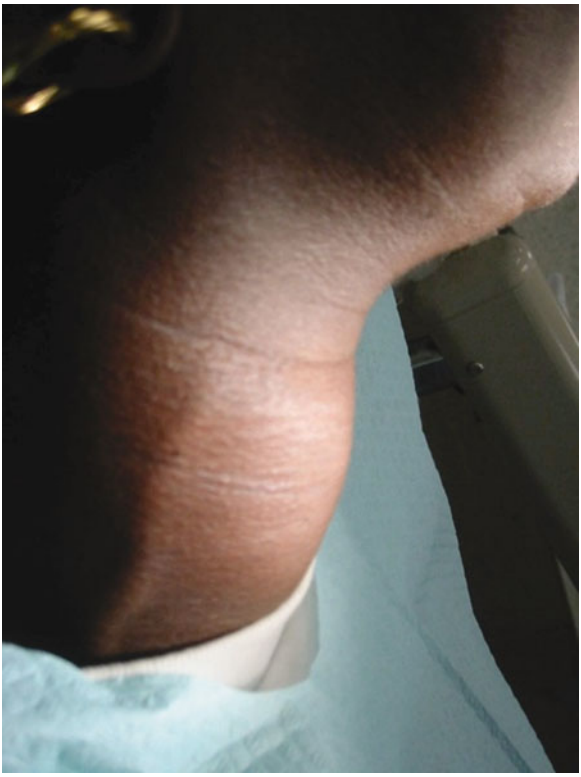

Fig. 8.31 Goiter, or enlargement of the thyroid gland, in the anterior neck

Although some goiters are caused by autoimmune disease (i.e. toxic goiter caused by Graves disease), other goiters can be caused by environmental factors such as iodine deficiency in endemic areas (endemic goiter) [127]. Other causes of goiter may be hormonal (dyshormonogenic goiter) and idiopathic (nontoxic nodular goiter) [127]. Endemic goiter areas include the Himalayas, South America, the European Alps and some areas of coastal Europe, China, and central Africa [127]. Nontoxic nodular goiter is a common form of goiter in the United States [127]. It is most common in women over age 50 in areas of iodine deficiency [226]. Goiters appear histologically as diffuse glandular enlargement and treatment depends on the type, whether or not there is hyperthyroidism, and whether carcinoma is suspected [127].

Thyroid tissue may be damaged by radiation, both external and via radioactive iodine used to treat other thyroid disorders [127]. Prior radiation exposure increases the risk of the development of thyroid cancer [12]. Multiple medications may also cause damage to the thyroid [12]. Acute damage can result in acute inflammation and hypothyroidism. The gland may become atrophic and fibrosed [127]. Biopsy may show nuclear atypia and vessel wall damage [127].

8.7 Conclusions

Although the head and neck is home to many different tissue types, common themes run through the pathologies seen in the various tissues. A sound knowledge of these is invaluable to both the clinician and the pathologist. In addition, many forms of pathology are distinctive to the head and neck and familiarity of these disorders will aid in developing a sound differential diagnosis of lesions and tumors involving these areas. Common conditions may be easy for the seasoned clinician to recognize, but some conditions are more difficult to diagnose. The DAMIEN algorithm, in which the clinician considers the potential disease process as well as the tissue in which the lesion has arisen, can be a valuable aid to clinicians and pathologists in the work-up of unusual lesions.

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Chapter 9
Pathology of Head and Neck Cancer I: Epithelial and Related Tumors

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Contents

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Abstract Over 90% of head & neck cancers are squamous cell carcinomas. This presents both advantages and challenges to clinicians and researchers. The frequency of squamous cell carcinoma allows most otolaryngologists to become very familiar with range of clinical presentations and current treatment options for this disease. New treatment protocols can be evaluated with a large patient base. Archival material (banked tissues, datasets) facilitates investigations into the molecular basis of these tumors. The wide range of other tumors arising in the head & neck are therefore relatively infrequent, leading to uncertainty in diagnosis, treatment and opportunities for meaningful research.

In this chapter we begin with squamous cell carcinoma and its histologic variants, linking new findings in molecular pathology with conventional and novel prognostic features. We next consider the evaluation of "undifferentiated" tumors of the head & neck. Appropriate classification has important prognostic and therapeutic implications. This leads to a consideration of the spectrum of neuroendocrine tumors. The spectrum of tumors arising in salivary glands is as wide as anywhere in the body. We will provide a framework for understanding the diversity of morphologic appearances, and summarize current prognostic features. We finish the chapter with a review of ameloblastoma, the major odontogenic tumor.

Keywords Head and Neck Cancer • Squamous cell carcinoma • Salivary gland carcinoma • Neuroendocrine carcinoma • Sinonasal carcinoma

Abbreviations

ACC	Adenoid cystic carcinoma
AR	Androgen receptor
EBV	Epstein-Barr virus
EMC	Epithelial-myoepithelial carcinoma
ES	Ewing's sarcoma
FISH	Fluorescence in situ hybridization
HER2	Human epidermal growth factor receptor-2
HPV	Human papillomavirus
ITAC	Intestinal-type adenocarcinoma
LCNC	Large cell neuroendocrine carcinoma
LOH	Loss of heterozygosity
MASC	Mammary analog secretory carcinoma
MEC	Mucoepidermoid carcinoma
N:C	Nucleus to cytoplasm ratio
NPC	Nasopharyngeal carcinoma
ONB	Olfactory neuroblastoma
PCR	Polymerase chain reaction
PLGA	Polymorphous low grade adenocarcinoma
PR	Progesterone receptor

PNET Primitive neuroectodermal tumor
SNUC Sinonasal undifferentiated carcinoma
UV Ultraviolet

9.1 Introduction

To the practicing pathologist, specimens from the head and neck fall into one of three categories. The most frequent consists of generally mundane benign specimens: sinus contents, tonsils, extracted teeth. The second category contains squamous cell carcinoma, its precursors and mimics. The final category consists of "everything else". While the second category is challenging enough, the third creates its own unique difficulties based on both the rarity of many of the lesions, and their overlapping morphologic features. The purpose of this chapter is to make sense of the spectrum of epithelial malignancies (carcinomas) seen in the head and neck. The following chapter will address the non-epithelial malignancies (sarcomas and lymphomas) arising in this region. Knowledge of the normal regional histology of the head and neck and a familiarity with the benign and pre-malignant lesions described in the previous chapter are important for understanding the spectrum of malignancies seen in the head and neck.

9.2 Squamous Cell Carcinoma

9.2.1 Conventional Squamous Cell Carcinoma

Squamous cell carcinoma and its variants constitute more than 90% of all head and neck cancers. Traditionally these tumors were thought to primarily arise in elderly males with a history of tobacco (or other regional carcinogen, i.e. betel nut) use. Additional features-alcohol use, poor oral hygiene, nutritional deficiency, chronic mucositis (e.g., lichen planus) and genetic or racial factors may potentiate a carcinogen's effect or act independently [1]. Females or younger males without prior tobacco use were occasionally seen, suggesting the presence of other etiologic factors [2]. As cigarette smoking diminished in the United States, it was expected that the incidence of head and neck squamous cell carcinoma would fall. That did not happen. The incidence of oropharyngeal squamous carcinoma actually increased [3].

Patients with oropharyngeal squamous cell carcinoma tend to be younger (less than 45 years of age) and more frequently non-smokers than those whose tumors arise in other head and neck sites. The same high-risk human papillomavirus (HPV) types responsible for cervical cancer were frequently identified in the oropharyngeal tumors, particularly in males, likely acquired through oral sex. In contrast to the squamous carcinomas seen in smokers, these HPV-related tumors were more

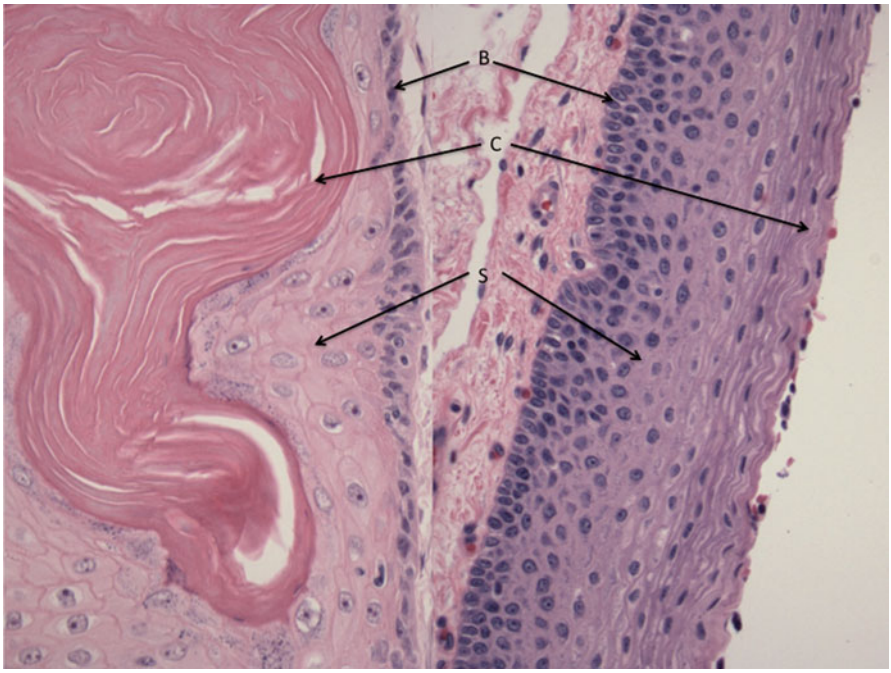

Fig. 9.1 Well-differentiated squamous cell carcinoma (*left*) shares many morphologic features with normal squamous mucosa (*right*). The basal cell layer (*B*) contains small, immature, mitotically active cells. As these mature into the spinous layer (*S*), they acquire more abundant cytoplasm and a larger nucleus. The nucleus subsequently condenses (parakeratosis) or disappears (orthokeratosis), leaving a cornified layer (*C*)

frequently of basaloid or papillary subtypes (discussed below) and to respond better to radiation therapy [4]. The differences between carcinogen-induced and HPV-associated head and neck squamous carcinomas are discussed more fully in Chap. 12 (head and neck – cervix CA connection). The histologic features of conventional squamous carcinoma and its common variants are described below.

Squamous cell carcinoma arises from normal squamous epithelium through a stepwise process called dysplasia, discussed in detail in Chap. 8. Squamous cell carcinoma is a neoplasm with morphologic features of squamous epithelium that has penetrated through the basement membrane, extending into the underlying connective tissue stroma. Figure 9.1 illustrates the shared features between squamous mucosa and squamous carcinoma. A strip of squamous epithelium, rolled into a circle, gives the general architecture of a nest of invasive squamous cell carcinoma. The cells at the periphery of a tumor nest correspond to the normal basal layer. These are mitotically active immature cells with a dark oval nucleus and scant cytoplasm, yielding a high nucleus to cytoplasmic (N:C) ratio. In some cases, the nuclei line up perpendicular to the basement membrane, giving a picket-fence (palisaded) appearance. Inward from the periphery, the cells become larger, with a lighter-staining

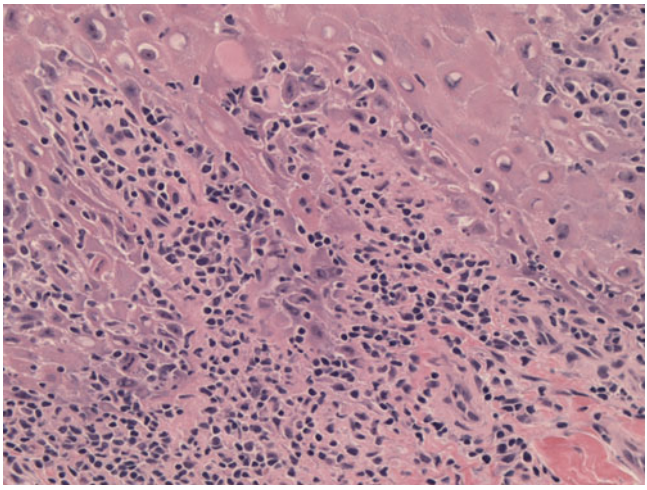

Fig. 9.2 In microinvasive squamous cell carcinoma, cells penetrate the basement membrane, entering the underlying stroma. The irregular interface between epithelium and stroma is a clue to the presence of microinvasion

nucleus and abundant cytoplasm, yielding a lower N:C ratio. Intercellular bridges (desmosomes) between adjacent cells, like those of the normal stratum spinosa, may be prominent. Just as the surface of squamous mucosa is covered by a layer of keratin, in well-differentiated squamous carcinoma, the center of tumor nests often contain whorls of keratin, referred to as "keratin pearls". This maturation process, where the cells in the center of the nest are morphologically different from those at the periphery, is the basis for the histologic grading of squamous cell carcinoma (discussed below).

By definition, squamous cell carcinoma extends beyond the sub-epithelial basement membrane. The extent of this invasion varies and is used as a component of tumor staging. The term "microinvasion" was first introduced to denote a set of cervical carcinomas that while extending beyond the basement membrane did not reach the level of the mucosal lymphatic system. Such a tumor should have no metastatic potential, and a 100% cure rate would be expected after complete excision of the lesion. In the head and neck, the true vocal cords come closest to an analogous anatomic site. None-the-less, use of the term has been expanded to include many sites, regardless of their anatomic lymphatic distribution. The criteria for defining microinvasion are largely outcomes-based and site-specific [5]. Figure 9.2 illustrates a microinvasive squamous cell carcinoma.

The majority of squamous carcinomas invade as groups of cells arranged in irregular nests and cords, or as individual cells. They induce a variable fibroblastic (desmoplastic) and inflammatory host response. These conventional squamous cell carcinomas can be subdivided into keratinizing and non-keratinizing types, based on the presence or absence of extracellular keratin pearls (Fig. 9.3). Within each category, tumors are subjectively graded as well- (grade 1), moderately- (grade 2) or

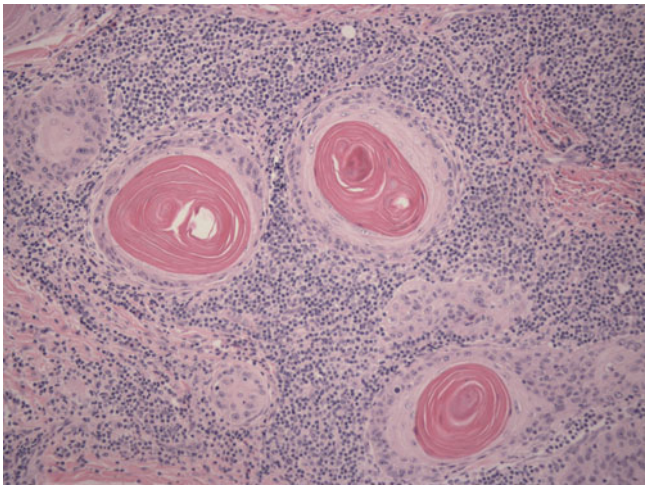

Fig. 9.3 Keratinizing squamous cell carcinomas are characterized by the presence of keratin pearls. These are concentric arrays of keratin material; the remnants of dead squamous epithelial cells

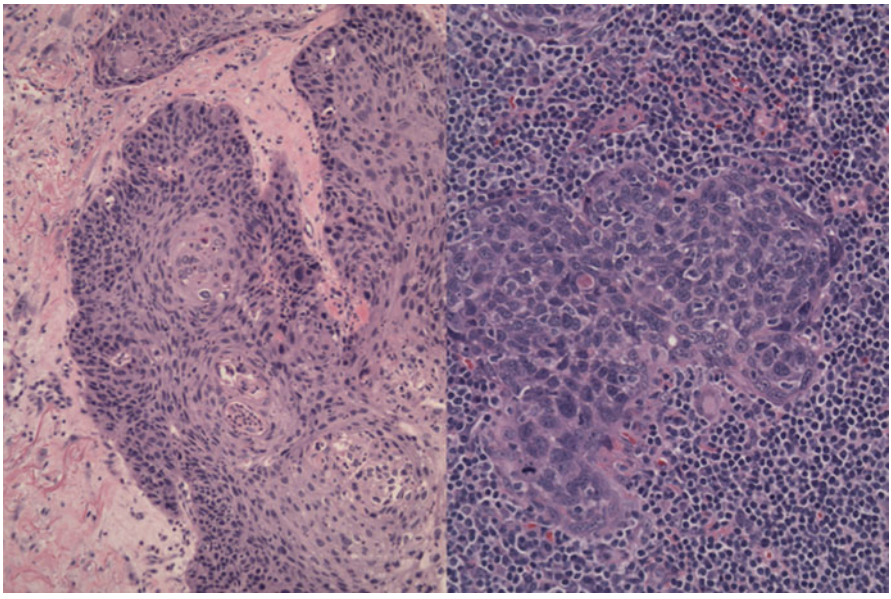

Fig. 9.4 Moderately (*left*) and poorly (*right*) differentiated squamous cell carcinoma. Note central cells with abundant cytoplasm indicating differentiation on the *left*. The tumor nest on the right shows no peripheral to central maturation. Compare these with the well-differentiated carcinoma in Fig. 9.3

poorly-differentiated (grade 3), based on the degree of peripheral to central maturation (as described above), mitotic activity, presence of abnormal mitotic figures, nuclear pleomorphism, and pattern of invasion. Well-differentiated squamous carcinoma shows prominent peripheral to central maturation, has limited mitotic activity, and often has a broad, pushing invasive front. Poorly differentiated squamous cell carcinoma, in contrast, shows little, if any peripheral to central cellular maturation. Their nuclei are more variable in size and shape (pleomorphic), with frequent mitotic figures, including atypical forms. The invasive front is often irregular, with small nests and individual cells variably extending into the underlying stroma. Moderately differentiated tumors are intermediate in these features. Figures 9.3 and 9.4 illustrate the spectrum of differentiation in conventional squamous cell carcinoma.

9.2.2 Squamous Cell Carcinoma Variants

The classification and sub-classification of tumors is an important component of pathology. This process has progressed from classification schemes based on gross examination, to modern systems using microscopic visualization with histochemical stains, now augmented by the use of immunohistochemical, molecular and genetic techniques. This reiterative process creates successively more homogenous clinical-pathologic groupings. This allows improved prognostication, and importantly, facilitates studies into the molecular basis of individual cancers. Such insights will eventually be the basis for selecting individualized treatment plans, targeting specific molecular derangements in a patient's tumor, and may even allow the development of prophylactic treatments to prevent cancer from developing. As an early step in this process, a number of subtypes (histologic variants) of squamous cell carcinoma have been recognized. Some differ in etiology, pursue a more or less aggressive disease course, or respond differentially to particular therapies. We will review the most common of these variants below.

Verrucous Carcinoma often presents clinically as an overtly malignant-appearing warty mass, measuring up to 10 cm. In the head and neck, it most often involves the oral cavity and larynx of elderly male smokers. These tumors are locally destructive but have limited, if any, metastatic potential. Thus, recognition of this tumor is important to avoid overtreatment. Correctly diagnosing verrucous carcinoma, however, is not straightforward. Despite the alarming gross appearance, the histology is bland, resembling a common wart with its "church-spire" pattern of keratinization. In fact, a diagnosis of malignancy cannot be made with assurance from a superficial biopsy lacking the deep tumor-stroma interface. The deep aspect of a verrucous carcinoma has a pushing border, with blunt bulbous projections in a chronically inflamed stroma, located below the level of the adjacent epithelium (Fig. 9.5). Early reports warned that radiation therapy caused some tumors to transform into more aggressive squamous carcinomas. These likely were hybrid tumors, containing a component of conventional squamous cell carcinoma within the verrucous carcinoma. Adequate histologic evaluation is important in excluding such hybrid tumors.

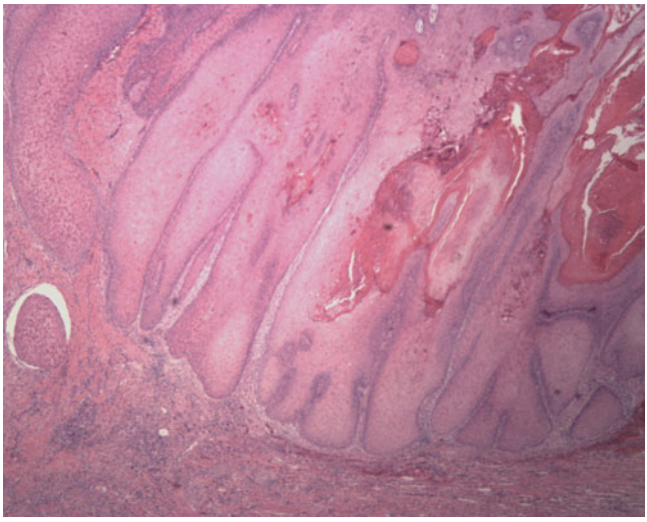

Fig. 9.5 Verrucous carcinoma is a well-differentiated variant of squamous carcinoma with a wart-like surface and a blunt, pushing-type invasive front

While surgical excision remains the treatment of choice for verrucous carcinoma, radiation or laser ablation are accepted therapies when surgical excision is not possible [6].

Papillary squamous cell carcinoma is an uncommon variant with an improved prognosis, relative to conventional squamous cell carcinoma. These tumors most often arise in the larynx of males with a history of tobacco and alcohol use, but evidence of HPV may be found in one third of cases overall and more than half of those arising in the oropharynx [7]. These tumors grow as blunt or narrow, often branching, papillae containing fibrovascular cores (Fig. 9.6). Stromal invasion is difficult to demonstrate. Rather, the diagnosis of carcinoma is made based on the malignant cytologic features of the lining epithelium. Testing for evidence of HPV is warranted, as the prognosis for HPV-positive tumors is better than for HPV-negative cases.

Basaloid squamous cell carcinoma was first described as an aggressive variant presenting as an advanced stage tonsilar or oropharyngeal tumor in elderly males with a history of smoking and alcohol use [4, 8]. These tumors resemble basal cell carcinoma of the skin, growing as solid or cribriform nests of small cells with high nuclear to cytoplasmic ratios, and frequent palisading of tumor cells at the periphery of nests. Because of the cell size, high mitotic rate and frequent presence of necrosis, the histologic differential includes small cell (neuroendocrine) carcinoma. Foci of co-existing conventional squamous cell carcinoma, in situ or invasive, may be seen, and when present, aid in the diagnosis. The presence of high-molecular weight cytokeratin and absence of neuroendocrine markers by immunohistochemistry allow a definitive diagnosis in the remaining cases. As with papillary squamous cell carcinoma, HPV can be demonstrated in a proportion of tumors, generally in the oropharynx. Testing for HPV is appropriate in all cases, as HPV-positive tumors

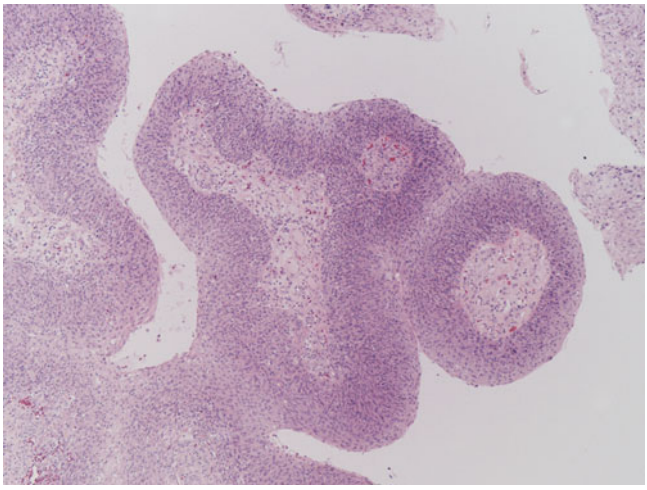

Fig. 9.6 Papillary squamous carcinoma is an exophytic tumor with crowded, atypical epithelial cells lining branching fibrovascular cores. Invasion is difficult to detect on biopsy specimens

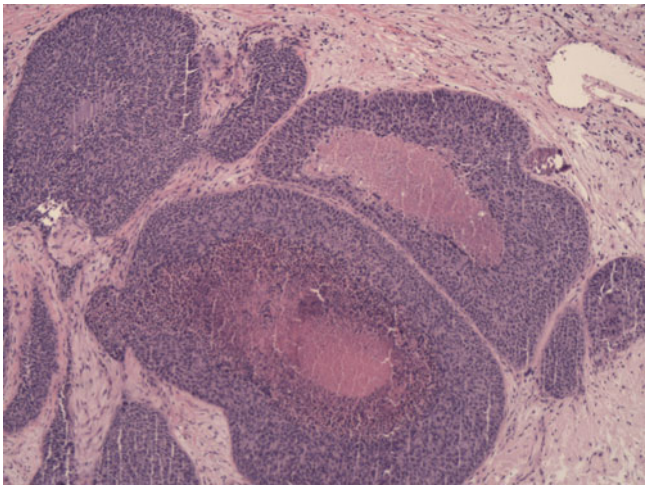

Fig. 9.7 Basaloid squamous carcinoma consists of nests of small basaloid cells with peripheral palisading. Central necrosis is often prominent

respond better to radiation therapy, improving an otherwise dismal prognosis. Figure 9.7 illustrates the key histologic features of this tumor.

Spindle cell squamous cell carcinoma (sarcomatoid carcinoma) is an unusual variant of squamous carcinoma not linked to tobacco or alcohol use. These tumors generally present in elderly patients as a polypoid mass arising in the oral cavity, oropharynx or larynx. In addition to areas of conventional squamous carcinoma,

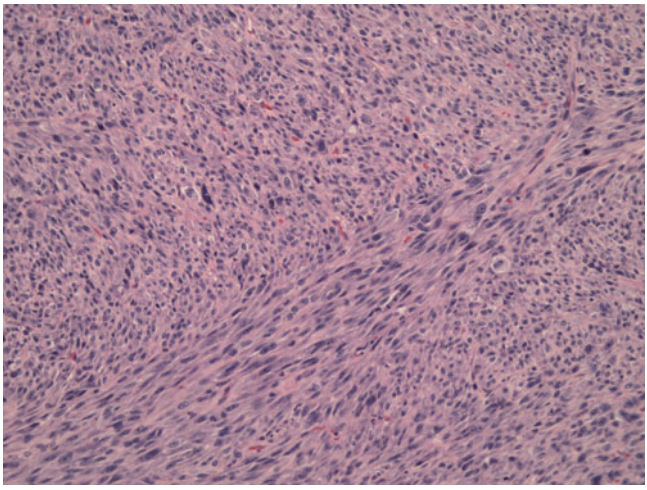

Fig. 9.8 Spindle cell or sarcomatoid carcinoma can closely resemble a sarcoma. The intersecting fascicles seen here suggest a high-grade smooth muscle tumor. Other foci in the tumor showed conventional squamous cell carcinoma

the tumor contains fascicles of malignant spindle cells and in some cases, foci of malignant bone or cartilage (Fig. 9.8). Small biopsies may miss the conventional carcinoma, raising the possibility of a sarcoma. In such cases immunohistochemical detection of epithelial or squamous markers (cytokeratin, p63) may be useful in confirming the diagnosis. These tumors frequently recur locally, purely exophytic tumors less often then deeply invasive tumors. Matched stage for stage, the prognosis is similar to that of conventional squamous carcinoma [9].

The term "**lymphoepithelial carcinoma**" or simply "**lymphoepithelioma**" is frequently used to denote an Epstein-Barr Virus (EBV)-related undifferentiated carcinoma of the nasopharynx, composed of nests or single cells, in a background of lymphocytes. This tumor is further discussed below. Similar tumors, without the unique clinical features or EBV association, can be found at sites throughout the body.

9.2.3 Site-Specific Differences

There are important clinical and biologic differences among squamous cell carcinomas arising in different head and neck sub-sites. Carcinomas arising in the oral cavity tend to be better differentiated than those in the hypopharynx. Tumors arising on the true vocal cord present at a lower stage, often with only in-situ disease, because of changes in voice quality. In contrast, the first sign of a tonsilar crypt or hypopharyngeal carcinoma is often metastatic disease involving cervical lymph nodes. Whereas exposure to carcinogens (smoking) is the primary etiologic factor for most squamous cell carcinomas in the head and neck, infection with the human papillomavirus (HPV) plays an important role in a subset of oropharyngeal and

tonsilar tumors, as does Epstein-Barr Virus (EBV) in non-keratinizing carcinomas of the nasopharynx. Overall 5-year survival rates for head and neck cancer vary between 75% (lip) and 27% (hypopharynx) [10]. These site-specific differences are important reminders that squamous cell carcinoma is not a single disease, even within the head and neck.

9.3 Carcinoma of the Nasal Cavity, Paranasal Sinuses and Nasopharynx

In addition to the squamous cell carcinomas previously described, the nasal cavity and paranasal sinuses are the sites of origin for a variety of tumors. The three sub-types of Schneiderian papillomas are discussed in Chap. 8. Both inverted and oncocytic (cylindrical cell) papillomas are associated with concurrent or subsequent carcinoma, usually squamous, in 5–15% of cases. The sero-mucinous glands lining the nasal passages can give rise to the spectrum of salivary gland carcinomas discussed below, and to a unique set of intestinal and non-intestinal type sino-nasal adenocarcinomas.

9.3.1 Intestinal and Non-intestinal Type Sinonasal Adenocarcinoma

Intestinal-type adenocarcinomas (ITAC) are a spectrum of locally aggressive tumors that resemble those found in the colon (Fig. 9.9). They are seen in adults, generally in the fourth–seventh decade, and have an increased incidence in wood and leather workers. These tumors are sub-classified into papillary, tubular, solid or mucinous types, with the latter further divided into colloid (tumor cells floating in a pool of extracellular mucin) and signet ring cell (individual cells with a single mucin-filled vacuole and compressed peripheral nucleus). These last two in particular may be indistinguishable from metastatic colonic adenocarcinoma, necessitating clinical and radiographic correlation to arrive at the appropriate diagnosis [11, 12].

Defining the site of origin is not problematic for low-grade non-intestinal-type sinonasal adenocarcinomas, as they closely resemble normal sero-mucinous glands. Rather, distinguishing tumor from normal sero-mucinous glands may be the challenge. The identification of fused glands, occasional papillary structures and the absence of a second cell layer (myoepithelial cells) are the key diagnostic features. Subtlety is not an issue with a high-grade non-intestinal-type sinonasal adenocarcinoma. This is an obviously malignant tumor with a solid growth pattern, presence of necrosis, marked nuclear atypia and frequent mitotic figures (Fig. 9.10). As these tumors can have a variety of morphologic appearances, the challenge in these cases is to distinguish these tumors from the other poorly differentiated or undifferentiated carcinomas involving the nasal cavity or paranasal sinuses (discussed below) [12, 13].

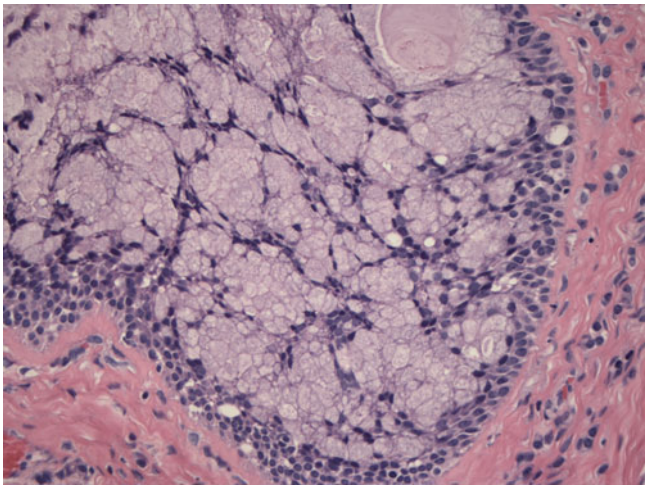

Fig. 9.9 Intestinal-type sinonasal adenocarcinoma can have a range of appearances, mirroring the spectrum seen in the GI tract. This tumor consists of cribriform nests of mucin-producing cells

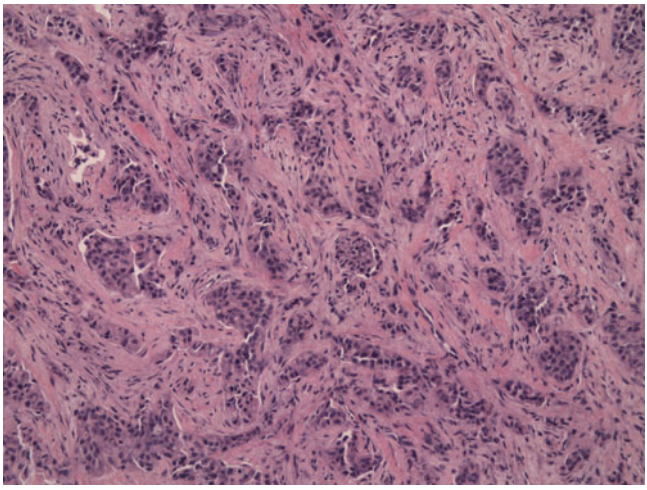

Fig. 9.10 High-grade non-intestinal sinonasal adenocarcinoma showing invasive nests and cords of tumor cells in a desmoplastic stroma

9.3.2 Sinonasal Undifferentiated Carcinoma

Sinonasal Undifferentiated Carcinoma (SNUC) is an aggressive, rapidly growing tumor of uncertain etiology. The tumor consists of sheets or nests of mitotically active large cells with prominent nucleoli (Fig. 9.11). The histologic (and often clinical) differential includes melanoma, large cell lymphoma, olfactory neuroblastoma,

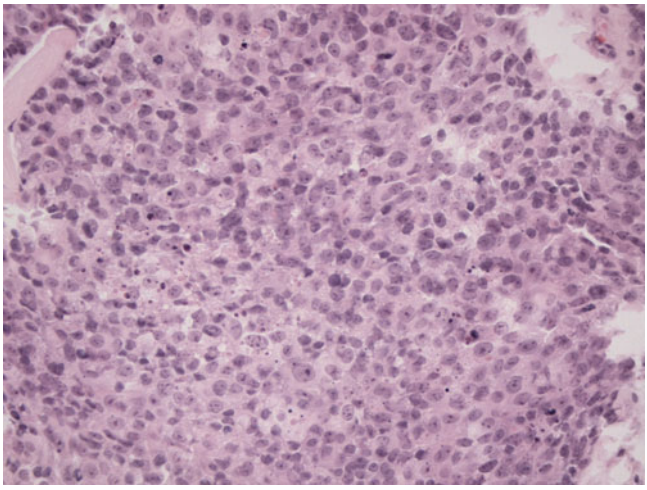

Fig. 9.11 Sinonasal undifferentiated carcinoma often grows as sheets of large pleomorphic cells with prominent nuclei, abundant mitotic figures and areas of necrosis

nasopharyngeal carcinoma, and other poorly differentiated carcinomas. Immunohistochemical studies are helpful in excluding entities (melan-A and HMB-45 for melanoma, LCA, T- and B-cell markers for lymphoma, EBV-LMP for nasopharyngeal carcinoma) from the differential [14]. Interestingly, p16 expression in the absence of HPV has been described in SNUC [15]. It is not clear if this sheds light on an underlying molecular mechanism, but does caution against use of this marker in isolation to classify an undifferentiated tumor as an HPV-related squamous carcinoma. Overall 5-year survival for SNUC remains under 25%, despite surgery and multi-agent chemotherapy [16].

9.3.3 Olfactory Neuroblastoma

Olfactory Neuroblastoma (ONB, esthesioneuroblastoma) is a rare tumor that may presents as nasal obstruction or bleeding in either teenagers or older adults. The tumor forms a polypoid mass in the superior aspect of the nasal cavity, paranasal sinuses or nasopharynx. The prognosis is largely dependent on tumor stage; patients with lesions confined to the nasal cavity have an 80–90% survival rate, compared to 40–50% for patients whose tumors extend beyond the nasal cavity and paranasal sinuses. Well-differentiated tumors show a lobular architecture, with uniform small blue cells, often arranged in rosettes, in an abundant, fine neurofibrillary background (Fig. 9.12). As the tumor grade increases (i.e., more poorly differentiated), the lobular architecture becomes less apparent and necrotic areas appear. The

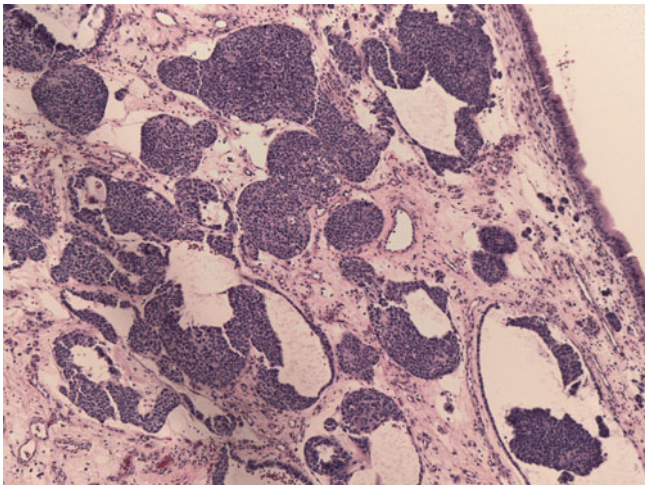

Fig. 9.12 Olfactory neuroblastoma often appears as rounded nodules of *blue cells* in an edematous vascular stroma. Note normal respiratory type epithelium on the *right*

fibrillar background gives way to a more reactive fibrous stroma. Tumor cells have larger, more pleomorphic nuclei with increased mitotic figures. The least differentiated (grade 4 in the Hyams grading system) may be difficult to distinguish from sinonasal undifferentiated carcinoma or primitive neuroectodermal tumor (PNET). In contrast to carcinoma, olfactory neuroblastoma is generally negative for cytokeratin, but commonly expresses neuroendocrine markers such as neuron-specific enolase, synaptophysin and chromogranin [17]. Recently, the immunohistochemical expression of calretinin, a calcium-binding protein expressed by mesothelial and other cells, has been reported as an additional useful marker to distinguish ONB from its mimickers [18].

9.3.4 Nasopharyngeal Carcinoma

The World Health Organization separates squamous cell carcinomas arising in the nasopharynx into keratinizing nasopharyngeal carcinoma (NPC), non-keratinizing NPC and non-keratinizing undifferentiated carcinoma (lymphoepithelioma). This classification has important etiologic and prognostic implications [19]. Keratinizing NPC is histologically identical to conventional squamous cell carcinoma arising at other head and neck sites, and is not significantly related to Epstein-Barr Virus (EBV) infection. The latter two NPC types are distinct, with strong associations with EBV. Histologically, non-keratinizing differentiated NPC appears similar to conventional non-keratinizing squamous carcinoma. Thus, all such tumors arising in the nasopharynx should be tested for EBV. Any NPC found to be EBV-negative, or not limited to the nasopharynx should also be tested for HPV to exclude an oropharyngeal primary [20]. The non-keratinizing undifferentiated form is the

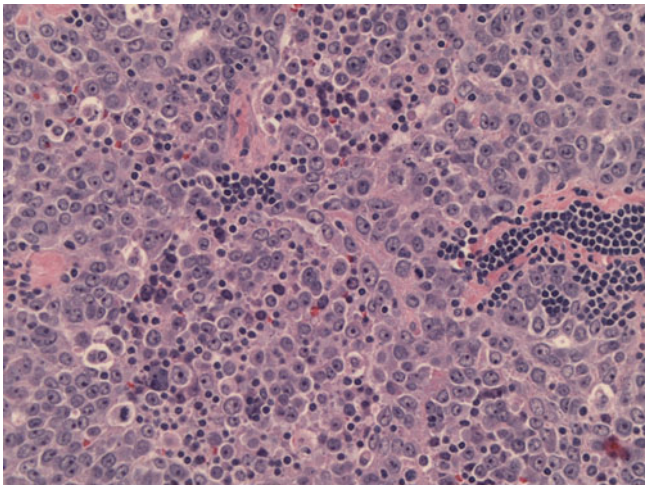

Fig. 9.13 This undifferentiated nasopharyngeal carcinoma shows large round to polygonal cells with large nuclei and a prominent nucleolus. Note the *small dark* lymphocytes scattered within the tumor

tumor usually thought of as 'nasopharyngeal carcinoma'. This tumor consists of large cells with prominent nucleoli and scant pale cytoplasm. These cells can be arranged as clusters or as individual cells within a sea of lymphocytes (Fig. 9.13). While NPC is predominantly an adult malignancy, the non-keratinizing undifferentiated form is a common pediatric tumor in Northern and Central Africa.

9.3.5 Ewing's Sarcoma/Primitive Neuroectodermal Tumor

Ewing's Sarcoma (ES) / Primitive Neuroectodermal Tumor (PNET) is a family of small blue cell tumors with a characteristic t(11;22) translocation involving the EWS and FLI-1 genes. Ewing's sarcoma is predominantly limited to adolescents and young adults, with sheets of small uniform round cells with scant, glycogen-rich pale cytoplasm. PNET differs from Ewing's in that it may be seen in any age group, has a higher proliferative rate, and shows histologic or immunophenotypic evidence of neuroendocrine differentiation (Fig. 9.14). These tumors show membranous staining for CD99, the product of the MIC2 gene. While supportive of the diagnosis, CD99 expression is seen in a variety of other tumors, including carcinomas, sarcomas and lymphomas. Current multimodality therapy has improved the 5-year survival rate up to 75%, with increasing tumor size and extent, and the presence of a p53 mutation being adverse prognostic features. In the head and neck, it is often difficult to tell whether the tumor is arising in bone or from an extra-osseous location. Those tumors arising from soft tissue of the sinonasal cavity appear to have a better prognosis than ES/PNET overall [21].

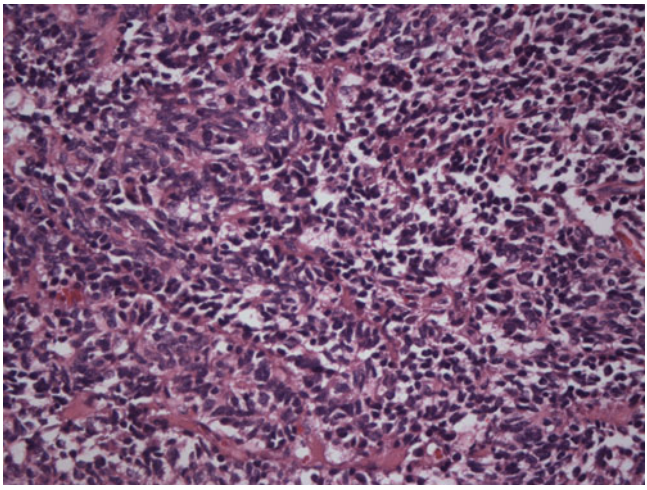

Fig. 9.14 Ewing's sarcoma/primitive neuroectodermal tumor (PNET) consists of small round to slightly spindled cells with scant stroma. Tumors expressing neuroendocrine markers or forming rosettes, such as this case, can be categorized as PNET

9.4 Neuroendocrine Tumors of the Head and Neck

The spectrum of neuroendocrine tumors seen in the lung also occurs in the head and neck region [22]. **Carcinoid tumor** represents the low-grade end of this spectrum. In contrast to the lung, this is a rare tumor in the head and neck. It presents as a submucosal mass, primarily in the larynx, and is composed of uniform cells with round nuclei with a stippled ("salt and pepper") chromatin pattern. The tumor is well circumscribed, without either mitotic activity or necrosis. Despite the bland histologic appearance, as many as one third of carcinoid tumors metastasize.

9.4.1 Atypical Carcinoid Tumor/Large Cell Neuroendocrine Carcinoma

Atypical carcinoid tumors differ in many aspects from typical carcinoids. Etiologically, atypical carcinoid tumors are strongly related to tobacco use. Atypical carcinoid tumors are infiltrative tumors, commonly with lympho-vascular invasion. The component cells are more pleomorphic, with mitotic activity and focal necrosis (Fig. 9.15). Five-year survival rates are under 50%, in part due to early metastasis and the radio-resistance of these tumors.

Until recently, large cell neuroendocrine carcinoma (LCNC) was classified with the atypical carcinoid tumors. It is now recommended that those meeting the same diagnostic criteria used in the lung (i.e., large cells with abundant cytoplasm, a

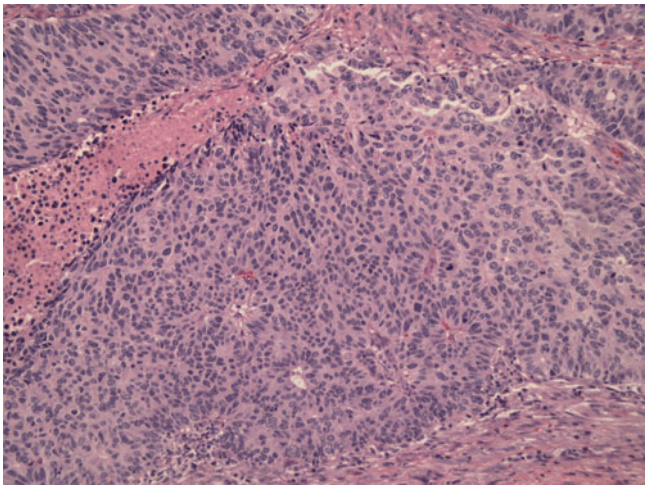

Fig. 9.15 Large cell neuroendocrine carcinoma demonstrates frequent mitotic figures and abundant necrosis. Until recently, this lesion would have been classified as an atypical carcinoid tumor

"neuroendocrine" growth pattern and immunophenotype, more than ten mitotic figures per ten high power microscope fields) be classified as LCNC. Thus defined, patients with LCNC have a significantly poorer prognosis than those with atypical carcinoid tumors [23].

9.4.2 Small Cell Neuroendocrine Carcinoma

Small cell neuroendocrine carcinoma histologically and immunophenotypically resembles its namesake in the lung. As with their pulmonary counterpart, most cases are seen in males with a significant smoking history, and have metastatic disease at the time of diagnosis. As small cell neuroendocrine carcinoma is rare as a primary head and neck tumor, it is important to exclude metastatic disease. In addition to a lung primary, **Merkel cell carcinoma**, a primary small cell neuroendocrine carcinoma of the skin, should be considered. Like other small cell carcinomas, Merkel cell carcinoma is an aggressive tumor with frequent nodal and distant metastasis. This tumor has a predilection for the head and neck region, with nearly half of all cases originating here. Those arising from the lip have been reported to be more aggressive than those arising in other head and neck skin sites [24]. Sun exposure, particularly ultraviolet radiation, and a recently described Merkel cell polyomavirus (MCPyV), appear to be important in the pathogenesis of this tumor. MCPyV can be detected by PCR in most cases, though immunohistochemical studies are more practical for diagnosis. Merkel cell carcinoma, in contrast to other small cell carcinomas, commonly shows a

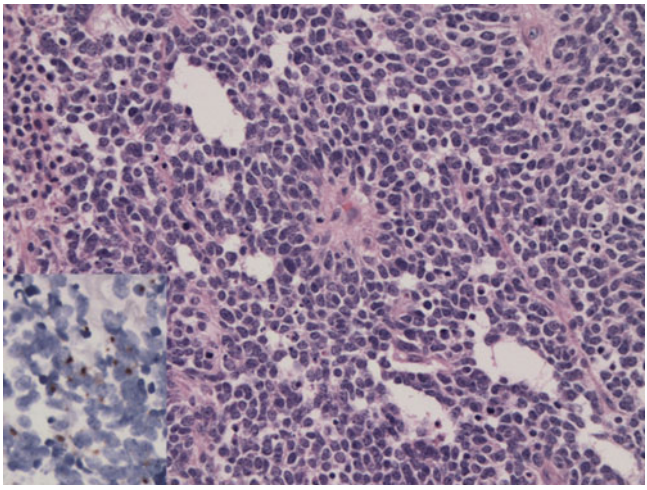

Fig. 9.16 Merkle cell carcinoma can be distinguished from other small cell neuroendocrine carcinomas by dot-like staining for cytokeratin 20 (*insert*)

perinuclear dot-like staining with cytokeratin 20 (Fig. 9.16). The MCPyV large T protein may be detected by immunohistochemistry in 7–97% of cases [25].

9.5 Melanoma

Melanoma is called the great mimicker in pathology, as it enters the histologic differential of almost any tumor composed of sheets or nests of large or small epithelioid cells, fascicles of spindle cells and of biphasic tumors with both epithelioid and spindle cell components. The great majority of melanomas of the head and neck arise from sun-exposed skin, and behave similar to those arising on skin elsewhere on the body. Occasionally a melanoma is identified in peri-parotid lymph nodes. A careful clinical history may reveal a remote history of a pigmented scalp lesion. This does not entirely exclude a new primary, and in the absence of obvious melanin pigment in the tumor cells, confirmation by immunohistochemical stains is required. S100 protein is a sensitive, but not specific marker for melanoma. With the exception of the desmoplastic spindle cell melanoma variant, most melanomas also stain with more specific markers, such as melan-A and HMB-45.

Up to 5% of head and neck melanomas arise from squamous mucosa, rather than skin. These are most commonly seen in the oral cavity, but may arise anywhere from the paranasal sinuses to the larynx. Smoking, rather than UV radiation from sun-exposure, has been offered as a possible explanation for the occurrence of these tumors, but in fact, their etiology remains uncertain. Mucosal melanomas may be flat or nodular lesions, and may consist of nests of large epithelioid cells, fascicles of spindle cells with prominent red nucleoli, or a mixture of the two (Fig. 9.17). In contrast to skin melanomas, the traditional Clark and Breslow staging systems do

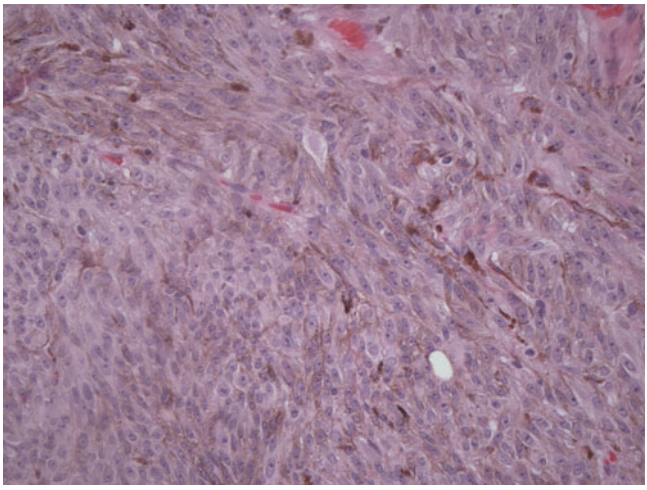

Fig. 9.17 This mucosal melanoma consists of sheets of plump spindle cells with oval nuclei and a prominent red nucleolus. Note the abundant brown melanin pigment in this case. Some melanomas fail to produce melanin (amelanotic melanoma)

not correlate with prognosis; all mucosal melanomas have a poor prognosis [26]. Wide surgical excision is currently the treatment of choice, with newer chemotherapeutic or immunomodulating agents under study.

9.6 Salivary Gland Malignancies

Salivary Gland Malignancies are as varied in their appearance as the benign salivary gland tumors. Some are malignant counterparts of the benign tumor. For example, basal cell adenocarcinoma may be histologically identical to a basal cell adenoma, except for the presence of invasion into adjacent normal salivary tissue. Some carcinomas represent malignant degeneration of a pre-existing benign salivary gland tumor. Sudden growth of a mass lesion that may have been present for 10 years or more is a common presentation of a carcinoma arising in a pleomorphic adenoma (hence, carcinoma-ex-pleomorphic adenoma). For most salivary gland malignancies, relationships with normal cell types are seen. Normal salivary gland ducts and acini have two cell layers, an outer (or abluminal) layer composed of myoepithelial (with contractile muscle fibers) or basal (without muscle) cells, and an inner luminal cell layer. Malignant tumor composed entirely of cells from the outer layer would be termed *myoepithelial carcinoma* or *basal cell adenocarcinoma*, respectively. Tumors composed entirely of cells lining the luminal side of the salivary gland acini are termed *acinic cell carcinoma*. The classification of salivary gland carcinoma becomes more complex, as many salivary gland carcinomas (unlike those arising in the breast, prostate or other organ systems) contain a mixture of both luminal and abluminal cell types.

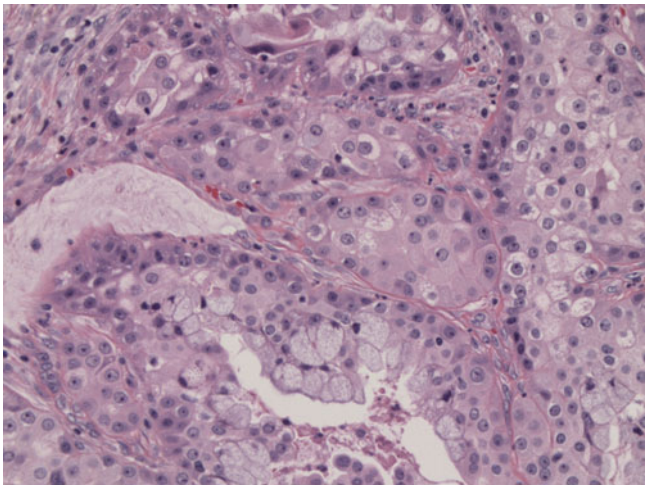

Fig. 9.18 Mucoepidermoid carcinoma contain a mixture of mucous cells, squamous-like epidermoid cells, and a population of smaller intermediate cells

9.6.1 Mucoepidermoid Carcinoma

Mucoepidermoid Carcinoma (MEC) is the most common malignant salivary gland tumor, comprising one third of all cases, and is seen in a wide age range. These tumors vary from well-circumscribed cystic lesions to ill-defined invasive solid masses. Three basic cell types are characteristic of MEC, and vary in frequency with the grade of the tumor. Mucous cells, columnar epithelial cells with a small basal nucleus and single large mucous vacuole filling the cytoplasm, are most common in low-grade tumors. Large polygonal epidermoid cell have abundant eosinophilic cytoplasm, and a central round vesicular nucleus. Intermediate cells vary in appearance, some being small cells with small dark nuclei and scant eosinophilic cytoplasm, whereas others are somewhat larger oval cells, containing nuclei with lighter staining chromatin and eosinophilic or clear cytoplasm. Low grade MEC generally presents as a slow-growing, well-circumscribed cystic tumor with a predominant mucous cell component (Fig. 9.18). High-grade MEC is a rapidly growing invasive tumor composed predominantly of epithelioid and intermediate cells. Intermediate-grade MECs have variable clinical and histologic appearances. High-grade MEC may be difficult to distinguish from squamous cell carcinoma, adenosquamous carcinoma or other high-grade salivary gland tumors [27]. The absence of mucin by histochemical stains, the presence of keratin pearls, markedly pleomorphic tumor cells, or presence of in situ carcinoma in the overlying mucosa are all features of squamous cell carcinoma. The glandular component is distinct from the squamous/epidermoid component in adenosquamous carcinoma, in contrast to the intermingled cell types of MEC. A recent review of the MD Anderson experience showed that patients with low- and intermediate grade MEC had significantly better outcomes than patients

with high-grade MEC. DFS was 88 and 90% for low and intermediate grade MEC, compared to only 43% for high-grade tumors. Advanced tumor stage and the presence of perineural invasion were identified as additional adverse prognostic indicators [28].

A t(11;19) translocation, producing a CRTC1-MAML2 (or rarely CRTC3-MAML2) fusion protein has been reported to be a favorable prognostic factor in MEC [29]). The translocation is found most commonly in low- and intermediate-grade tumors. Its frequency and significance in high-grade MEC is unsettled, as translocation-negative high-grade cases may represent other entities, as discussed above [27, 29, 30].

9.6.2 Adenoid Cystic Carcinoma and Polymorphous Low Grade Adenocarcinoma

Distinguishing Adenoid Cystic Carcinoma (ACC) from Polymorphous Low Grade Adenocarcinoma (PLGA) in a biopsy of a minor salivary gland tumor may be difficult, as these tumors share a number of morphologic features, yet have distinct clinical behaviors. Both are composed of relatively uniform cells invading into adjacent tissue, often with perineural invasion. Whereas PLGA is almost exclusively a tumor of minor salivary glands (usually in the palate), ACC can arise from either major or minor salivary glands, where it is the currently second most common salivary gland carcinoma. The incidence of ACC appears to be falling. This is in part due to the reclassification of a proportion of cases as PLGA, but other factors may be involved as well [31].

Architecturally, ACC grows as tubules, cribriform structures or solid nests (Fig. 9.19). The amount of the solid component serves as the basis for the most common architectural grading system. An ACC that is more than 30% solid is considered poorly differentiated. In addition to the solid pattern, the presence of lymph node metastasis, particularly with extracapsular extension of the tumor, are risk factors for distant metastasis [32]. The term "polymorphous" in PLGA refers to the varied architectural patterns seen within an individual tumor (Fig. 9.20). In addition to the patterns shared with adenoid cystic carcinoma, PLGA may show areas with individual cells, cords or even a few papillary structures. It should be noted that cases with a significant papillary component are clinically more aggressive, and have been reclassified as **low-grade papillary adenocarcinoma**.

Cytologically, ACC contains small uniform cells with dark-staining (hyperchromatic) nuclei and scant, pale cytoplasm. Particularly in areas of tubule formation, two distinct cell types with luminal or abluminal differentiation may be seen. In poorly differentiated ACC, the cells may be larger and somewhat more pleomorphic, with increased mitotic activity, compared to low- and intermediate-grade tumors. Despite the name, the cells composing PLGA are uniform, with light-staining oval nuclei and modest amounts of light pink cytoplasm. On low-magnification microscopy, ACC usually appears as a blue tumor, whereas PLGA is more often

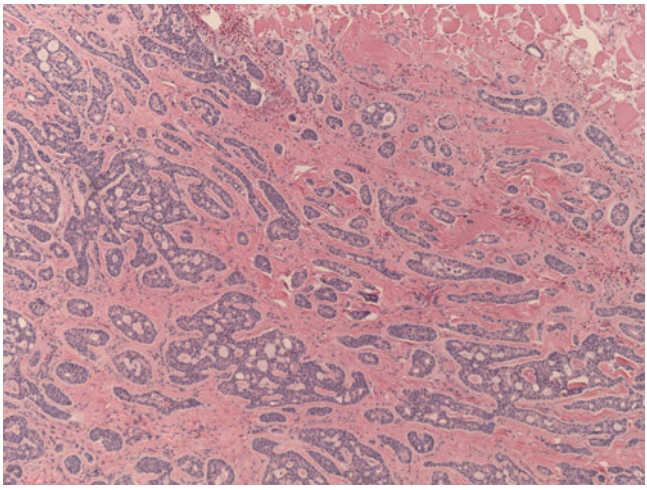

Fig. 9.19 This adenoid cystic carcinoma shows an infiltrative pattern of tubules and cribriform nests. Note occasional larger *pink* cells in the center of nests, indicating luminal differentiation

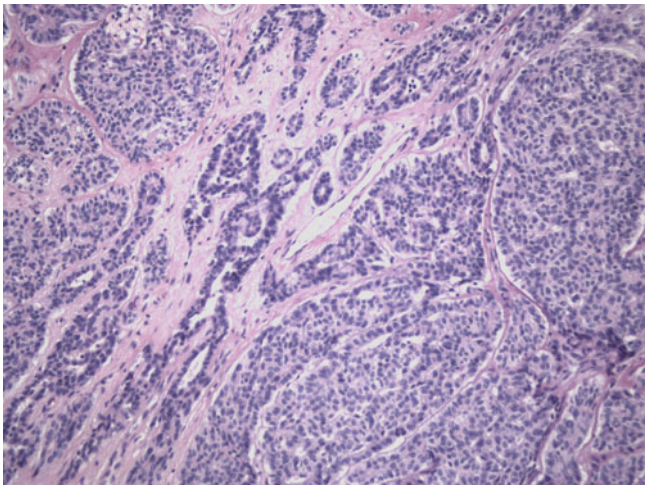

Fig. 9.20 Polymorphous low grade adenocarcinoma (PLGA) shows overlapping histologic features with adenoid cystic carcinoma. Both are invasive tumors with tubular and cribriform growth patterns. Perineural invasion is common in each. Distinct luminal differentiation is usually not seen in PLGA

pink in appearance. At higher magnification, no distinct luminal vs. abluminal differentiation is evident in PLGA.

Conservative surgical excision with clear margins is generally considered adequate therapy for PLGA. Those cases arising from extra-palatal sites, particularly the tongue base may be more aggressive, with a propensity for lymph node

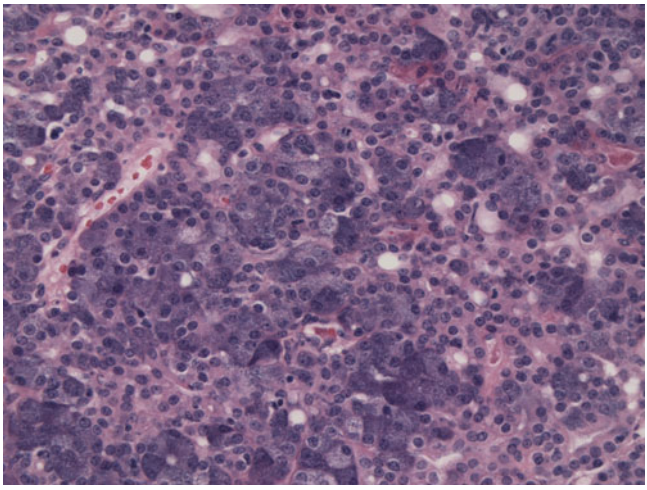

Fig. 9.21 Acinic cell carcinoma may closely mimic normal parotid tissue. The tumor cells are large and polygonal, with abundant purple (to pink) granular cytoplasm

metastasis [33]. Adenoid cystic carcinoma is a more aggressive tumor, prone to late recurrences. As a result, the overall 5-, 10- and 15-year survival rate for ACC is 90%, 80% and 70%, respectively [31]. Consequently, ACC is generally treated with a wider local excision, often followed by post-operative radiation therapy.

9.6.3 Acinic Cell Carcinoma/Mammary Analog Secretory Carcinoma

Acinic Cell Carcinoma generally arises as a circumscribed, slow-growing parotid mass, usually in adults, but may be seen in teenagers. A well-differentiated acinic cell carcinoma may closely mimic the normal parotid gland, with acini lined by polygonal cells with abundant basophilic granular cytoplasm and round dark nuclei (Fig. 9.21). In such cases, recognizing an absence of ducts may be the only clue to the correct diagnosis. Tumors with solid, papillary, micro- or macrocystic architectures are less subtle. Most acinic cell carcinomas are low-grade tumors, and may be cured with conservative excision with negative margins. These are not entirely benign tumors, as local recurrence has been reported in up to 15% and lymph node metastasis in 8% of cases [34]. A proportion of tumors have foci with more significant nuclear pleomorphism and a higher mitotic rate, indicating transformation to a higher-grade tumor. Such tumors behave more aggressively, with a mean overall survival of 40 months, vs. 125 months for cases without high-grade transformation [34].

Recently a subset of adenoid cystic carcinomas with minimal cytoplasmic granules have been reclassified as **Mammary Analog Secretory Carcinoma (MASC)**, based on the presence of a t(12;15) translocation creating the same ETV6-NRTK2

fusion found in (juvenile) secretory carcinoma of the breast [35, 36]. In contrast to typical acinic cell carcinomas, these tumors lack zymogen granules and show strong immunoreactivity for s100 protein. They have a marked male predominance, and may arise from major or minor salivary glands. While generally low-grade tumors, local recurrence is not uncommon and distant metastasis have been described [37].

9.6.4 Basal Cell Adenocarcinoma

We have previously noted that an otherwise typical basal cell adenoma (one form of monomorphic adenoma) with even focal invasion into adjacent tissue is considered to be a basal cell adenocarcinoma. As with both pleomorphic and monomorphic adenomas, basal cell adenocarcinoma usually arises in the superficial lobe of the parotid, where it is composed of tubules, trabeculae or solid nests with palisading of the peripheral columnar cells. A prominent basement membrane is characteristic, as are scattered hyaline globules of basement membrane material scattered within the nests. With few exceptions, these are low-grade tumors that are adequately treated with complete surgical excision.

9.6.5 Epithelial-Myoepithelial Carcinoma

While many salivary gland carcinomas show luminal (epithelial) and abluminal (myoepithelial or basal cell) differentiation, epithelial-myoepithelial carcinoma (EMC) shows the highest degree of this two cell type differentiation. EMC most often presents as a slow-growing, circumscribed parotid mass in an elderly patient. Rarely, a long-standing EMC begins rapidly enlarging, indicating transformation to a high-grade carcinoma (similar to the presentation for carcinoma-ex-pleomorphic adenoma, below) [38]. At low magnification, EMC appears as nodules invading into the surrounding tissue. Closer examination reveals at least focal areas containing bi-layered ducts, with inner columnar epithelial cells and outer myoepithelial cells with prominent clear cytoplasm (Fig. 9.22). The proportion of epithelial to myoepithelial cells varies between tumors, as does the degree of ductal architecture. Most EMCs are adequately treated with complete surgical excision, although late local recurrences have been reported.

9.6.6 Salivary Duct Carcinoma

Salivary Duct Carcinoma is an intriguing tumor with morphologic similarities to breast carcinoma. Although a low-grade variant exists, most cases present as a rapidly growing parotid mass, frequently with metastatic disease involving regional lymph nodes and distant sites. Histologically, the tumor consists of infiltrating cords, papillae and large circumscribed nests with central (comedo) necrosis, similar to a

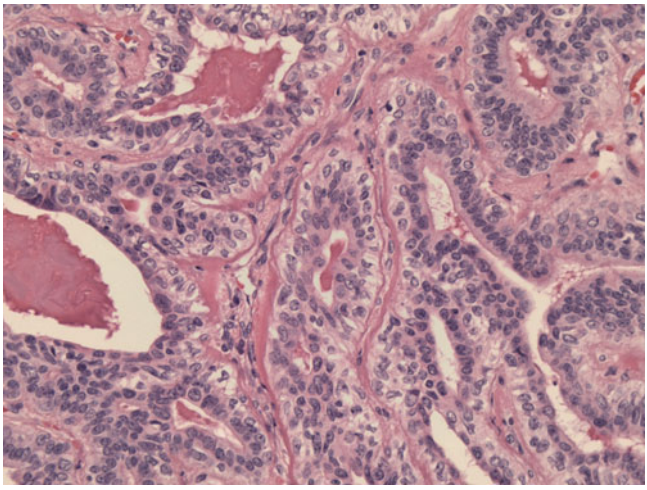

Fig. 9.22 While many salivary gland tumors have a mixture of luminal and abluminal type cells, epithelial-myoepithelial carcinoma is distinctive with tubules lined by a well defined dual cell population, including peripheral myoepithelial cells with clear cytoplasm

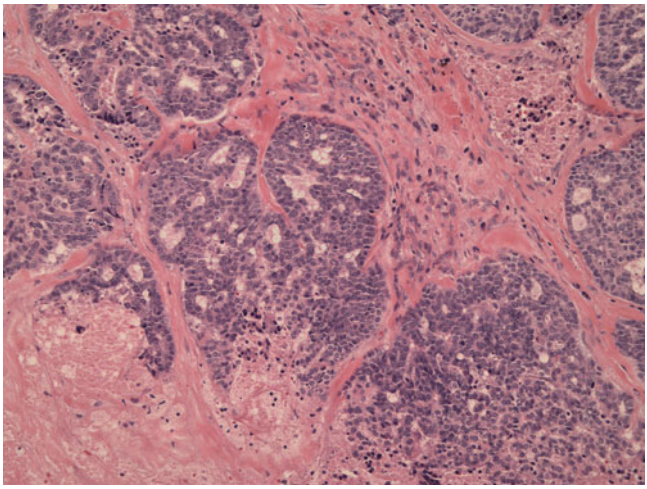

Fig. 9.23 Salivary duct carcinoma is a high-grade tumor that morphologically resembles in-situ or invasive ductal carcinoma of the breast. This case shows cribriform to solid nests of tumor with abundant necrosis

high-grade ductal carcinoma of the breast (Fig. 9.23). Salivary duct carcinoma frequently expresses androgen receptor (AR) but is usually negative for estrogen (ER) and progesterone receptor (PR). HER2 is frequently overexpressed by immunohistochemistry and amplified by FISH. A few studies have documented clinical response with trastuzumab-based therapy in HER2-positive cases, and to androgen deprivation therapy in AR+ cases [39].

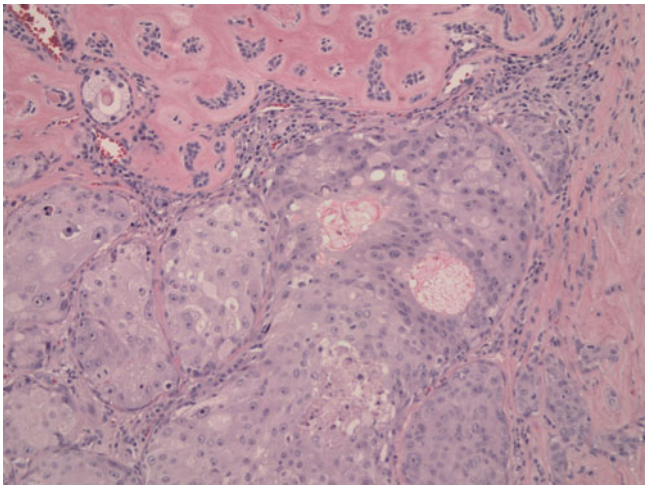

Fig. 9.24 Nests of small bland cells in a hyalinized stroma from the residual pleomorphic adenoma (*top*) give rise to nests of larger cells with necrosis in this example of carcinoma ex pleomorphic adenoma

9.6.7 Carcinoma ex Pleomorphic Adenoma

Pleomorphic Adenoma (benign mixed tumor) has been discussed in Chap. 8. Up to 5% of untreated pleomorphic adenomas eventually enter a phase of rapid growth, denoting malignant transformation. Histologically the malignant component is usually an adenocarcinoma, thus termed Carcinoma ex Pleomorphic Adenoma (Fig. 9.24). Rarely the malignant component is mesenchymal (sarcoma-ex-pleomorphic adenoma) or exceptionally, has both malignant epithelial and mesenchymal components (a true malignant mixed tumor). While the diagnosis is usually straightforward, it can prove to be more difficult in cases where the malignant component overgrows and completely replaces the pre-existing pleomorphic adenoma. Extensive histologic sampling of the tumor may reveal some residual chondromyxoid matrix or a scar, suggesting the correct diagnosis.

There appears to be sequential molecular alterations underlying malignant transformation in pleomorphic adenomas. Loss of heterozygosity (LOH) on the long arm of chromosomes 8 is commonly found in pleomorphic adenoma, resulting in the overexpression PLAG1 and MYC gene products. LOH in a region of the long arm of chromosome 12 is more commonly found in tumors that have undergone malignant transformation, with alterations in HMGIC, HMGA2 and MDM2 genes being implicated in the process [40]. The behavior of these tumors is dependent on the type of malignancy, the extent of invasion and whether the carcinoma was arising within a primary or recurrent pleomorphic adenoma [41]. The cases with the best prognosis were those where a low-grade carcinoma arose in a primary pleomorphic adenoma and showed no more than 5 mm of invasion

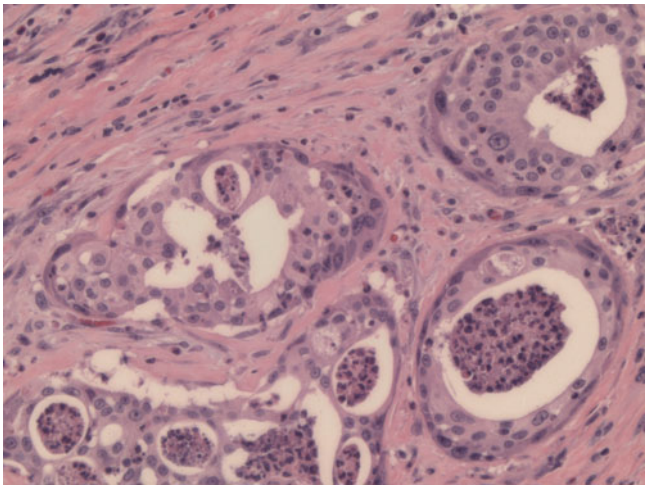

Fig. 9.25 Ceruminous gland adenocarcinoma shows invasive nests of large cells with granular *pink* cytoplasm Note necrotic and inflammatory debris within luminal spaces

beyond the capsule of the adenoma. These were usually cured with complete surgical excision of the lesion. Post-operative radiation is useful in more advanced cases.

9.7 Ceruminous Gland Adenocarcinoma

Ceruminous Gland Adenocarcinoma, arising from glands lining the external auditory canal, has overlapping features with the salivary gland carcinomas. Typically presenting as a polypoid mass, the tumor grows as infiltrative cribriform nests or glands that may resemble mucoepidermoid carcinoma, adenoid cystic carcinoma, or have apocrine features and pink to brown cytoplasmic granules resembling normal ceruminous glands (Fig. 9.25). The latter two patterns have a dual cell population, consisting of luminal epithelial cells and abluminal myoepithelial cells. These tumors are prone to local recurrence, and are treated with surgical excision with or without postoperative radiation [42].

9.8 Ameloblastoma

Odontogenic tumors, epithelial or biphasic (epithelial and mesenchymal) tumors arising from odontogenic epithelium and associated stroma are a complex group of lesions. **Ameloblastoma**, a tumor resembling the enamel organ of the developing

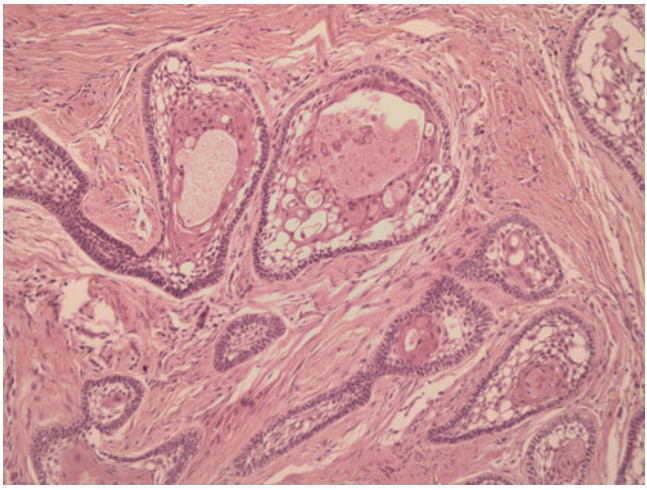

Fig. 9.26 This case of ameloblastoma shows irregular nests of tumor with palisading of the peripheral low-columnar epithelial cells, a loose stellate reticulum and central areas of keratinization

tooth, may present as a localized expansion of the jaw (posterior mandible more frequently than the posterior maxilla or the anterior of either bone) or may be found incidentally on dental X-rays. A lytic, soap-bubble appearance on X-ray is characteristic, but not diagnostic. The lesions are often curetted for diagnosis, yielding variable amounts of hemorrhagic soft tissue and bone. Microscopically, the tumor is composed of solid epithelial nests or cysts with a variable amount of fibrous stroma. These tumors demonstrate a distinctive form of peripheral palisading, where nuclei are uniformly placed at the top of the columnar cells, away from the basement membrane. Cells in the center of the nests are loosely arrayed (termed "stellate reticulum") with variable cyst formation (Fig. 9.26). Ameloblastomas generally are benign tumors that have a propensity for local recurrence (particularly following enucleation). Wide local excision decreases local recurrence [43]. Overtly malignant ameloblastic carcinomas do occur, but are exceedingly rare.

9.9 Conclusions

Epithelial and related carcinomas of the head and neck show a wide range of appearances and behaviors. Carcinogens such as those found in tobacco smoke are the key etiologic factor in many of these tumors. Other factors, such as HPV and EBV are important in specific subsets. Refinements in the classification of these tumors continue to be made based on prognostic considerations (e.g. separating large cell neuroendocrine carcinoma from atypical carcinoid tumor), the identification

of new causative agents (Merkel cell polyomavirus), or the discovery of specific molecular alterations (t(11;19) in MEC and t(12;15) in MASC). These efforts help provide more accurate prognostic information to patients, and increase the opportunity to develop more effective treatments.

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Chapter 10
Pathology of Head and Neck Cancer II: Mesenchymal and Lymphoid Tumors

G. Kenneth Haines III

Contents

Abstract Whereas head and neck squamous cell carcinoma is primarily a disease of middle age and older adults, malignant mesenchymal tumors (sarcomas) are more commonly seen in infants to young adults. The breadth of mesenchymal and lymphoid tumors is at least as that wide as among the epithelial tumors. In many respects, this is a more difficult group of lesions to study. The relative rarity of the sarcomas necessitates retrospective collection of cases over long periods of time (during which diagnostic approaches and treatment options may have undergone

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dramatic changes), or multi-institution prospective studies. This chapter will review the more common mesenchymal and lymphoid neoplasms affecting the head and neck. We will begin with matrix-producing tumors, i.e., those that make bone or cartilage, then turn to skeletal muscle tumors (rhabdomyosarcoma), a common pediatric tumor frequently involving head and neck sites. From there we will survey the remaining spectrum of malignant soft tissue tumors. Finally, we turn to the lymphomas, where newer molecular techniques play a vital role, not only in our theoretic understanding of disease pathogenesis, but in the classification and treatment of this group of tumors.

Keywords Head and neck cancer • Osteosarcoma • Chondrosarcoma • Rhabdomyosarcoma • Lymphoma

Abbreviations

AIDS	Acquired immunodeficiency syndrome
ASPS	Alveolar soft parts sarcoma
DLBCL	Diffuse large B-cell lymphoma
EBV	Epstein-Barr virus
EMA	Epithelial membrane antigen
FISH	Fluorescence in situ hybridization
HIV	Human immunodeficiency virus
LOH	Loss of heterozygosity
MALT	Mucosa-associated lymphoid tissue
MERT	Malignant extrarenal rhabdoid tumor
MF/10 HPF	Mitotic figures per 10 high power fields
NHL	Non-Hodgkin's lymphoma

10.1 Introduction

Over 90% of head & neck cancers are squamous cell carcinomas. Other epithelial malignancies account for an additional 5–8%. The remaining 2–5% of tumors are of more clinical significance than their relative frequency would suggest. Most of the tumors discussed in this chapter occur more commonly in other regions of the body. Some of these have unique clinical or pathologic features when occurring in the head & neck that warrant special consideration.

In this chapter we begin with the matrix-producing tumors—those tumors that form bone or cartilage. Malignant bone forming tumors of the jaw (gnathic osteosarcomas) have clinical and pathologic features distinct from those occurring at other sites. Among the non-matrix-producing tumors, rhabdomyosarcoma, a malignant tumor showing differentiation towards skeletal muscle, is most frequently found in

the head & neck region, usually in children. We will emphasize the appropriate sub-classification of these tumors, as there are important clinical, therapeutic and prognostic differences among the subsets of rhabdomyosarcoma. We will then review a series of rare mesenchymal malignancies, emphasizing new immunohistochemical or molecular findings that further our understanding of these tumors.

The next major section covers lymphomas of the head and neck. We will follow the standard division between Hodgkin's disease and non-Hodgkin's lymphoma; the latter further divided into B-cell and T-cell types. The emphasis will be on extranodal lymphomas, as these are particularly common in the head and neck. This section provides an overview of the diagnostic features and their underlying molecular defect(s).

10.2 Matrix-Producing Tumors

What exactly are "matrix-producing" tumors? All tumors, whether benign or malignant, epithelial or mesenchymal, produce matrix—the blood vessels necessary to supply the growing tumor with nutrients and carry away wastes, the connective tissue cells that participate in a complex array of cytokine-based feedback loops influencing tumor growth, differentiation and invasion, and the extracellular organic ground substance to which cells anchor allowing polarization of individual and groups of cells. Matrix production may be direct (that is, produced by the tumor cells) or indirect (produced by non-neoplastic stromal cells, under the influence of the neoplastic cells). Most often a mixture of direct and indirect matrix production occurs. In practice, the term "matrix-producing" is restricted to those tumors where the neoplastic cells directly produce osteoid (bone), cartilage or a cartilage-like material (chondroid). As bone and cartilage are normal products of a set of non-neoplastic mesenchymal cells (osteoblasts/osteocytes and chondroblasts/chondrocytes, respectively), it is not surprising that most matrix-producing tumors are mesenchymal. Exceptions to this generalization occur, as we have seen in both benign (pleomorphic adenoma) and malignant (sarcomatoid carcinoma) epithelial tumors.

10.2.1 Bone-Producing Tumors

Between 5 and 10% of all **osteosarcomas** occur in the head and neck region. The overwhelming majority arises in the mandible or maxilla, with fewer cases involving the skull or rarely, cervical vertebrae. Osteosarcoma may be classified as primary (de novo) or secondary (arising in the setting of a predisposing condition such as Paget's disease, or following radiation therapy). Up to half of all cranial osteosarcomas are secondary. Such patients are on average 25 years older than those with primary osteosarcoma, and have a dismal prognosis. In one series, the median survival was 7.25 and 33 months for Paget's or post-radiation osteosarcoma, respectively [1].

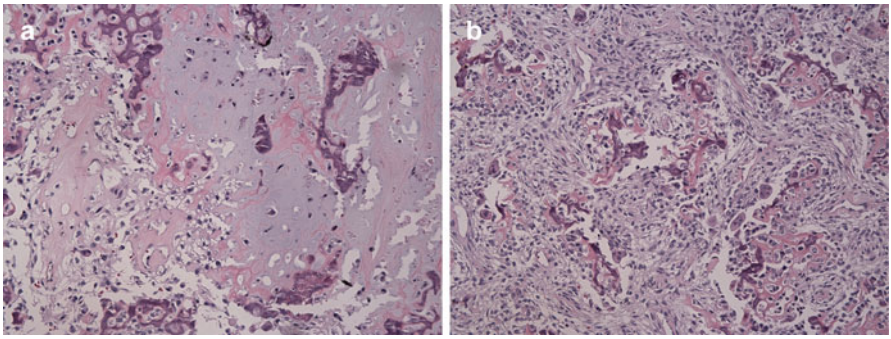

Fig. 10.1 Osteosarcomas of the head and neck are usually high-grade tumors. They may show a predominance of bone or cartilage (**a**) production, or have a fibroblastic appearance (**b**) with limited osteoid deposition

Osteosarcoma arising in the paranasal sinuses or skull bones has a worse prognosis than those arising in the jaws [2].

Gnathic osteosarcoma (osteosarcoma of the jaw bones) accounts for less than 10% of all cases of osteosarcoma, but is the most common site of involvement for head and neck osteosarcoma. Gnathic osteosarcoma is seen in an older age group, most commonly in the third to fourth decade, than those involving long bones. The tumor presents as a swelling or mass lesion, loosening of the teeth or pain/numbness. Radiographs may show a lytic destructive lesion, a sclerotic lesion, or a mixed pattern, usually with extension into soft tissues. Histologically, the tumors resemble conventional osteosarcoma from other sites, with osteoblastic, chondroblastic and fibroblastic patterns all common (Fig. 10.1). The histologic pattern does not appear to influence prognosis. Gnathic osteosarcoma appears less aggressive than those arising in the extremities, with a lower incidence of metastatic disease and improved survival rates [3]. These tumors are generally treated by radical excision with or without neoadjuvant chemotherapy. Factors associated with poorer survival rates include tumor recurrence, secondary osteosarcoma, and residual disease (positive surgical margins). Maxillary tumors have a worse prognosis, largely due to a lower rate of clear margins [4]. Whether neoadjuvant chemotherapy or extent of post-treatment tumoral necrosis affects survival is controversial, with no effect demonstrated in several series [3, 5].

10.2.2 Cartilage-Producing Tumors

Chondrosarcoma is uncommon as a primary tumor in the head and neck, yet it is the most common sarcoma involving the larynx. Myxoid and mesenchymal chondrosarcoma are the two major forms of extraskeletal chondrosarcoma. The former is exceedingly rare in the head and neck, and will not be discussed further.

Laryngeal chondrosarcoma is a tumor of latter life, occurring in the sixth to ninth decade. The tumor may present with voice changes, airway obstruction, or as a mass lesion in the neck. Radiographic studies show a characteristic circumscribed mass with stippled calcifications. Grossly, the tumors are lobulated grey solid to cystic masses. Areas with a "fish-flesh" appearance should be well sampled as they may denote a dedifferentiated component. The majority of tumors in this site are low-grade, slow-growing tumors consisting of lobulated nodules of cartilage with increased cellularity and hyperchromatic nuclei with mild nuclear pleomorphism (Fig. 10.2). High-grade tumors are more cellular and show marked nuclear atypia (Fig. 10.3). In addition to the cartilaginous component, dedifferentiated tumors contain foci of a high-grade sarcoma, usually composed of pleomorphic spindle cells. While laryngeal chondrosarcoma is generally widely excised, low-grade tumors may be managed by a conservative surgical procedure in select cases [6]. Chondrosarcomas arising at other head and neck sites (primarily the maxilla and mandible) are seen at a younger age (fourth decade) than those in the larynx. These are primarily treated by surgery, yielding an overall 5-year survival rate of 56% [7]. Tumor size, grade, and clear surgical margins appear to be the most important prognostic factors.

Mesenchymal Chondrosarcoma is a rare form of chondrosarcoma with a predilection for the craniofacial bones. This aggressive tumor typically strikes patients in the second and third decades of life [8]. X-rays show an osteolytic lesion with calcifications, extending into adjacent soft tissues. Less commonly, the tumor arises as an extraosseous mass. Grossly, the tumor forms a lobulated mass with grey-tan soft tissue admixed with cartilage. Microscopically, the tumor has a distinctive biphasic appearance. Nodules of well-differentiated hyaline cartilage are surrounded by sheets of small round or spindled cells with hyperchromatic nuclei and scant cytoplasm (Fig. 10.4). The cartilaginous component stains for s100 protein, similar to a conventional chondrosarcoma. The small cell component stains for CD99, neuroendocrine and occasionally skeletal muscle markers. While the histologic appearance is very characteristic, small biopsies containing only the undifferentiated component may mimic Ewing Sarcoma/Primitive Neuroectodermal Tumor. As both tumors express CD99 (and often neuroendocrine markers), correlation with radiographic studies is often essential. Staining for Sox9, a nuclear transcription factor involved in chondrogenesis, may allow distinction from other small blue cell tumors [9]. These are aggressive tumors, prone to late local recurrences and metastasis. The 10-year survival rates in the literature range from 20 to 67%, with patients being treated by surgery with or without adjuvant chemotherapy or radiation therapy. The ability to achieve adequate surgical excision appears to be the single most important prognostic factor [10].

Chordomas are locally aggressive tumors that derive from remnants of the notochord, an embryonic structure running midline from the sphenoid bone to the coccyx. About a third of cases arise in the head and neck- primarily the skull base, with the remainder located in the sacrococcygeal region or along the vertebral column. Radiographically, chordomas appear as destructive osteolytic lesions with calcifications that may extend into adjacent soft tissue. As skull base lesions are

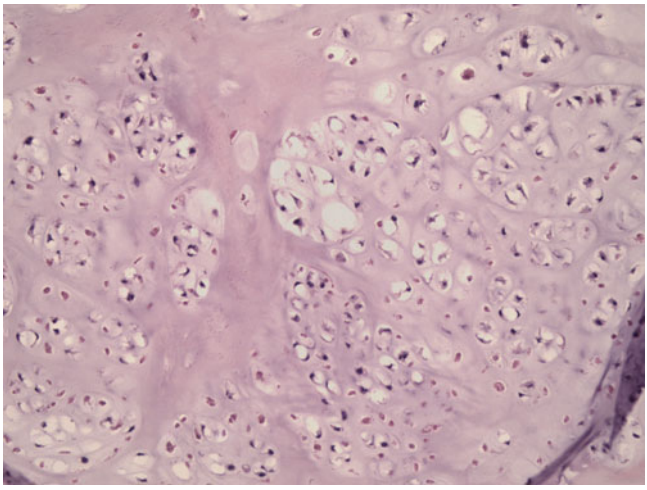

Fig. 10.2 Low-grade chondrosarcomas grow as nodules of slightly hypercellular cartilage with mild nuclear enlargement and hyperchromasia (atypia). These may be difficult to distinguish histologically from an enchondroma or other benign cartilaginous lesions

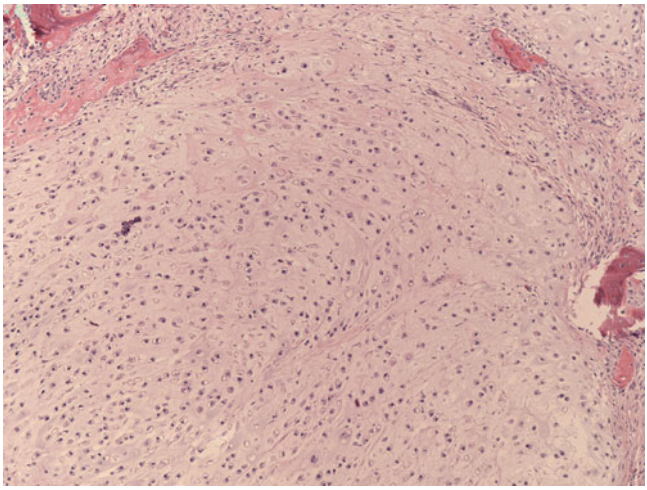

Fig. 10.3 Higher-grade chondrosarcomas show significantly more nuclear atypia. Note the infiltrating tumor boarder and desmoplastic host stromal response

removed piecemeal, surgical specimens appear as gelatinous solid or partially cystic pink-gray tissue fragments. Microscopically chordomas can be divided into conventional, chondroid and dedifferentiated types.

Conventional chordomas are peudoencapsulated tumors, with fibrous bands dividing the lesion into lobules. The tumor cells grow in cords, sheets or even pseudo-glandular structures, all floating in a mucinous matrix. The characteristic

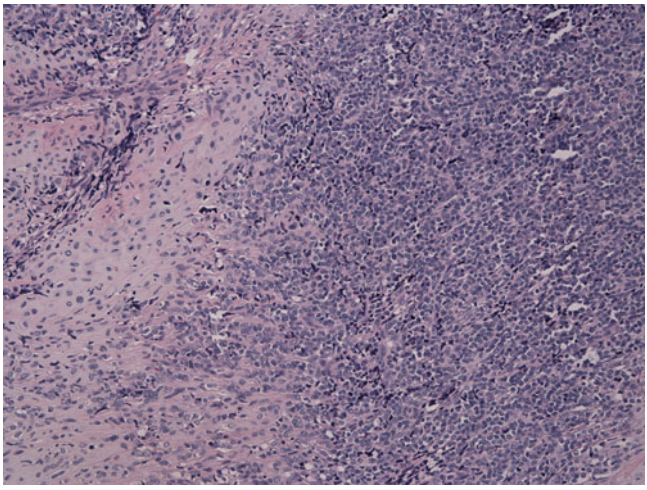

Fig. 10.4 This mesenchymal chondrosarcoma is composed of sheets of cells with round to oval nuclei and scant cytoplasm, interspersed with islands of hyaline cartilage. Note the enlarged atypical nuclei in the chondrocytes identifying this as neoplastic cartilage

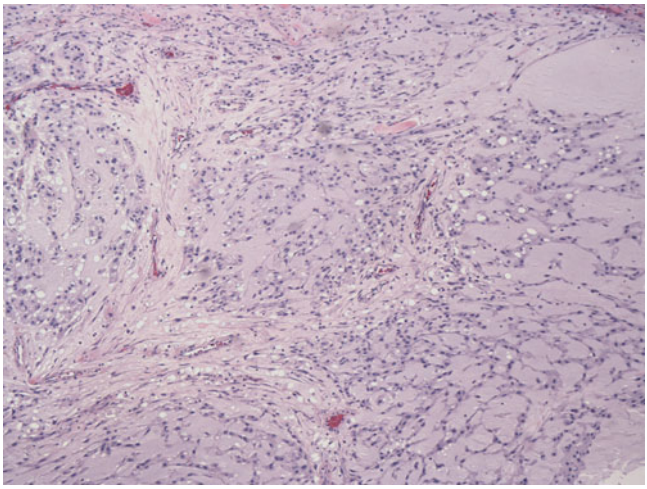

Fig. 10.5 A conventional chordoma with a vaguely lobular growth pattern. Lightly eosinophilic or vacuolated (physaliferous) tumor cells float or stream along in a myxoid stromal background

physaliferous cell is a large epithelioid cell with its nucleus compressed and indented by multiple mucin or glycogen-containing cytoplasmic vacuoles (Fig. 10.5). Aside from this cell, most tumors show little nuclear pleomorphism and only rare mitotic figures. Less than 5% of chordomas contain an overtly malignant sarcomatous component. These **dedifferentiated chordomas** show a highly aggressive clinical course with frequent metastases and early death. Chordomas are overwhelmingly a disease of middle age adults. Less than 5% of cases occur in children or adolescents,

usually involving the skull base. Within this population, an additional group of cellular chordomas has been identified. These cases lack the myxoid matrix of conventional chordomas, instead demonstrating sheets of small epithelioid cells with little cytoplasm. These poorly differentiated chordomas are aggressive tumors with 83% of patients dying of disease, compared to 19% among all cases [11].

Immunohistochemistry plays an important role in distinguishing chordoma and its variants from mimickers. The typical chordoma expresses epithelial markers cytokeratin and epithelial membrane antigen (EMA), as well as those typical of cartilaginous tumors (s100 protein, vimentin). Importantly, chordomas do not express myoepithelial markers such as p63 or calponin, allowing distinction from pleomorphic adenoma (benign mixed tumor).

Chondroid chordomas demonstrate all of the histologic features of a conventional chordoma, plus in addition contain foci of cartilage. This variant comprises 10% of all chordomas, and up to a third of those in the head and neck. Cytokeratin and EMA expression cannot be identified in some cases of chondroid chordoma, raising the possibility of a low-grade chondrosarcoma. Expression of brachyury, a nuclear transcription factor active in the developing notochord, may help confirm the correct diagnosis [12].

10.3 Non-matrix Producing Tumors

10.3.1 Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is primarily a tumor of infants, children and young adults, accounting for 8% of all childhood cancers. One-third of these arise in the head and neck, where they commonly involve the orbit or parameningeal region. Other common sites include the nasal cavity and paranasal sinuses, the nasopharynx and ear canal.

The current international classification system divides rhabdomyosarcoma into three prognostic groups, with botryoid and spindle cell RMS having a superior prognosis, embryonal RMS an intermediate prognosis, and alveolar RMS having a poor prognosis. Within the head and neck, embryonal rhabdomyosarcoma accounts for 70% of cases, alveolar rhabdomyosarcoma for 15%, botryoid for less than 5% of cases.

Embryonal rhabdomyosarcoma most often arises in the head and neck of children less than 4 years of age, but extends into the adolescent and young adult populations. Histologically, these tumors range in appearance from undifferentiated small round cell tumors to those with fascicles of elongated spindle cells with abundant eosinophilic cytoplasm, resembling fetal muscle (Fig. 10.6). The tumor often alternates between dense hypercellular areas and myxoid hypocellular zones. Cytoplasmic cross striations, the histologic hallmark of skeletal muscle, are seen in about half of cases. Immunohistochemical demonstration of skeletal muscle-specific markers (e.g. myo-D1, myogenin) is necessary for classification as a rhabdomyosarcoma in poorly differentiated cases. Cytogenetic studies demonstrating loss of heterozygosity (LOH) at chromosome 11p15.5 or trisomy 8 may be useful

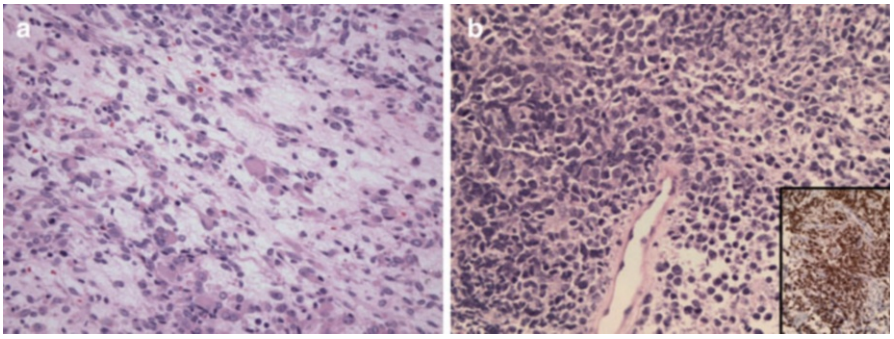

Fig. 10.6 Embryonal rhabdomyosarcoma can vary from cords and clusters of spindled cells with occasional cross-striations to plump rhabdomyoblasts with abundant eosinophilic cytoplasm (**a**) to a small round blue cell tumor (**b**), where immunohistochemical expression of myoD1 (*insert*) are necessary to arrive at the correct diagnosis. Note the variably edematous stoma in both examples

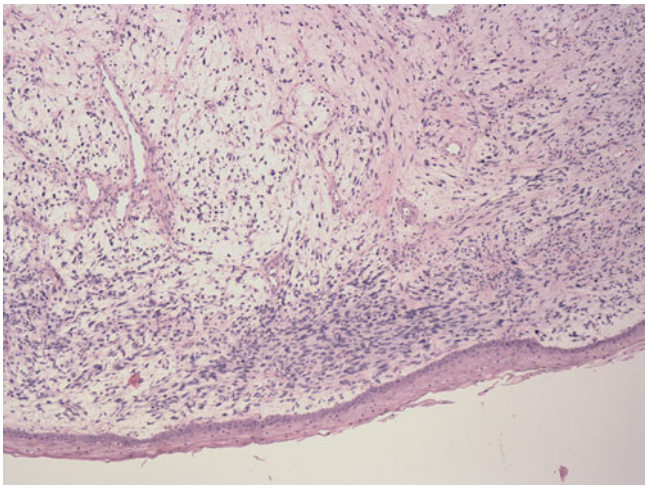

Fig. 10.7 Botryoid rhabdomyosarcomas grow as polypoid masses into preexisting cavities such as the nasopharynx. Note the variable cellularity through the tumor, with a hypercellular cambium layer underneath the squamous mucosa

for separating embryonal rhabdomyosarcoma from solid variants of alveolar rhabdomyosarcoma (discussed below).

Botryoid rhabdomyosarcoma is a favorable-prognosis variant of embryonal rhabdomyosarcoma. This variant is generally found growing as a polypoid botryoid (grape-like) mass into a cavity (e.g. bladder, vagina, nasal cavity or nasopharynx). Histologically, the tumor forms polypoid masses lined by the preexisting normal or metaplastic epithelium. A peripheral hypercellular zone of tumor cells (cambium layer) is separated from the overlying epithelium by a hypocellular layer of connective tissue (Fig. 10.7). Deep to the cambium layer, the tumor is arranged as spindled or stellate cells in a loose myxoid stroma.

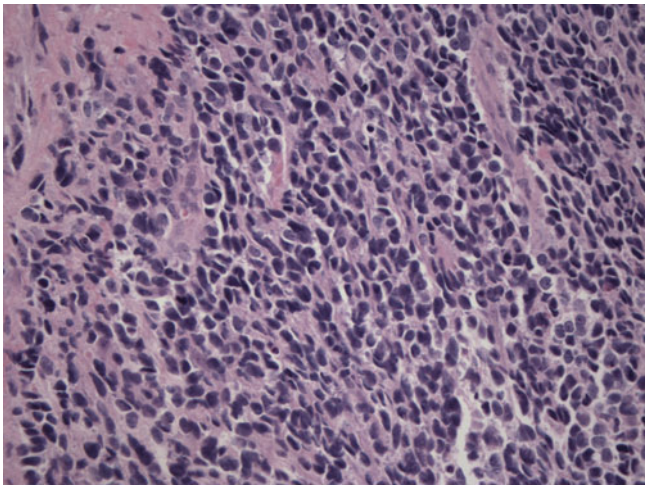

Fig. 10.8 Solid variants of alveolar rhabdomyosarcoma may be indistinguishable from embryonal rhabdomyosarcoma on routine H&E stained sections. Molecular detection of the PAX3-FOXO1 or PAX7-FOXO1 fusions can confirm the diagnosis in the majority of cases

Alveolar rhabdomyosarcoma accounts for a third of all rhabdomyosarcomas, involving the extremities of older children more often than the head and neck region. Rare cases have been reported in adults [13]. Histologically, the tumor consists of small round cells separated into irregular nests by dense fibrous septae. The cells are characteristically discohesive in the center of the nest, yielding an "alveolar" appearance. Solid variants do exist, closely resembling embryonal rhabdomyosarcoma or other small round cell tumors (Fig. 10.8). Immunohistochemical studies are generally able to separate rhabdomyosarcoma from the other small round cell tumors. Separating alveolar from embryonal rhabdomyosarcoma is also important, as alveolar rhabdomyosarcoma carries a significantly worse prognosis than the embryonal type.

Up to 80% of alveolar rhabdomyosarcomas have either a t(2:13)(q35;q14) or t(1;13)(p36;q14) translocation, yielding a PAX3-FOXO1 or PAX7-FOXO1 rearrangement, respectively. The resultant chimeric protein acts as a transcription factor, driving the expression of genes with PAX binding sites. Cases with the PAX7-FOXO1 translocation appear to have a longer disease-free survival than those with PAX3-FOXO1 translocations. The remaining cases may contain other novel translocations [14].

Other variants of rhabdomyosarcoma can involve the head and neck region, including pleomorphic, epithelioid and sclerosing rhabdomyosarcoma. Pleomorphic RMS is unusual in that it is almost exclusively a tumor of older adults. It appears as sheets of bizarre mononuclear and multinucleated tumor cells with abundant eosinophilic cytoplasm and frequent mitoses (Fig. 10.9). Epithelioid RMS was first described in 2011 as a tumor of older adults, characterized by sheets of mitotically active large cells with abundant eosinophilic cytoplasm and large nuclei with

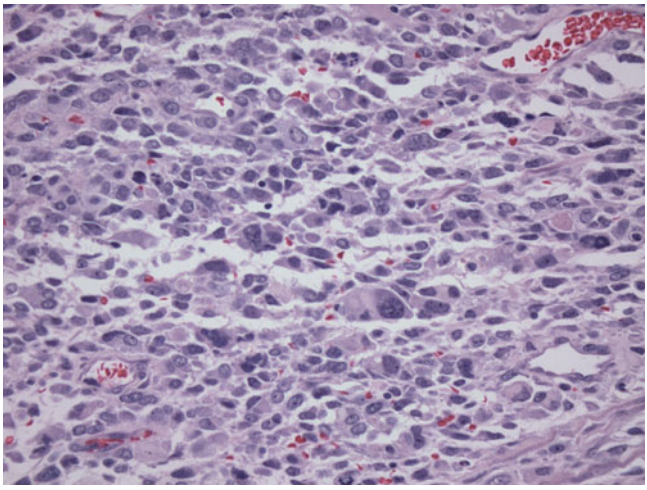

Fig. 10.9 Pleomorphic rhabdomyosarcoma is a disease of older adults. Markedly atypical mononuclear and multinucleated tumor cells, both with abundant eosinophilic cytoplasm, characterize the tumors

prominent nucleoli, mimicking high-grade carcinoma [15]. Spindle cell RMS was first reported as a variant of embryonal RMS in children, where it was associated with a favorable prognosis. Adult forms were subsequently recognized in the head and neck, and appear to be more aggressive than their pediatric counterparts. Sclerosing RMS has some overlap with spindle cell RMS, being composed of rather primitive spindled tumor cells. In addition, the sclerosing variant has a prominent chondroid to chondromyxoid stromal matrix. This form is most commonly seen in the head and neck, where it can be confused with other chondromyxoid tumors [16].

10.3.2 Mesenchymal Tumors of Uncertain Histogenesis

Malignant Extrarenal Rhabdoid Tumor (MERT) is a rare, highly aggressive neoplasm characterized by the presence of rhabdoid cells (large polygonal cells with an eccentric round nucleus, prominent nucleolus, an abundant eosinophilic cytoplasm with a perinuclear hyaline inclusion) and loss of nuclear INI1 expression. Initially thought to be a variant of Wilm's tumor in the kidney, these tumors have been identified in various sites including the central nervous system, where they are termed "atypical teratoid and rhabdoid tumor" [17]. As rhabdoid cells are seen in a variety of carcinomas and sarcomas, and MERT can variably express a variety of markers including cytokeratin, vimentin, neural and muscle markers, demonstration of the loss of INI1 immunoreactivity is important in excluding mimics.

Alveolar soft parts sarcoma (ASPS) is a rare tumor of uncertain histogenesis, generally occurring in the lower extremities of teenagers and young adults. A subset

of cases occurs in infants and children, where there is a predilection for the orbit and tongue. The tumor typically presents either as a slow-growing painless mass, or as metastatic disease involving the lung or brain. The tumors are highly vascular, sometimes producing an audible bruit. Grossly, the tumors are poorly circumscribed with prominent areas of hemorrhage and necrosis. The tumor is delineated into nests of discohesive cells by an anastomotic sinusoidal vascular network, giving it an alveolar appearance. The large polygonal tumor cells have round nuclei and abundant eosinophilic cytoplasm, often with diastase-resistant PAS-positive rhomboid crystals. The tumor has an unbalanced der(17)t(x;17)(p11;q25) translocation, as seen in a subset translocation renal cell carcinomas. Two alternative ASPL-TFE3 fusion proteins (type 1 and 2) are produced, leading to transcriptional deregulation. Although detection of the ASPSCR1-TFE3 fusion transcript by RT-PCR is highly specific, immunohistochemical detection of nuclear TFE3, or granular cytoplasmic staining for CD147 may be sufficient for diagnosis [18, 19]. Despite the name and cytoplasmic (but not nuclear) expression of the skeletal muscle marker, MyoD1, the histology of this tumor is quite distinct from alveolar rhabdomyosarcoma.

Hemangiopericytoma and solitary fibrous tumor have largely been merged into a single category due to overlapping (but not identical) clinical, histologic and immunophenotypic features. Hemangiopericytoma was first described as a cellular tumor in deep soft tissues, composed of round to fusiform cells arranged around variably hyalinized blood vessels with a staghorn appearance. Solitary fibrous tumor was first described as a pleural-based lesion consisting of spindled cells set in a hyalinized fibrous stroma without a consistent architecture (“patternless pattern”). Staghorn vessels may be present, but are not prominent. With recognition of similar tumors in extrapleural sites, expression of CD34 in both hemangiopericytoma and solitary fibrous tumor, and recognition of tumors with mixed histologic features, these may be considered two ends of a spectrum, rather then as distinct entities (Fig. 10.10). The differential for such tumors is broad, ranging from reactive conditions (nodular fasciitis), benign (myoepithelioma, schwannoma) and malignant neoplasms (sarcomatoid carcinoma, melanoma) [20]. Criteria for malignancy have varied in different studies, but in general, large tumors with high cellularity, marked cytologic atypia, necrosis and a high mitotic rate behave aggressively. Tumors with only mild to moderate cytologic atypia and few mitoses (1 mitotic figure per 10–20 high power microscopic fields) are categorized as having a low malignant potential. Those tumors lacking any of the above features are generally cured by complete surgical excision.

While most hemangiopericytoma/solitary fibrous tumors occur outside of the head and neck, a few variants primarily arise in this site. **Meningeal hemangiopericytoma/solitary fibrous tumor** was previously classified as a form of meningioma. In contrast to the typical meningioma, this tumor is negative for s100 protein and EMA by immunohistochemistry, and lacks a mutation in the NF2 gene as seen in other meningiomas. **Infantile hemangiopericytoma** is commonly seen in the oral cavity of infants and children. Microscopically, the tumor is often multi-lobulated, more often extending into adjacent soft tissue than adult forms. These tumors may have increased mitotic activity and even focal necrosis, without denoting malignancy. **Hemangiopericytoma-like tumor of nasal passages**

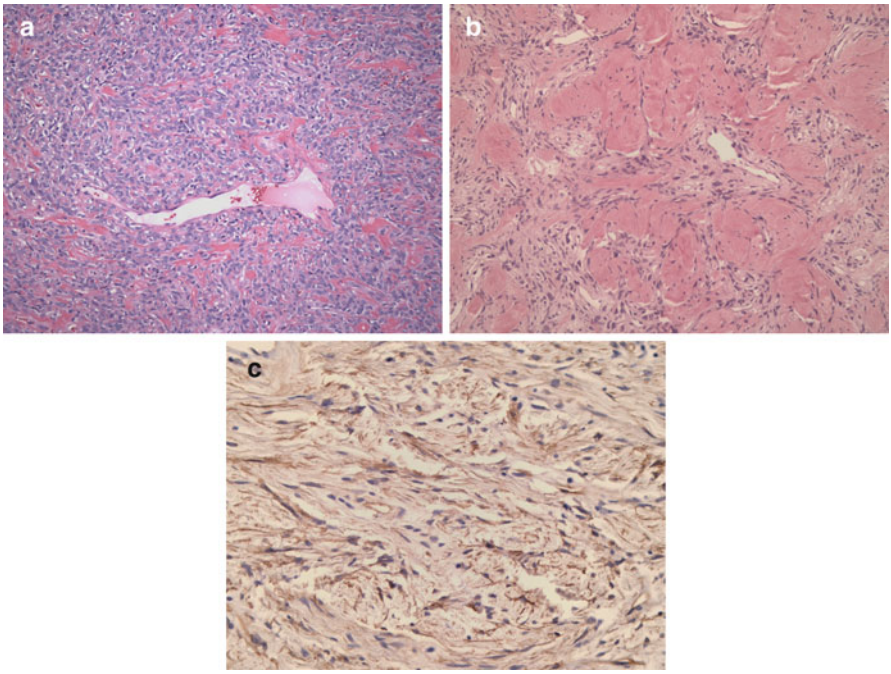

Fig. 10.10 Hemangiopericytoma (HPC) and solitary fibrous tumor (SFT) are now considered to be part of the same spectrum of spindle cell neoplasms. HPC tends to be a more cellular tumor, with plump spindle cells (**a**), whereas the cellularity of SFT is more variable (**b**). Both tumors show staining for CD34 (**c**)

(glomangiopericytoma) appears more closely related to a glomus tumor than to soft tissue hemangiopericytoma [21]. This tumor presents as a polypoid mass composed of spindled to oval cells in a fascicular, storiform or whorled pattern. Occasionally, staghorn vessels are seen (Fig. 10.11). Smooth muscle and muscle-specific actin are commonly expressed, while desmin is negative. CD34 is expressed in only a minority of cases. The majority of cases are benign, although those with marked cytologic atypia may pursue a more aggressive clinical course.

Synovial sarcoma accounts for 5–10% of all soft tissue sarcomas, with more than 80% of cases arising near large joints in the leg or arm. Fewer than 10% arise in the head and neck region, mostly from paravertebral connective tissue in the retropharyngeal region, parotid and temporal regions. Synovial sarcoma is primarily a disease of young adults, with a mean age of 35 [22]. Although some cases present as a rapidly growing infiltrative mass, most tumors are slow growing, and may have been present for several years before diagnosis. Radiographically, the tumor appears as a lobulated mass with scattered calcifications. Most cases are grossly circumscribed, solid or cystic masses measuring up to 6 cm. An attachment to an adjacent tendon or joint capsule may be evident. Rapidly growing tumors tend to be poorly circumscribed, with areas of hemorrhage and necrosis.

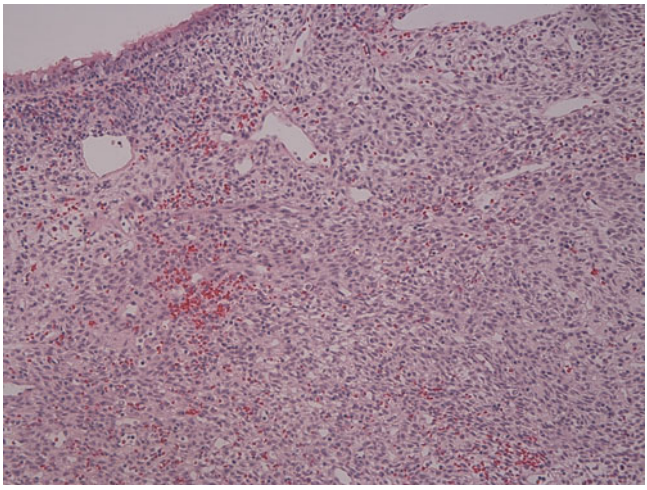

Fig. 10.11 Hemangiopericytoma-like tumor of nasal passages (glomangiopericytoma) is composed of plump spindle cells with a variety of growth patterns. Focal staghorn (HPC-like) blood vessels may be seen. Unlike soft tissue hemangiopericytoma, these tumors usual are negative for CD34 and pursue a benign course

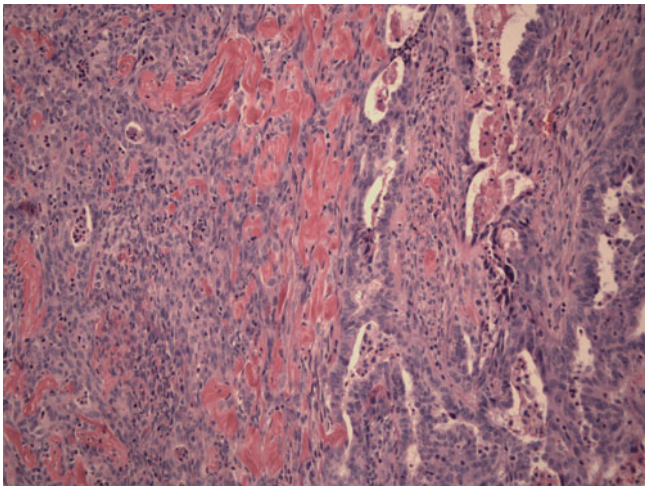

Fig. 10.12 In this biphasic synovial sarcoma, malignant glands (*right*) are admixed with sheets and anastomotic cords of malignant spindle cells (*center* and *left*). Monophasic synovial sarcomas almost always consist of only the spindle cell component

Microscopically, the most common appearance (monophasic fibrous synovial sarcoma) consists of sheets of plump uniform spindle cells with hyperchromatic nuclei and scant pale cytoplasm. Rarely, the tumor consists entirely of epithelioid cells with large vesicular nuclei and abundant pale cytoplasm, arranged in cords, nests or glands (monophasic epithelial synovial sarcoma). Not infrequently scattered nests of epithelioid cells are seen in a background of spindled cells (biphasic

synovial sarcoma) (Fig. 10.12). A subset of either monophasic or biphasic tumors may contain a high-grade component, consisting of mitotically active small round cells, large epithelioid cells, or pleomorphic spindle cells. Tumors with these poorly differentiated components are more likely to metastasize. The histologic differential diagnosis for synovial sarcoma is wide, and depends on the cellular components present. In contrast to most spindle cell sarcomas, synovial sarcomas express epithelial markers, particularly epithelial membrane antigen (EMA) and cytokeratin 7 (CK7), among others. A characteristic t(X;18)(p11;q11) translocation can be identified by fluorescence in situ hybridization (FISH) in most cases. This translocation results in a fusion of the SYT gene on chromosome 18 with the SSX1, SSX2 or rarely SSX4 genes on the X chromosome. The SYT-SSX1 fusion is seen in most biphasic synovial sarcomas, whereas the SYT-SSX2 fusion is present in most monophasic synovial sarcomas. In synovial sarcoma of the head, tumor size >5 cm and high mitotic count (>10 mf/10 hpf) were more commonly seen in patients who died of disease [22]. While surgical excision is the mainstay of treatment, multimodality treatment is commonly used to reduce the rate of recurrence. In contrast to most tumors in the histologic differential, more than 75% of synovial sarcomas are reported to express the NY-ESO-1 cancer testis antigen. This may not only be a useful marker diagnostically, but makes expressing tumors potential candidates for targeted T-cell receptor-based gene therapy [23].

10.4 Dendritic Cell Tumors

Follicular Dendritic Cell Sarcoma occurs at many sites, but has a predilection for cervical lymph nodes and extranodal lymphoid tissue in the head and neck. In low-grade cases, the normal nodal architecture is effaced by a proliferation of relatively uniform oval to spindle cells in a fascicular, storiform or diffuse pattern, often associated with a variable amount of lymphocytes. Higher-grade lesions show more pleomorphic cells with frequent mitotic figures. The pathologic differential often includes carcinoma, melanoma, sarcoma and lymphoma. Immunohistochemical work-up is generally required to make the diagnosis, with tumor cells being positive for dendritic cell markers, CD21, CD23 and CD35. The possibility of a dendritic cell sarcoma must be kept in mind, as expression of EMA, cytokeratin, and even TTF-1 may lead to an incorrect diagnosis [24]. These are generally slow-growing tumors with a propensity for local recurrence, up to 40% in some series, and distant metastasis in a quarter of patients [25].

10.5 Lymphoma

Lymphomas are broadly divided into Hodgkin's disease and Non-Hodgkin's Lymphoma (NHL). Hodgkin's disease involving the head and neck usually presents as cervical lymphadenopathy, but may present in extranodal sites, including the

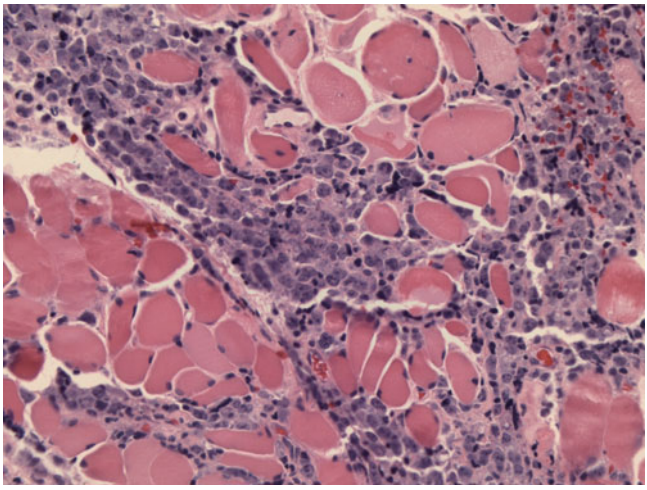

Fig. 10.13 This extranodal diffuse large B-cell lymphoma consists of sheets of large, pleomorphic cells with moderate amounts of amphophilic cytoplasm, infiltrating between large eosinophilic bundles of skeletal muscle

tonsil, nasopharynx, parotid and other sites [26]. The clinical and histopathologic features are similar to Hodgkin's disease involving other sites, and will not be further discussed here. The classification of NHL continues to evolve with the incorporation of new molecular and immunophenotypic findings. NHL as a group constitutes 5% of all malignant head and neck tumors; where up to half of the cases involve extranodal sites. Waldeyer's ring, the collections of lymphoid tissues in the nasopharynx, tonsils and base of tongue, is the most common site for these lymphomas. The ocular adnexa and salivary glands constitute the next major site, with the remainder arising in other mucosal sites. The frequencies of NHL types vary by location, in part reflecting whether the underlying lymphoid tissue is native or reflects a chronic inflammatory process.

10.5.1 Diffuse Large B-Cell Lymphoma (DLBCL)

DLBCL is the most common lymphoma of the head and neck, comprising 75% of the lymphomas arising in Waldeyer's ring. It usually occurs in patients over age 50, and may present as a tonsilar mass or ulceration, or as nasal obstruction. It is an aggressive lymphoma, but combination chemotherapy can induce a complete remission in two thirds of patients, and a 5-year survival rate over 40%. The tumor consists of sheets or clusters of mitotically active intermediate to large cells, often with large areas of necrosis (Fig. 10.13). The tumor cell nuclei may resemble centroblasts (large cells with an oval nucleus, vesicular chromatin and several peripherally located nucleoli), immunoblasts (similar to centroblasts, but with a prominent

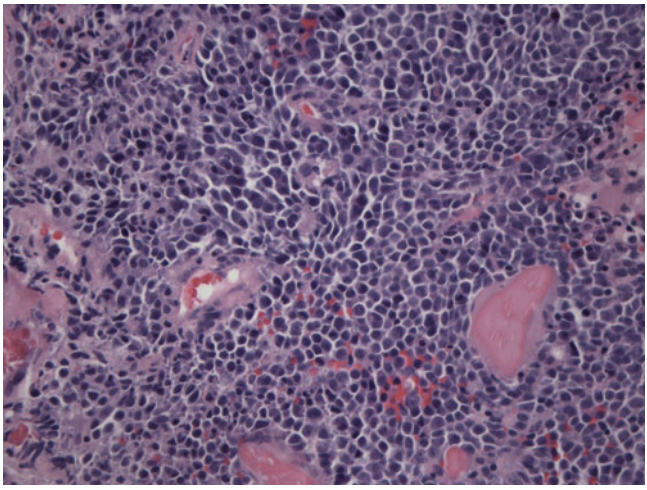

Fig. 10.14 Plasmablastic lymphoma is seen predominantly in immunocompromised patients. It consists of sheets of large cells with eccentric round nuclei and abundant amphophilic cytoplasm

central nucleolus) – sometimes with plasmacytoid features, or have large clefted nuclei. Not infrequently, a low-grade lymphoma is adjacent to the DLBCL, suggesting its transformation into the high-grade lymphoma.

DLBCL can be divided immunophenotypically into germinal-center (BCL-6 +, CD10 +, MUM-1 -) and non-germinal center (activated B-cell) (BCL-6 +/–, CD10 -, MUM-1 +) types. The former is associated with a BCL2 rearrangement through a t(14;18)(q32;q21) translocation, and is reported to have an improved survival**.** DLBCL occurring in Waldeyer's ring often presents at an earlier stage than the corresponding nodal disease, accounting for a more favorable prognosis

10.5.2 Plasmablastic Lymphoma

Plasmablastic lymphoma is an uncommon variant of DLBCL first described as an AIDS-associated lymphoma with plasmacytic differentiation and a predilection for the oral cavity. The tumor consists of a diffuse proliferation of large plasmacytoid cells with an eccentric nucleus, prominent central nucleolus and abundant basophilic cytoplasm (Fig. 10.14). The tumor may have a "starry sky" pattern, with abundant apoptotic bodies. Mitotic figures are numerous and necrosis is common. The immunophenotype is typically more like plasma cells than B-cells, and EBV is detected in most cases. This is an aggressive tumor, with a median time to death of only 7 months in immunocompromised patients. Plasmablastic lymphoma has subsequently been reported in HIV-negative and non-immunocompromised patients, who respond better to aggressive therapy [27].

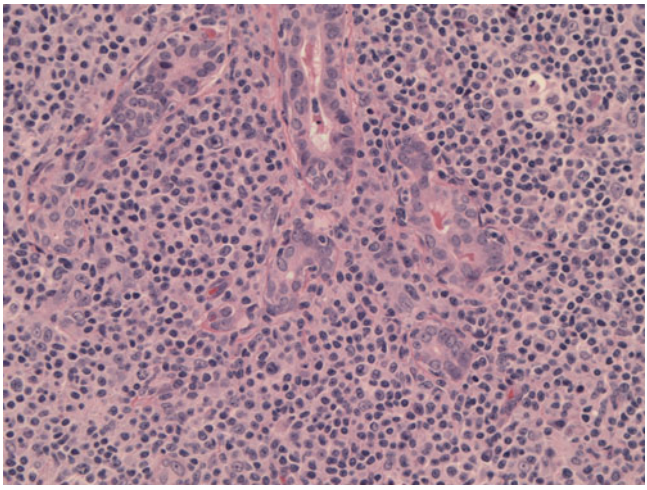

Fig. 10.15 MALT lymphoma involving the parotid gland. A dense infiltrate of intermediate sized lymphoid cells, some with plasmacytic features, fills the interstitium between ducts. The ducts have increased numbers of intraepithelial lymphocytes, and are in the process of becoming lymphoepithelial lesions

10.5.3 MALT Lymphoma

The head and neck is the second most common site for extranodal MALT lymphoma (or more properly, extranodal marginal zone B-cell lymphoma of MALT-type), with a predilection for the lacrimal gland and conjunctiva (ocular adnexa) and salivary glands. As low-grade tumors, MALT lymphoma may form a mass lesion, but are more frequently identified upon evaluation of a chronic inflammatory process. When involving the ocular adnexa, infection with *Chlamydia psittaci* can be detected in over 75% of cases, whereas 20% of salivary gland tumors arise in a background of Sjögren's syndrome.

The neoplastic cells of MALT lymphoma are small to medium sized lymphocytes with scant (centrocyte-like) or abundant (monocytoid) pale cytoplasm, or with plasmacytic features. A minor component of large centroblast-like cells are scattered through the lesion. Marked expansion of this latter population indicates transformation into a high-grade lymphoma (DLBCL), which portends a worse prognosis [28].

In early stages, the tumor cells aggregate around pre-existing lymphoid follicles, expanding the marginal zone. As the disease progresses, the tumor colonizes and replaces the follicles, giving the tumor a nodular appearance. In lacrimal and salivary tissue, small lymphoid cells infiltrate glandular epithelium, forming lymphoepithelial lesions (Fig. 10.15).

A variety of chromosomal translocations have been described in MALT lymphoma, with their frequency varying with the tumor location. Overall, the t(11;18)(q21;q21) translocation is most frequent, although it is rarely identified in salivary lesions.

10.5.4 Extranodal NK-/T-Cell Lymphoma of Nasal Type

Extranodal NK-/T-cell lymphoma of nasal type is a rare EBV-related lymphoma in Western countries, but is more common in Asia, Central and South America. The tumor presents as a destructive, ulcerated mass in the nasal cavity or nasopharynx. The tumor is composed of a mixture of small, medium and large, mitotically active cells with irregular nuclei and variable amounts of pale cytoplasm. There is often a admixed reactive chronic inflammatory infiltrate, and the overlying mucosa ranges from ulcerated to hyperplastic. Most cases express CD56, a natural killer cell marker, and some T-cell antigens, but lack a T-cell receptor rearrangement. Such T-cell receptor rearrangements, favoring a T-cell origin, are identified in at least 10% of cases from the upper aerodigestive tract [29].

10.5.5 Burkitt's Lymphoma

Burkitt's lymphoma is an aggressive form of NHL that most often presents in extranodal sites. It occurs in three distinct settings. The endemic form was first described in equatorial Africa, where it presents as a large mass in the mandible or maxilla of children. In this setting, EBV is detected in nearly all cases. Sporadic forms of Burkitt's lymphoma have a worldwide distribution, presenting as an abdominal mass in teenagers and young adults. These cases have the same 3:1 male to female ratio as the endemic form, but EBV is found in only a minority of cases. The third form is immunodeficiency (primarily HIV) associated, and can arise in nodal or extranodal sites. The histologic features are the same in each form, with sheets of uniform medium sized lymphoid cells with frequent mitoses. The characteristic "starry-sky" appearance results from interspersed macrophages with phagocytized apoptotic tumor cells (Fig. 10.16). The majority of cases demonstrate a t(8;14)(q24;q32) translocation, resulting in constitutive activation of the cMYC oncogene. With current therapy, the overall cure rate for sporadic cases is about 90% [30]. Adult cases, often associated with an immunodeficiency state, have a poorer prognosis.

10.5.6 Plasmacytoma

Plasmacytoma is a mass-forming neoplasm of plasma cells. The majority of extramedullary plasmacytomas involve the head and neck of middle age adults, particularly the nasopharynx, paranasal sinuses or tonsil. These tumors are rarely associated with multiple myeloma or systemic amyloidosis. Histologically, the tumors resemble sheets and nests of plasma cells to a variable extent. Well-differentiated or grade 1 plasmacytoma can be difficult to distinguish from a reactive plasma cell infiltrate without the use of immunohistochemical stains or

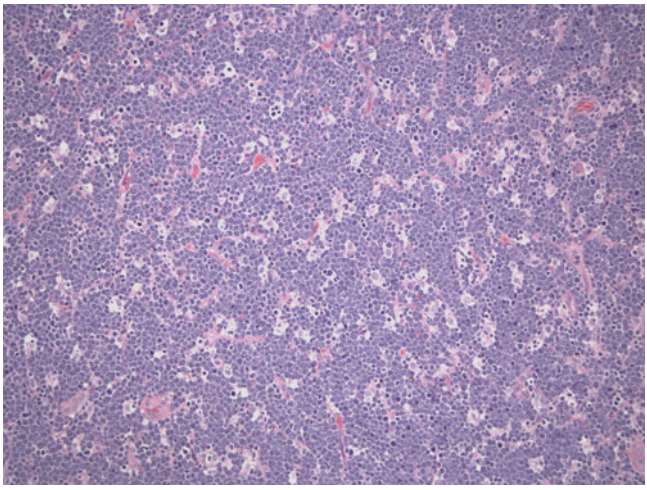

Fig. 10.16 The classic "starry-sky" appearance in Burkitt's lymphoma is caused by the macrophages, interspersed within the sheet of lymphoma cells, engulfing remnants of apoptotic tumor cells

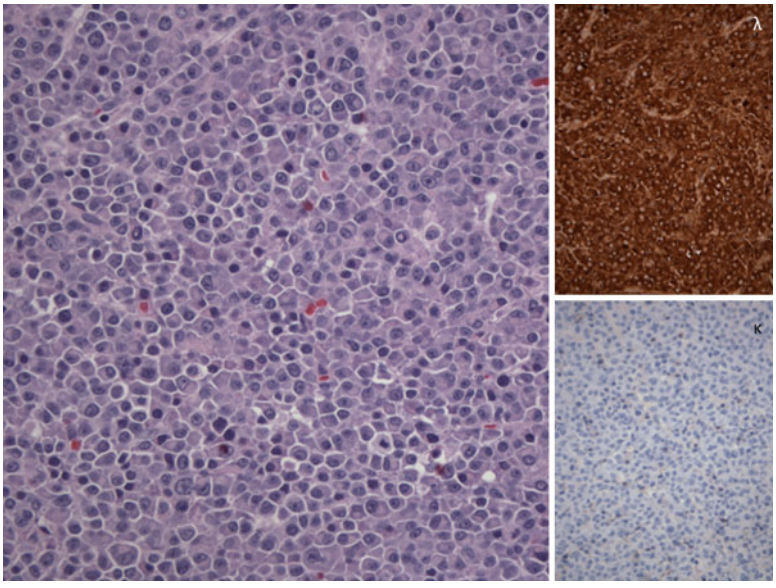

Fig. 10.17 Well-differentiated plasmacytoma appears as sheets of mildly atypical plasma cells, with eccentric nuclei, abundant cytoplasm and a slight perinuclear clearing (huff). Inserts show the tumor to express lambda but not kappa immunoglobulin light chain, confirming clonality of the lesion

in situ hybridization to demonstrate clonality (Fig. 10.17). At the other extreme, poorly differentiated or grade 3 tumors show plasmablastic features, with large nuclei, open chromatin and a prominent nucleolus. Mitotic figures are abundant, and scattered multinucleated tumor giant cells are seen. Well-differentiated tumors tend to be indolent and respond well to radiation therapy. High-grade tumors, particularly in the absence of adequate treatment have a significantly poorer outcome [31].

10.6 Conclusions

Mesenchymal and lymphoid tumors of the head and neck are a complex group of neoplasms due to their relative rarity, the sometimes overlapping clinical and histopathologic features, and evolving classification schemes based on newer molecular and immunophenotypic features. We have seen that some of the tumors, such as those forming cartilage, have subtle and overlapping histologic features that can blur the distinction between a benign tumor and a low-grade malignancy. Other tumors, such as the embryonal and alveolar rhabdomyosarcoma, can have an identical appearance on routine stained sections, yet quite different behaviors. Application of newer molecular techniques, FISH or RT-PCR, may be necessary for an accurate diagnosis. The classification of lymphoid tumors, particularly non-Hodgkin's lymphoma, has undergone repeated reclassification, as molecular and immunophenotypic data have supplemented traditional clinicopathologic findings.

If successful, this survey will have provided a framework to think about the nature of these tumors, and a basis for understanding the continuing evolution in our approach to these tumors, as additional molecular findings are applied to their diagnosis and treatment.

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Chapter 11
Cytopathology of Head and Neck Lesions

Gabor Tarjan

Contents

Abstract Cytopathology is the morphologic study of diseased cells. The diagnosis is based on the microscopic appearance of cells, sometimes with intercellular material, dispersed on glass slides. Cells from lesions in the head and neck (H&N) region are generally collected by fine needle aspiration (FNA). FNA is an outpatient procedure that does not require anesthesia, is minimally discomforting to the patient, and has rapid turnaround time. In the hands of experienced individuals, FNA is highly sensitive and specific. Of all potential FNA sites, the H&N area is one of the most complex, since it includes a number of different structures (various types of lining epithelium, exocrine and endocrine glands, lymphoid organs, etc.) from which both benign and malignant tumors may arise. The most common diseases of the three frequently aspirated H&N sites (salivary glands, thyroid, and

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cervical lymph nodes) are the main focus of this chapter. Important cytological mimics of these mainly neoplastic lesions are also included. Microscopic photographs of representative cases illustrate the majority of the discussed diseases. In the photographs, cytological and histological features of the same lesions are presented side by side to facilitate an understanding of the cytological characteristics. Current trends to use FNA to test for molecular biomarkers of diagnostic and prognostic value are also discussed.

Keywords Cytopathology • Fine needle aspiration • Salivary gland • Thyroid • Lymph node

Abbreviations

ACAC	acinic cell adenocarcinoma
ADCC	adenoid cystic carcinoma
BCA	basal cell adenoma
DLBCL	diffuse large B-cell lymphoma
DQ	Diff-Quik stain
FNA	fine needle aspiration
FVPC	follicular variant of papillary carcinoma
HCN	Hurthle cell neoplasm
HD	Hodgkin's disease
H&N	head and neck
HE	hematoxylin and eosin
LBC	liquid-based cytology
LN	lymph node
MEC	mucoepidermoid carcinoma
N/C ratio	nuclear to cytoplasmic ratio
PA	pleomorphic adenoma
PLGA	polymorphous low grade adenocarcinoma
Pap	Papanicolaou stain
PC	papillary carcinoma
SCCA	squamous cell carcinoma

11.1 Introduction

Cytopathology is the morphologic study of diseased cells. Histopathology, discussed in a previous chapter, examines tissues in which the cell-to-cell connections and the intercellular stroma (the substance between the cells) maintain the architecture (the relationship between the cells) in a structured, rigid form. Cytopathology, on the other hand, renders the diagnosis based on the appearance of a limited number

of individual cells or groups of cells, which, with or without some stromal substance, are taken out from their tissue context and dispersed on glass slides. Therefore, the cytological evaluation relies less on the architectural pattern – although the relationship between the cells and the stroma remains important – and focuses more on the features of individual cells. For example, there are characteristic cytological features of malignant cells, which include increased nuclear to cytoplasmic ratio, abnormally dark (hyperchromatic) or light (hypochromatic) nuclear staining, irregular nuclear membranes and chromatin pattern, marked pleiomorphism (variation of nuclear size and shape), and abnormal cell-to-cell interactions (crowded, overlapping nuclei; cell within another cell; dissociation of cells when they are expected to be cohesive).

The acceptance of diagnostic cytology as a valid discipline of medicine is mostly due to the work of Papanicolaou (1883–1962) who studied cervicovaginal cells for hormonal evaluation and in the early 1940s concluded that this cytological method was of value in the diagnosis of uterine cervical cancer.

By now several methods of cell collection have been developed to reach virtually any site of the body. For example, sputum can be evaluated for lower airway cells, urine can be examined for altered bladder or kidney cells, fluids from body cavities can be aspirated and examined for abnormal floating cells, inner body surfaces – airways, bowels, etc. – can be washed and brushed to sample the lining cells, and fine needle aspiration (FNA) may be able to reach more hidden sites.

In the head and neck (H&N) area FNA has become the most commonly used cell collection method, hence it is discussed in detail in this chapter. Aspiration cytology began to gain popularity in the United States in the 1970s. H&N specialists were among the first to recognize the value of aspiration cytology in the study of thyroid nodules [1] and in the diagnosis of metastatic malignancy in cervical lymph nodes [2, 3]. Of all the potential FNA sites, the H&N area is probably the most complex since it includes numerous different structures from which both benign and malignant tumors may arise. This chapter focuses on the discussion of the cytopathology of the most common, mainly neoplastic, diseases of the three most frequently aspirated H&N sites: salivary glands, thyroid, and cervical lymph nodes. Important mimics of neoplastic lesions are also included to help prevent rendering an incorrect diagnosis.

11.2 FNA Method

11.2.1 Technique of Sampling

The target lesion/nodule can be localized and the aspiration can be guided by palpation or ultrasound. With ultrasound guidance, the aspirator is able to perform FNAs of smaller, non-palpable lesions and target the solid portion of complex (solid and cystic) lesions with accuracy, thus achieving a better outcome. A 25-gauge (0.02 in./0.51 mm outer diameter), or less frequently a 23-gauge (0.025 in./0.64 mm outer diameter) “fine” needle is attached to a syringe and inserted into a syringe

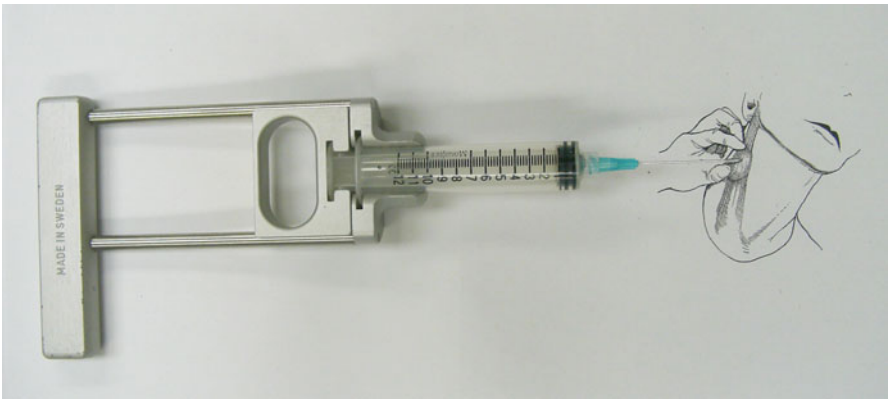

Fig. 11.1 Instruments prepared for FNA procedure: syringe holder with syringe and needle

holder. The needle quickly penetrates the overlying skin – local anesthesia is unnecessary – and is directed into the lesion (Fig. 11.1). A few rapid short strokes are made with the needle tip within the lesion while 2–3 cc of vacuum is applied with the syringe. Before the needle is pulled out of the lesion, the vacuum is released. (Rarely, the procedure is performed using only the needle without a syringe and without creating vacuum; the so-called French technique.) Once the needle is withdrawn, the aspirated material can be expelled from the needle onto glass slides to make direct smears, or flushed into a liquid to be used for the liquid-based cytology method (LBC), cell block, flow cytometry or molecular studies (discussed in the following section).

11.2.2 Processing of the Aspirated Sample

The aspirated sample (the "aspirate") may be directly smeared on glass slides and air-dried or alcohol fixed for staining with Romanowsky-type (Diff-Quik, Wright-Giemsa, Wright) stain or Papanicolaou stain, respectively. The preference of stain depends on the tissue/lesion aspirated. For example, Romanowsky stained slides are preferred for assessing hematopoetic elements (cells originating from bone marrow and lymphoid organs), because variations in cell size are accentuated on air-dried smears and immaturity of the chromatin (the intranuclear DNA-protein complex) and the cytoplasmic characteristics are better appreciated.

The application of LBC to thyroid FNA was first suggested in the 1990s [4]. Contrary to direct smears, LBC methods (ThinPrep, SurePath, Cytospin preparations) require special instrumentation for preparing a monolayer of cells after aligning them on a membrane. Advocates of LBC prefer this method for the ability to screen fewer, consistently well-fixed, and less blood-containing slides.

Cell blocks can be prepared from the centrifuged sediment of suspended cells in the needle rinse fluid. The sediment is congealed into a solid mass with the help of plasma/thrombin, then fixed in formalin and embedded in paraffin. Most importantly, immunostains can be performed on thin sections of this cell block to characterize the cells by their specific binding of a labeled antibody.

FNA can provide sample for flow cytometry which is used primarily to immunophenotype hematopoetic malignancies. Since this method requires about one million cells, two FNA passes (two courses of aspiration) should provide a sufficient number of cells. Using this method, numerous cells can be analyzed for the coexpression of two or three different cell surface markers simultaneously, facilitating the detection of even a small monoclonal/neoplastic cell population.

If an infectious lesion is suspected, the aspirate from a separate designated "pass" can be sent to the microbiology laboratory for microbiologic examination (Fig. 11.5d).

Molecular diagnostic methods are also available for samples obtained using FNA. These include conventional karyotype cytogenetics (analysis of total chromosomes), polymerase chain reaction (a method of DNA/RNA amplification used for analyzing short segments of the genetic material), and in situ hybridization. In situ hybridization is an "on-slide" technique that permits microscopic visualization of specific chromosomal segments using nucleic acid probes usually linked to a fluorescent label (FISH). It also allows the detection of numerical and/or structural abnormalities of chromosomes in cytological preparations where, conveniently, the cells are already disaggregated in a single layer on the slide.

11.2.3 Advantages and Potential Complications of FNA

Among its advantages it should be mentioned that FNA can be performed as an outpatient procedure, does not require anesthesia, is minimally discomforting to the patient, is cost effective, and has rapid turnaround time. In the hands of experienced individuals, FNA is highly sensitive (negative FNA result can safely predict if the final diagnosis will be negative) and specific (positive FNA result predicts the presence of malignancy with high probability). Positive and negative FNA test results prove to be correct predicting the final diagnosis in a high proportion of cases (FNA has high positive and negative predictive values). Review and meta-analysis of 3459 FNAs from all head and neck sites in 30 studies revealed 89.6% sensitivity, 96.5% specificity, 96.2% positive predictive value, 90.3% negative predictive value, and 93.1% accuracy [5]. Diagnostic errors are more likely to occur when the cytopathologist attempts to interpret the cytological findings without being fully informed of the exact location of the aspirated lesion and the patient's medical history, symptoms, and physical and radiological findings. As an example, note the similarities in the aspirates of a cystic SCCA metastasis, a branchial cleft cyst, an epidermal inclusion cyst, and a pilomatricoma (Figs. 11.26a, 11.32a, 11.33a, and 11.34a, respectively), making it obvious that being uninformed of the history and the exact location of the lesion may result in incorrect diagnosis. In the hands of a fully informed

cytopathologist, 100% sensitivity, 86% specificity, 97% positive predictive value, 100% negative predictive value, and 97% accuracy could be achieved performing H&N FNA with ultrasound guidance [6].

Potential complications of FNA are bleeding, infection, and tumor cell seeding. In the absence of a bleeding diathesis, which is a contraindication to FNA, the occasional local hemorrhage can usually be controlled with local pressure. Infection is very rare if the skin is thoroughly cleaned with 95% ethanol before FNA. Although occasional implantation of tumor cells along the needle track cannot be completely excluded, its clinical significance is questionable [7].

11.3 Cytopathology of Salivary Gland Lesions

FNA is a useful technique for evaluating masses both in the major – parotid, submandibular, and sublingual – salivary glands and in the numerous tiny minor salivary glands found throughout the oropharynx. Preoperative identification of non-neoplastic lesions (e.g. the benign gland enlargement called sialadenosis, inflammations, cysts, or intraparotid lymph nodes) can negate the need for a surgical procedure. Malignant neoplasms, carcinomas and lymphomas, are found in less than 10% of salivary gland FNAs. When FNA reveals neoplastic tissue, the distinction of benign from malignant neoplasms and the exact classification of malignant neoplasms may dictate the urgency and extent of the subsequent operation. Unfortunately, some salivary gland neoplasms are difficult to diagnose on FNA. Perhaps the main reason is that the majority of these tumors arise from the same epithelial and/or myoepithelial cell lines, rendering them alike. In addition, these cells are able to undergo squamous, mucinous, oncocytic, and sebaceous metaplastic changes hindering the identification of the lesion. (Metaplasia is the non-neoplastic transformation of one adult cell type to another.) Hence, although the sensitivity of salivary gland FNA is approximately 90% and its specificity is about 95% in expert hands [8, 9], specific classification of malignant neoplasms can be achieved in only about 85% of salivary gland FNAs. Following a non-diagnostic FNA, the sensitivity and specificity of a repeat FNA was reported to be 84 and 93%, respectively, in distinguishing benign from malignant tumors [10].

The salivary glands are complex structures composed of acinar, ductal, and mesenchymal tissues. Therefore, the FNA of a normal salivary gland will yield ductal cells and glandular elements composed of serous and/or mucinous acinar cells. Mature fat may also be present. Cytologically, the acinar cells have granular or finely vacuolated cytoplasm. They appear in globular/ball-like cohesive groups which may aggregate in grapelike clusters connected by ducts (Fig. 11.2). Occasional attached elongated myoepithelial cells may be present. The cohesive ductal cells appear in orderly sheets or tubules.

Chronic sialadenitis (chronic inflammation of the salivary gland), which can mimic a neoplasm, is one of the most often aspirated lesions of the major salivary glands. The smears show small groups of acinar cells and ductal cells admixed with lymphocytes (Fig. 11.3). As the sialadenitis progresses toward the atrophic phase

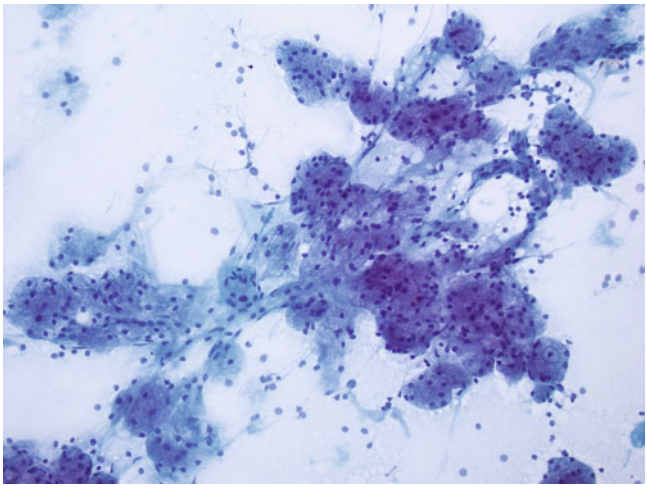

Fig. 11.2 A normal salivary gland was incidentally aspirated to reveal ball-shaped aggregates of acinar cells forming grape-like structures. Pap 200×

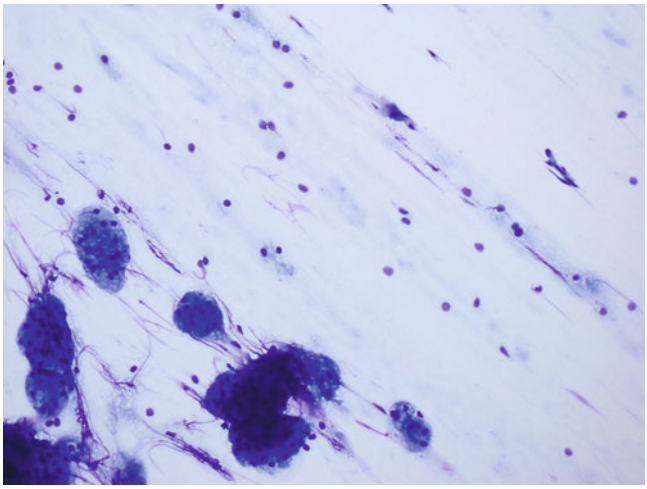

Fig. 11.3 Chronic sialadenitis (44 year old man with enlargement of the submandibular gland). The aspirate contained a reduced number of acinar cells with some lymphocytes. DQ 200×

and scar tissue keeps replacing the functioning lobules, the acinar cells gradually disappear from the aspirate. Mucinous or squamous metaplasia may occur, potentially leading to the incorrect diagnosis of mucoepidermoid carcinoma.

Benign lymphoepithelial lesions, which can develop in HIV infection and in autoimmune sialadenitis (including the localized Mikulicz's or the systemic Sjogren's disease) also yield numerous lymphoid cells on FNA. Ductal cells, groups of basal epithelial cells and myoepithelial cells are seen admixed with the lymphocytes, and, prior to the atrophic phase, some acinar cells are also present.

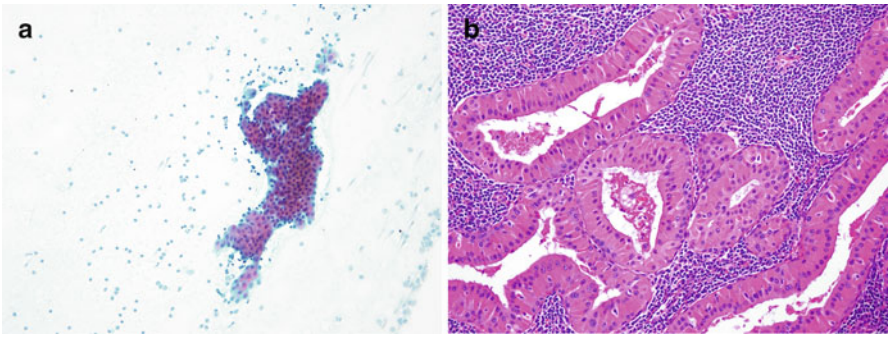

Fig. 11.4 Warthin's tumor (70 year old man with parotid mass). (**a**) FNA shows groups of oncocytic cells with a polymorphous population of lymphocytes in the background. Pap 200× (**b**) Histologic section demonstrates cystic spaces lined by oncocytic cells and surrounded by numerous lymphocytes. HE 200×

The benign **lymphoepithelial cyst** is another HIV-associated lesion showing a mixture of epithelial and lymphoid cells in the aspirate. It is an often multiple and bilateral cystic parotid lesion. The cyst is lined by squamous or rarely glandular epithelium which is surrounded by lymphocytes.

Warthin's tumor is the most common lesion in the parotid. It is also frequently bilateral and cystic. The cyst characteristically contains thick brown fluid resulting in a "dirty" proteinaceous background on the smear. The cyst and the invaginating papillary fronds are lined by a double layer of oncocytic epithelium. Thus, the aspirate reveals monolayer sheets of oncocytes reflecting the cyst lining and clusters of lymphocytes reflecting the lymphoid component that surrounds the cyst (Fig. 11.4). The oncocytes are large polygonal cells with centrally placed round to oval nuclei, prominent nucleoli, and abundant, uniformly granular cytoplasm due to the numerous large mitochondria. The differential diagnosis includes other lesions which also have oncocytes: **oncocytosis,** a metaplastic process in which the acinar cells are gradually replaced by oncocytes, and **oncocytoma**, a benign neoplasm composed of oncocytes. These lesions, however, lack the proteinaceous background and the significant lymphoid component characteristic of Warthin's tumor. As in chronic sialadenitis, mucinous or squamous metaplasia may also occur in Warthin's tumor causing diagnostic difficulties.

Since lymph nodes may exist within the parotid gland, usually in its superficial lobe, these nodes may get aspirated. Naturally, the aspirates of these **intraparotid lymph nodes** are very rich in lymphocytes, therefore the aspirate may raise suspicion for malignant lymphoma.

However, in all of the aforementioned lymphocyte-rich lesions (chronic sialadenitis, benign lymphoepithelial lesion, lymphoepithelial cyst, Warthin's tumor, intraparotid lymph node), the lymphoid cell population is polymorphous: most lymphocytes are small and mature, but intermediate and larger forms are also present. This is the appearance of a reactive/benign lymphoid process (Fig. 11.25). In sharp contrast, most non-Hodgkin's type **malignant lymphoma**s exhibit a monomorphic lymphoid

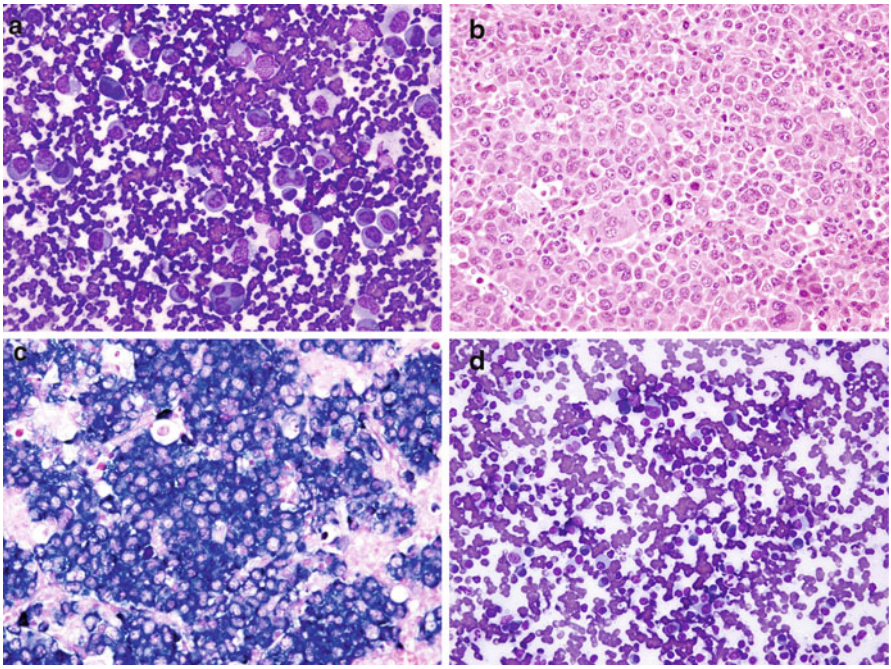

Fig. 11.5 Plasmablastic lymphoma (52 year old man with parotid mass). Plasmablastic lymphoma is a distinctive B-cell lymphoma, typically presenting as extranodal disease associated with human immune deficiency virus infection. (**a**) Shown in the aspirate are uniformly large discohesive lymphoid cells with excentric irregular nuclei. DQ 400× (**b**) The biopsy reveals a massive infiltrate of large lymphoid cells with round, vesicular nuclei, prominent nucleoli, ample cytoplasm, and multiple mitotic figures. HE 400× (**c**) The diffusely blue areas highlight the cytoplasmic lambda light chains. No cytoplasmic kappa light chain was found (not shown). These findings confirm the monoclonal neoplastic nature of the lymphoid cells. Lambda in situ hybridization 400× (**d**) Shown for comparison is an aspirate from a benign reactive submandibular lymph node of a HIV-infected man. The plasma cells are much smaller than the cells in Fig. 11.5a and show significantly greater variation in size and shape. The benign nature of the plasmacytosis was confirmed by special studies. The aspirate was also sent for bacterial and fungal cultures with negative results. DQ 400×

cell population: the neoplastic cells, although their size and shape depend on the type of lymphoma, are all similar to each other within the same lesion because they originate from the same clone (Fig. 11.5).

Pleomorphic adenoma (PA), also called benign mixed tumor, is the most common salivary gland tumor. It accounts for approximately 75% of salivary gland tumors. It contains epithelial cells, myoepithelial cells, and chondromyxoid stroma in variable proportions. The myoepithelial cells, which are immunoreactive for both epithelial and muscle markers, generally have elongated/oval shape, sometimes with clear cytoplasm, and may have excentric nuclei resembling plasma cells (hence the name plasmocytoid). In the aspirate of a pleomorphic adenoma, the stromal substance has a fibrillary appearance and stains purple with Romanowsky-type stains. The myoepithelial cells are typically embedded in this stromal material

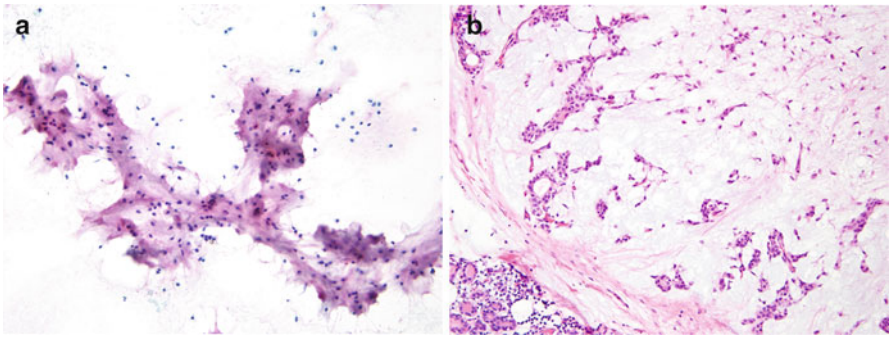

Fig. 11.6 Pleiomorphic adenoma (44 year old man with parotid mass). (**a**) Shown in the aspirate are some epithelial cells with round nuclei and myoepithelial cells with elongated nuclei mostly embedded in a fibrillary stroma. Pap 200× (**b**) In the histological section of the excised tumor, the PA with its epithelial, myoepithelial, and stromal components is clearly delineated from the adjacent uninvolved salivary gland tissue. HE 200×

(Fig. 11.6). Tyrosine-rich crystals may be present. In PA the epithelial component may undergo metaplastic squamous or oncocytic change and focal mucin production may occur. These changes should not be confused with a squamous, mucoepidermoid, or other type of carcinoma which can develop within pleomorphic adenoma. On the other hand, an aspirate that exhibits cytological features of both a pleomorphic adenoma and a malignant process (significant cellular atypia, necrosis, atypical mitosis) should raise suspicion for a carcinoma arising within PA, the so-called **carcinoma ex pleomorphic adenoma**. In this scenario, the carcinoma within the PA is usually an "adenocarcinoma not otherwise specified", but specific tumor types such as salivary duct carcinoma (Fig. 11.7), mucoepidermoid carcinoma, and adenoid cystic carcinoma may also occur.

As previously mentioned, the ratio of epithelial, myoepithelial, and stromal components varies widely in pleomorphic adenomas. **Myoepithelioma,** a close relative of PA, represents one end of this spectrum. The aspirate of this benign tumor shows a virtually exclusive population of myoepithelial cells. Cytology generally cannot distinguish myoepithelioma from the malignant counterpart, **myoepithelial carcinoma,** since the cytologic atypia is usually not pronounced in myoepithelial carcinoma. Therefore, a tissue biopsy revealing infiltrative growth is needed to render the diagnosis of myoepithelial carcinoma (Fig. 11.8).

An aspirate that includes numerous epithelial cells in addition to the myoepithelial cells should raise the possibility of an **epithelial-myoepithelial carcinoma**, a rare low grade malignant neoplasm characterized by a dual cell population of luminal ductal cells and abluminal myoepithelial cells.

It can be difficult to differentiate pleomorphic adenoma from two malignant neoplasms which likewise contain epithelial cells, myoepithelial cells, and stromal matrix: adenoid cystic carcinoma (ADCC) and polymorphous low grade adenocarcinoma (PLGA).

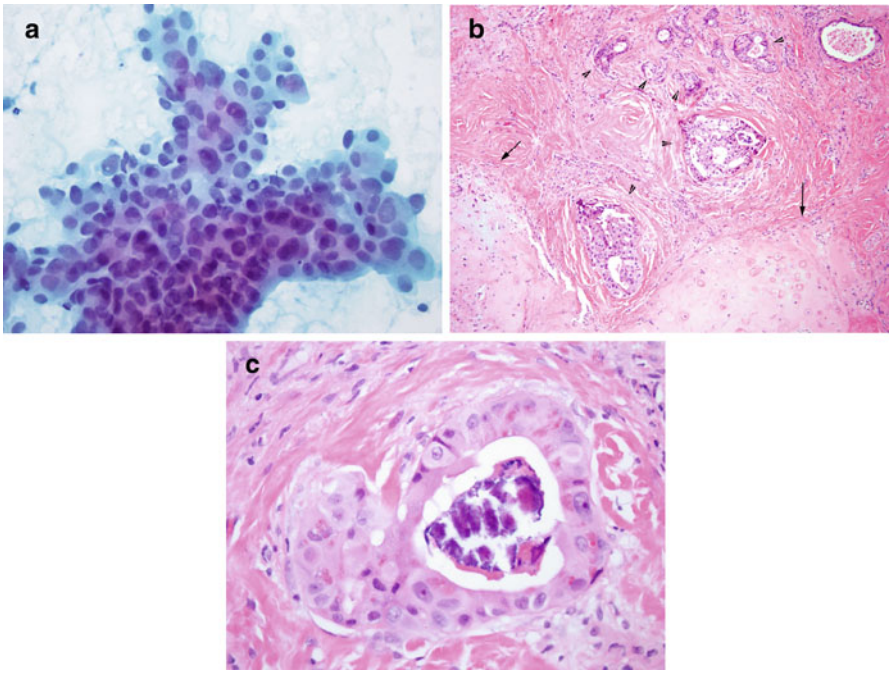

Fig. 11.7 Carcinoma ex pleiomorphic adenoma (68 year old man with parotid mass). (**a**) Shown in the aspirate is a cohesive group of carcinoma cells with overlapping nuclei and marked pleiomorphism. Pap 400× (**b**) Histology of the removed mass shows infiltrating malignant glands (*arrowheads*) adjacent to areas of PA (*arrows*). Note the cribriforming and comedonecrosis in the central malignant gland, consistent with salivary duct carcinoma. HE 100× (**c**) The features of the malignant cells are similar to those observed in the aspirate. The necrotic luminal content may become calcified as in comedo carcinoma of the breast. HE 400×

Adenoid cystic carcinoma accounts for approximately 1–2% of all salivary gland tumors. However, it is the most common malignancy of salivary glands other than the parotid, and it is the most common salivary gland carcinoma in children. FNA of a well differentiated ADCC provides relatively uniform small cells with hyperchromatic nuclei and scant cytoplasm. Of the cribriform, tubular, and solid histologic patterns of ADCC, the cribriform one is the least difficult to diagnose on cytology. In this case, the tumor cells tend to surround smooth-contoured round globules of stromal material (hyaline globules). The purple color of this material is similar to that found in PA, however, in ADCC this material is homogenous and not fibrillar, and is mostly acellular in contrast to PA (Fig. 11.9). Other patterns of ADCC may be difficult to differentiate on cytology from other tumors which have similar-appearing cells, such as monomorphic/basal cell adenoma (BCA), basal cell adenocarcinoma, small cell carcinoma, or PLGA.

Polymorphous low grade adenocarcinoma is found only in minor salivary glands, mainly in the hard palate. On histology, it is architecturally diverse with solid, tubular, trabecular, cribriform, or duct-like structures embedded in myxoid

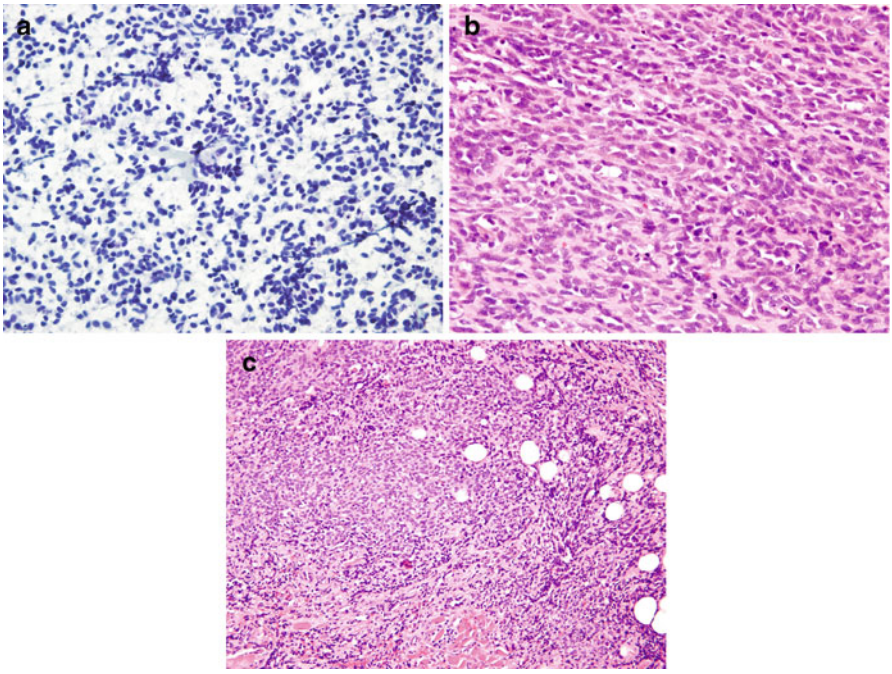

Fig. 11.8 Myoepithelial carcinoma (30 year old man with parotid mass). (**a**) Cellular aspirate exhibiting numerous spindle cells which are suggestive of myoepithelial cells. Their benign or malignant nature cannot be determined based on cytomorphology alone. Pap 400× (**b**) Histological section of the excised mass demonstrates the corresponding mitotically active oval to spindle cells. HE 400× (**c**) The malignant diagnosis was rendered based on the perineural invasion and infiltrative growth (shown). HE 200×

stroma. Cytologically, it may show small round/oval hyaline globules, similar to ADCC (Fig. 11.10), but the cells in PLGA have more round and less hyperchromatic nuclei than in ADCC. However, PLGA may be impossible to diagnose with certainty by cytology because its features may overlap with those of other tumors.

Monomorphic/basal cell adenoma (BCA) is a rare neoplasm of the major salivary glands. In the cellular aspirate of BCA, the uniform small tumor cells with round dark nuclei appear in cohesive groups often showing nuclear palisading at their periphery (Fig. 11.11). The very rare malignant variant of this tumor, **basal cell adenocarcinoma**, can be diagnosed only on histology by demonstrating that it has invaded into surrounding tissues or has metastasized.

Mucoepidermoid carcinoma (MEC) is the most common carcinoma in the parotid. The accurate diagnosis depends on the recognition of a mixed population of epidermoid cells, intermediate cells, and mucocytes (mucin-producing glandular cells). The intermediate cells range in size from that of a small basaloid cell to the size of an immature squamous metaplastic cell. They have scant or modest amount of cytoplasm, bland round nuclei, and occasional nucleoli. The intermediate cells, being specific to this neoplasm, are important in making the diagnosis of MEC. The three

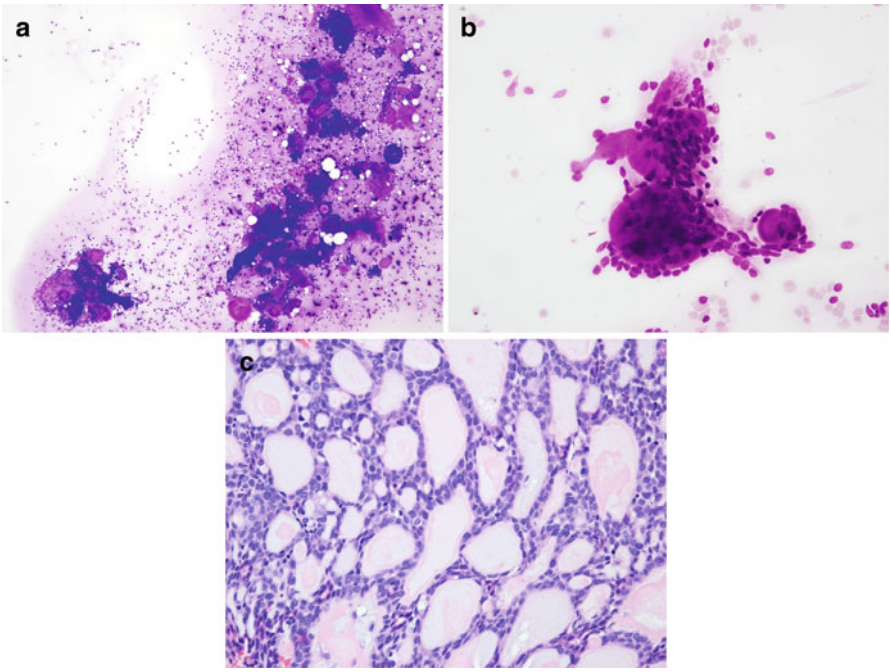

Fig. 11.9 Adenoid cystic carcinoma (60 year old woman with parotid mass). (**a**) Shown in the aspirate are clusters of small uniform dark cells surrounding cores of homogenous purple basement membrane material. DQ 100× (**b**) Higher magnification of the smear clearly demonstrates the spherical globules of homogenous, circumscribed, largely acellular basement membrane material surrounded by small cells with round to oval dark nuclei and scant cytoplasm. DQ 400× (**c**) The histological section of the tumor demonstrates that the features observed in the FNA correspond to the cribriform architecture. The Swiss cheese-like pattern is created by the interlocking rings of small basaloid cells that surround the basement membrane material (hyaline globules). HE 400×

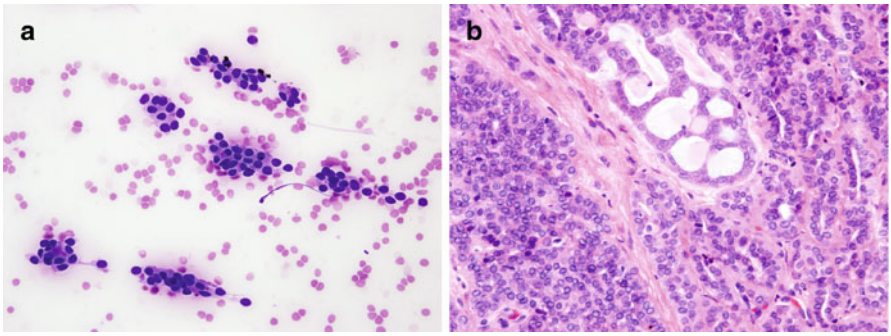

Fig. 11.10 Polymorphous low grade adenocarcinoma (74 year old woman with palate mass). (**a**) Shown in the aspirate in focal acinar arrangement are uniform cuboidal cells with oval nuclei, smooth nuclear membranes, indistinct nucleoli, and moderate pale cytoplasm. DQ 400× (**b**) Solid, tubular, and cribriform architectural patterns are displayed side by side even in a single section of the removed mass. The cells have uniform round and oval nuclei with vesicular chromatin and indistinct nucleoli. HE 400×

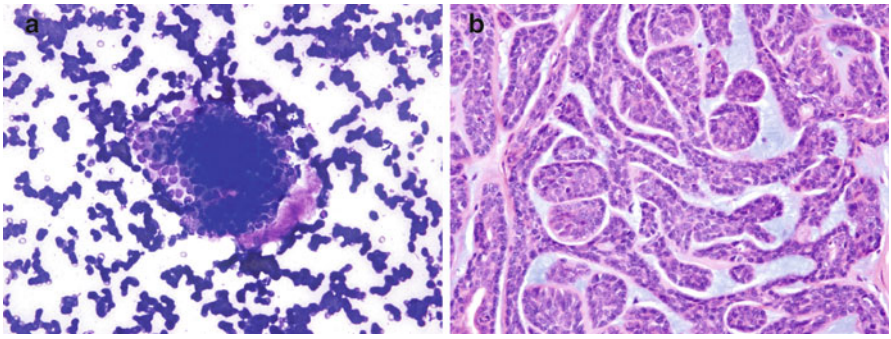

Fig. 11.11 Basal cell adenoma (79 year old woman with parotid mass). (**a**) Shown in the aspirate is a cluster of small uniform oval and polygonal cells with round to oval nuclei and fine chromatin. The location of the purple-staining stromal material at the periphery of the cluster is characteristic. DQ 400× (**b**) Histological examination of the encapsulated mass reveals a trabecular pattern of basaloid cells with thick bands of basal lamina. HE 400×

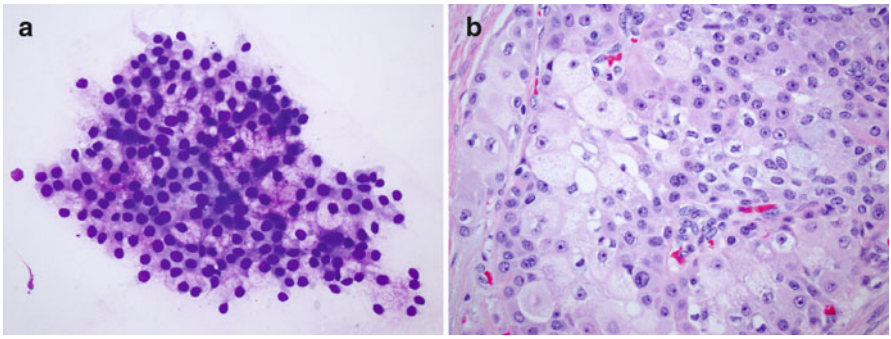

Fig. 11.12 Mucoepidermoid carcinoma (56 year old woman with parotid mass). (**a**) Shown in the aspirate are intermediate cells intimately intermixed with mucocytes. The mucocytes are large cells with vacuolated/fluffy cytoplasm filled with mucin. The smaller intermediate cells have round nuclei and scant to moderate amount of cytoplasm. DQ 400× (**b**) In the corresponding histological section, the intermediate cells are blending imperceptibly with mucocytes without a significant epidermoid component, indicating a low grade mucoepidermoid carcinoma. HE 400×

cell types, the mucocytes, the intermediate, and the epidermoid cells, are present in variable proportions depending on the grade of the tumor. Low grade, usually cystic, tumors have abundant mucocytes without significant atypia or mitotic activity (Fig. 11.12). In aspirates of low grade MEC, one may occasionally find predominantly mucin and only very scant embedded mucocytes. These findings may be misinterpreted as a **mucocele**. However, since a mucocele represents pools of mucin that leaked from a damaged duct into adjacent tissues, by its nature it yields only mucin without any embedded mucus cells. Low grade MEC may also be confused with the very rare **mucinous adenocarcinoma**, which also features mucin and glandular cells, but the

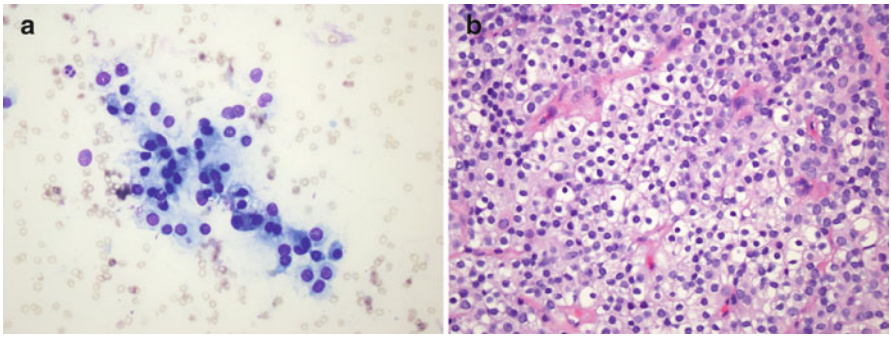

Fig. 11.13 Clear cell-rich mucoepidermoid carcinoma (56 year old woman with parotid mass). (**a**) Shown in the aspirate is a cohesive group of relatively large cells with clear/vacuolated cytoplasm. DQ 400× (**b**) Biopsy of the mass revealed an infiltrating carcinoma with clear cell change. HE 400× The positive MAML2 rearrangement by FISH supported MEC, while the negative EWS translocation and negative human papillomavirus DNA effectively excluded a hyalinizing clear cell carcinoma and a clear cell non-keratinizing SCCA, respectively

presence of intermediate cells is specific to MEC. At the other end of the spectrum, in high grade MEC, there are few mucocytes and the predominance of the squamous cell-like epidermoid cells yields a similar appearance to **squamous cell carcinoma** (SCCA). However, as with mucinous adenocarcinoma, SCCA contains no intermediate cells. Moreover, in MEC the epidermoid cells rarely show obvious keratinization, which is a key feature of the malignant squamous cells in SCCA (Fig. 11.26a). The presence of intermediate cells and the lack of keratinization also help to distinguish MEC from the more aggressive **adenosquamous carcinoma** which contains malignant glandular elements in addition to malignant squamous cells. In the future, molecular studies of fine-needle aspirates may assist in rendering the diagnosis of MEC (Fig. 11.13) and serve as prognostic indicators. The t(11;19) translocation that underlies MEC has been cloned [11]. The resulting MECT1/MAML2 translocation is highly specific for MEC and imparts a better prognosis [12].

Acinic cell adenocarcinoma (ACAC) occurs in both major and minor salivary glands. The cells aspirated from well differentiated ACAC bear a striking resemblance to the normal acinar cells from which they derive. However, in contrast to FNA of normal salivary gland tissue, FNA of ACAC yields a more cellular aspirate in which the tumor cells do not appear in balls but rather in sheets or cords, and other components of a normal salivary gland (ductal cells, fat) are not present (Fig. 11.14). Because of their ample cytoplasm and central nucleolus, the cells of ACAC may resemble cells of an oncocytic tumor but the granular or finely vacuolated cytoplasm is different from the uniformly granular cytoplasm of oncocytes.

The very aggressive **salivary duct carcinoma**, being histologically similar to the comedocarcinoma of the breast, will yield sheets of obviously malignant cells with high nuclear to cytoplasmic ratio and pleiomorphic nuclei in a necrotic background (Fig. 11.7a).

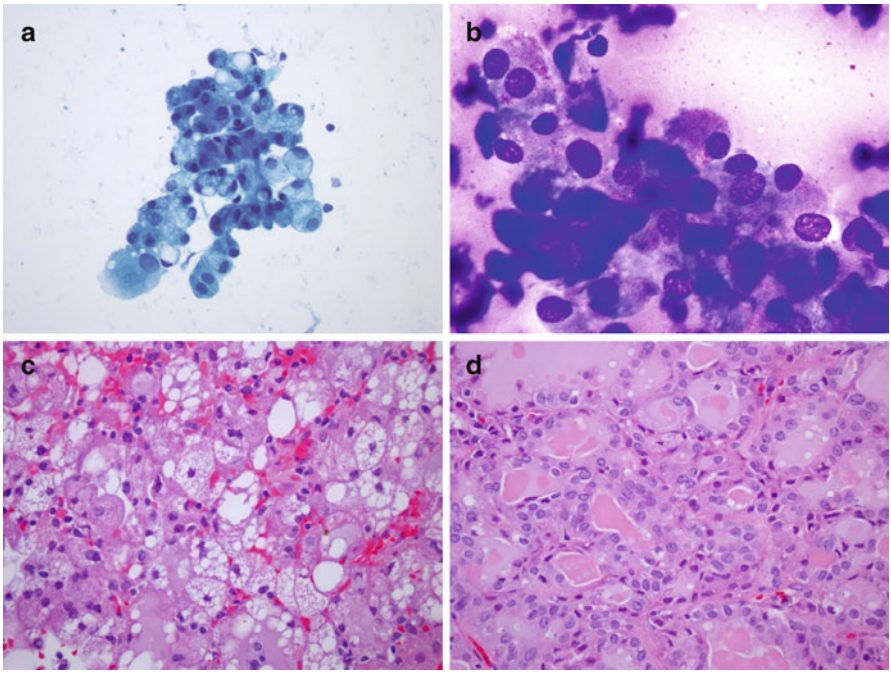

Fig. 11.14 Acinic cell carcinoma (56 year old woman with parotid mass). (**a**) Shown in the aspirate is a sheet of large cells with vacuolated cytoplasm. The nuclei are uniformly round and excentrically located. Pap 400× (**b**) In other smears, the Romanowsky-type stain highlights fine granules in the tumor cells' ample cytoplasm. DQ 1000× oil (**c**) The vacuolated cells can also be clearly identified in the histologic section of the tumor. HE 400× (**d**) However, other sections may show non-vacuolated tumor cells in a follicular pattern resembling thyroid tissue. HE 400×

The cytologic appearance of **small cell carcinoma** of the salivary gland is similar to that of the undifferentiated small cell carcinoma of the lung. In the highly cellular aspirates, the tumor cells have high nuclear to cytoplasmic ratio (N/C ratio), irregular fragile nuclear membranes with nuclear molding and frequent smearing artifact.

11.4 Cytopathology of Thyroid Lesions

Thyroid FNA is a safe, accurate, and cost-effective method for guiding the clinical management of thyroid nodules. Given that 4–7% of the adult population has palpable thyroid lesions and even more people have non-palpable nodules detected by ultrasound [13, 14], it is no wonder that thyroid FNA is one of the most commonly performed FNAs – over 350,000 thyroid FNAs are done annually in the USA. In expert hands, the diagnostic accuracy of thyroid FNA to distinguish benign lesions from malignant ones (which represent only a small fraction of the nodules) ranges

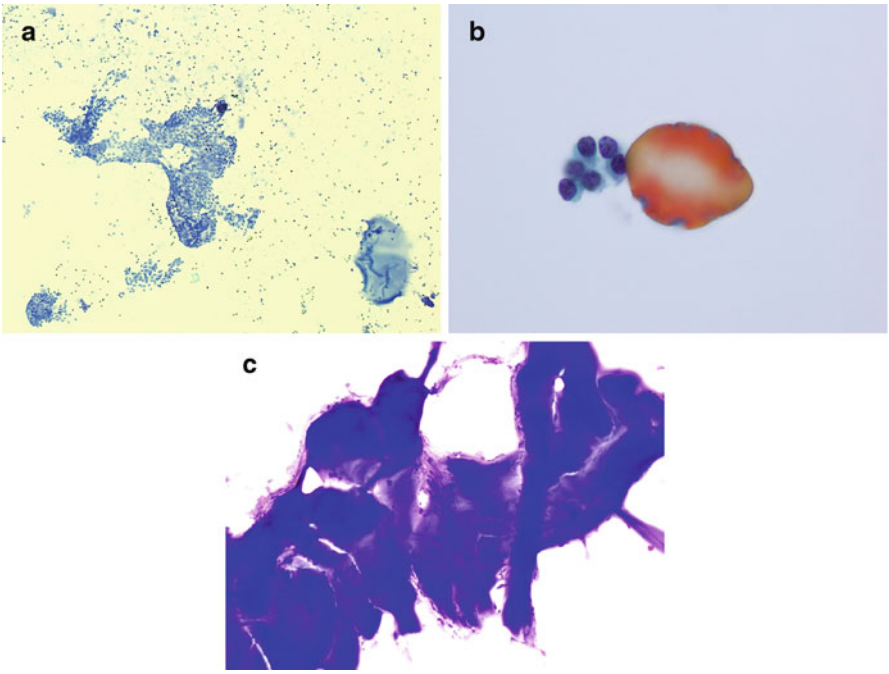

Fig. 11.15 (**a**) A sheet of follicular cells and colloid is seen in the aspirate of a hyperplastic thyroid nodule. Note the honeycomb arrangement of the cells and the wrinkled appearance of the colloid. Pap 100× (**b**) A thyroid microfollicle and a colloid "droplet" is shown in the aspirate of a follicular adenoma. Thinprep Pap 1000× oil (**c**) Accidentally aspirated skeletal muscle may resemble colloid. However, the cross-striation in the center is specific for skeletal muscle. DQ 200×

from 80 to over 95% [15]. This accuracy refers only to adequate specimens. The criteria for adequacy include the presence of a sufficient number of well-visualized thyroid follicular cells in the aspirate (six groups, each containing 10 follicular cells or 180–320 follicular cells using LBC method). The rare exceptions to this requirement are mentioned in the discussion of colloid nodule and chronic thyroiditis. The presence of even a large number of macrophages (members of the body's defense mechanism that engulf and digest cellular debris and pathogens) does not render a thyroid aspirate adequate in the absence of follicular cells. The presence of macrophages usually indicates cyst formation which is generally benign but may also occur in papillary carcinomas.

The two main components of a normal thyroid aspirate are hormone-producing follicular cells and colloid, the storage site of thyroid hormone. Scant lymphocytes may be seen but their presence is generally associated with inflammatory conditions. The neuroendocrine parafollicular C cells are too few to be recognized in normal thyroid FNA. The follicular cells are uniform, cuboidal-shaped cells with round granular and slightly hyperchromatic nuclei, smooth nuclear membranes, and scant pale cytoplasm (Fig. 11.15b). Individually scattered follicular cells may lose

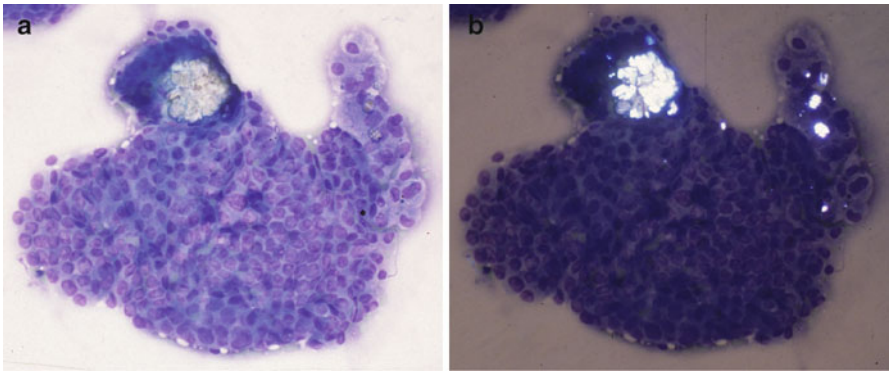

Fig. 11.16 Calcium oxalate crystals (44 year old woman with thyroid nodule). (**a**) Shown in the aspirate of a follicular variant of papillary carcinoma are crystals embedded in the colloid. DQ 400× (**b**) Polarized light highlights the crystals. DQ 400×

their cytoplasm and resemble lymphocytes. More often, however, benign follicular cells form flat, cohesive sheets with evenly distanced nuclei, yielding a honeycomb pattern. Normal follicles appear in the aspirate as macrofollicles, comprised of numerous follicular cells surrounding and/or surrounded by colloid (Fig. 11.15a). The appearance of colloid depends on its functional state, varying from watery to dense. Watery colloid has a thin membrane coating appearance in direct smears and a tissue-paper appearance in LBC preparations. Thick colloid can show linear cracking artifact in direct smears and appear as dense orange-blue droplets in LBC preparations (Fig. 11.15b). Especially when highlighted under polarized light, calcium oxalate crystals may occasionally be detected in thyroid aspirates of adults. These crystals can be found in any colloid-containing thyroid tissue, regardless if it is benign or malignant (Fig. 11.16) [16]. When follicular cells undergo reactive/reparative change, they may reveal enlarged nuclei with prominent nucleoli. However, they maintain their cohesiveness and their orderly macrofollicular arrangement.

Follicular cells may undergo oncocytic change, manifesting abundant finely granular cytoplasm, enlarged nuclei, and prominent nucleoli similar to the oncocytes described in the salivary glands (Fig. 11.19a). The cytoplasm of oncocytes is green or orange with Papanicolaou stain, blue or grey-pink with Romanowsky-type stains, and pink with hematoxylin-eosin stain. In the thyroid these cells are generally called Hurthle cells, despite the fact that their correct description was provided by Askanazy in 1898, and the cells described by Hurthle in 1894 are now believed to represent the parafollicular C cells.

A brown pigment consisting of neuromelanin and/or lipofuscin may accumulate in the cytoplasm of follicular cells due to the administration of tetracycline or minocycline resulting in the "**black thyroid syndrome**". Interestingly, the pigment does not deposit in autonomously functioning nodules; for example, a follicular adenoma would stand out from the otherwise uniformly black thyroid [17].

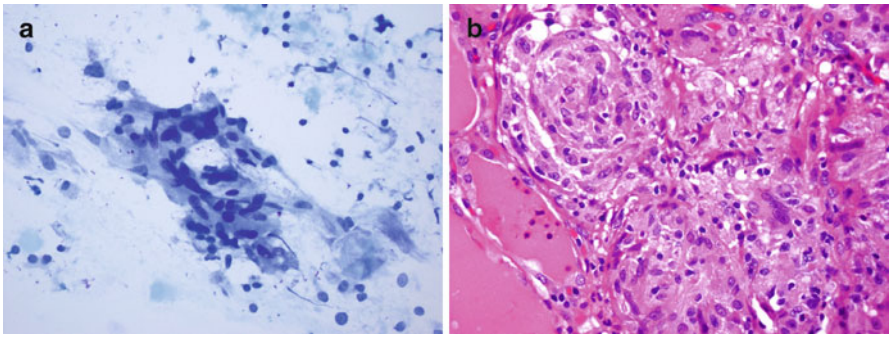

Fig. 11.17 Sarcoid of the thyroid (52 year old woman with goiter). (**a**) This aggregate of epithelioid histiocytes was an incidental finding in the aspirate of a multinodular goiter. The cells are oval to spindle shaped with elongated large pale nuclei, moderate amount of cytoplasm and indistinct cell membranes. Pap 400× (**b**) In the corresponding histological section, tight clusters of histiocytes and some multinucleated giant cells are seen forming the characteristic non-necrotizing granulomas. Microorganisms were not detected on acid fast bacterial and fungal stains. HE 400×

The thyroid in acute and subacute thyroiditis is aspirated only in those rare cases when malignancy is suspected clinically. **Acute thyroiditis** is an infectious condition usually seen in immunocompromised patients. Naturally, in the aspirate one will find an acute inflammatory infiltrate: numerous neutrophils associated with the blood component fibrin, dead (necrotic) cells, and usually very limited follicular cells and colloid. **Subacute (granulomatous, de Quervain's) thyroiditis** is a self-limiting inflammatory condition. The typical finding is the presence of aggregates of epithelioid histiocytes called granulomas. (The epithelioid histiocytes resemble epithelial cells but they are bone marrow-derived scavenger cells.) In addition, colloid-containing multinucleated giant cells, neutrophils, eosinophils, and lymphocytes can be seen depending upon the stage of the disease. There are other rare entities in which granulomas may appear in the thyroid aspirate. These include infectious diseases (e.g. tuberculosis, fungal infection), and sarcoid (Fig. 11.17), a multiorgan disease of unknown etiology.

Lymphocytic (Hashimoto's) thyroiditis is an autoimmune disorder, in which the immune system reacts against certain thyroid components resulting in an enlarged thyroid, called a goiter. The FNA, which is performed to rule out malignancy, contains numerous lymphoid cells including small mature lymphocytes and larger lymphoid cells. The latter represent cells of germinal centers in lymphoid follicles which are commonly present in this disorder. The finding of numerous polymorphous lymphocytes in the appropriate clinical setting is sufficient for the diagnosis of lymphocytic thyroiditis, even in the absence of follicular cells. In addition to lymphocytes, one may often find Hurthle cells, either as single cells or arranged in sheets. Hurthle cells may show anisonucleosis (variation in nuclear size) and nuclear grooves. These findings do not indicate papillary carcinoma in this setting.

In the case of the rare **Riedel's thyroiditis**, which results in progressive fibrosis of the tissues within and next to the thyroid, FNA usually yields non-diagnostic hypocellular aspirate.

In **Graves' disease** (or toxic diffuse hyperplasia), an autoimmune stimulus causes increased benign proliferation of follicular cells (*hyperplasia*), leading to *diffuse* enlargement of the thyroid associated with *toxic* thyroid hormone overproduction. FNA, though rarely performed in this condition, may show the morphologic signs of hyperactivity: the distinctive "flame cells", which are characterized by marginal cytoplasmic vacuoles and red frayed edges on Romanowsky stains secondary to the hyperfunctioning endoplasmic reticulum. The other findings, the variable number of follicular cells arranged in honeycomb sheets and the abundant colloid, are non-specific and are also seen in aspirates of benign hyperplastic nodules of a nodular goiter. The aspirate of Graves' disease treated with radioactive iodine or carbimazole may include crowded follicular cells with atypia. This represents treatment effect and knowledge of the clinical history helps to avoid overinterpreting them as signs of malignancy.

Nodule(s) of a **(multi)nodular goiter** are the most common lesions targeted in thyroid FNA. Nodular goiter is the result of repeated cycles of hyperplasia and involution, usually due to iodine deficiency. The resulting **hyperplastic nodule**s show cytological features similar to those in Graves' disease: abundant colloid and variable number of follicular cells in monolayer orderly sheets (Fig. 11.15a). Hurthle cell change is frequently encountered. Features of involution may be seen: macrophages in cystic degeneration; hemosiderin-laden macrophages in old hemorrhages; spindle cells or fibrous tissue fragments in fibrosis. Sometimes, the colloid content is so prominent in a nodular goiter that the FNA yields only abundant, essentially acellular (cell-free) colloid. In this case if there is no clinical or radiological sign of malignancy, the sample is considered adequate despite the absence of follicular cells, and the diagnosis of "**benign colloid nodule**" is rendered.

The previously discussed lesions (subacute thyroiditis, lymphocytic thyroiditis, Graves' disease, hyperplastic/colloid nodule) are reported as "Category: Benign follicular lesion" according to the 2010 Bethesda System for Reporting Thyroid Cytopathology. In this category, the false-negative rate (when a malignant lesion is incorrectly diagnosed as benign) is 1–10% [18]. Therefore, patients with benign cytology are generally followed for up to 3–5 years with ultrasonography and repeat FNA if clinically indicated (for significant growth of the nodule, presence of microcalcifications, etc.).

An aspirate, in which the number of follicular cells is significantly increased while the amount of colloid is decreased, raises suspicion for a **follicular neoplasm**. A follicular neoplasm, contrary to the hyperplastic nodule, is an unregulated independently functioning neoplastic lesion. It needs to be surgically excised because cytology cannot distinguish between a benign follicular adenoma and a malignant follicular carcinoma. (Only histological evaluation is able to disclose the diagnostic feature of malignancy: capsular and/or vascular invasion.) Therefore, it is important to make the often difficult distinction between a cellular hyperplastic nodule and a follicular neoplasm. The increased cellularity and scant colloid alone are not sufficient for the diagnosis

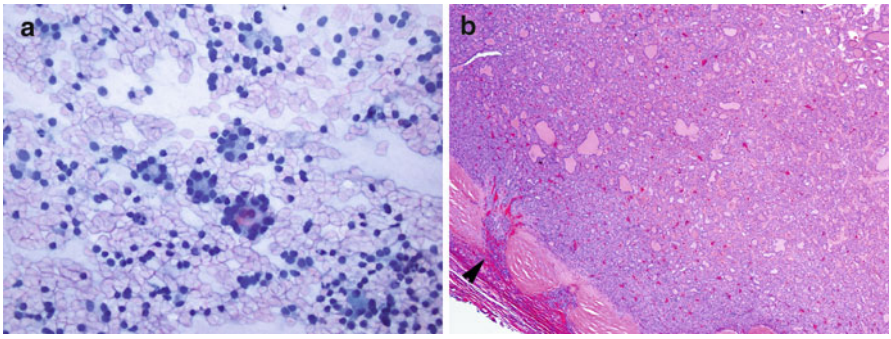

Fig. 11.18 Follicular thyroid carcinoma (25 year old woman with thyroid nodule). (**a**) In the cellular aspirate, the follicular cells are primarily arranged in microfollicles suggesting a follicular neoplasm. Pap 400× (**b**) Histological section of the lesion reveals an encapsulated lesion with a predominantly microfollicular pattern. The capsular invasion (*arrowhead*) is diagnostic for follicular carcinoma. HE 40×

of follicular neoplasm. To render this diagnosis, one has to see follicular cell crowding, overlapping, and microfollicle formation affecting the majority of the follicular cells (Fig. 11.18). The definition of a microfollicle is 6–12 (generally accepted as less than 15) follicular cells arranged in a ring, with or without a small amount of central colloid (Fig. 11.15b). The follicular cells may also form crowded ribbons/trabeculae and three-dimensional groups. The nuclei are round, slightly hyperchromatic, and in none of these lesions are the nuclear features of papillary carcinoma present.

Whether **Hurthle cell neoplasms** are separate entities or only oncocytic variants of follicular neoplasms is still being debated [19]. The typical aspirates are highly cellular and consist of a virtually exclusive population of Hurthle cells dispersed as isolated cells or forming crowded clusters and sheets. Marked variation in cell and nuclear size is common (Fig. 11.19).

Papillary carcinoma (PC) accounts for up to 80% of malignant thyroid lesions. FNA is well-suited to diagnose these common thyroid neoplasms because the diagnosis is mostly based on cytologic features: numerous oval nuclei with irregular nuclear membranes, finely granular (powdery) chromatin with several small marginally placed nucleoli, nuclear grooves imparting a coffee bean appearance, dense "squamoid" cytoplasm, and intranuclear pseudoinclusions. These pseudoinclusions are created by the invagination of the cytoplasm into the nucleus, therefore they are characterized by sharply defined edges and cytoplasmic staining qualities (Fig. 11.20). Certain cytological features reflect the characteristic histological features of papillary carcinoma: there may be papillae with or without fibrovascular cores in the aspirate of a conventional PC, and follicular structures in the aspirate of a follicular variant of papillary carcinoma (FVPC). Other possible findings include viscous stringy "bubble gum" colloid, multinucleated giant cells, and psammoma bodies. The latter are concentrically laminated calcifications believed to represent tips of papillae that became calcified.

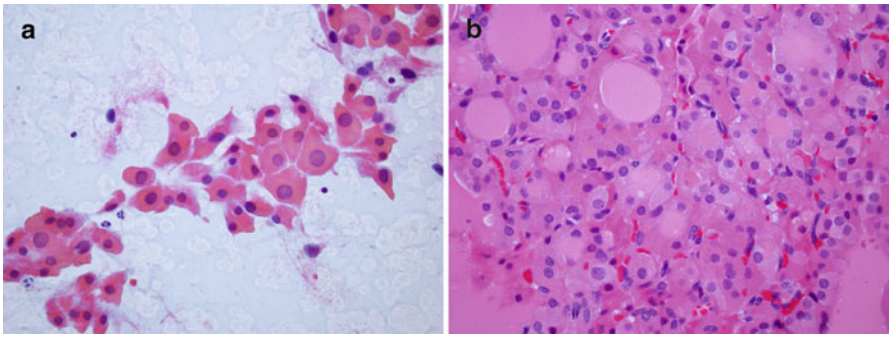

Fig. 11.19 Hurthle cell adenoma of the thyroid (35 year old man with thyroid nodule). (**a**) FNA of the thyroid nodule reveals numerous Hurthle cells with abundant orange-colored cytoplasm and round nuclei. The N/C ratio is still low despite the large nuclei. The smears were essentially devoid of colloid. Pap 400× (**b**) Histological section of the removed nodule shows Hurthle cells arranged mostly in microfollicles. The intracytoplasmic granules and the central nucleoli can be better appreciated than in the smear. The lesion was encapsulated without capsular or vascular invasion ruling out a Hurthle cell carcinoma. HE 400×

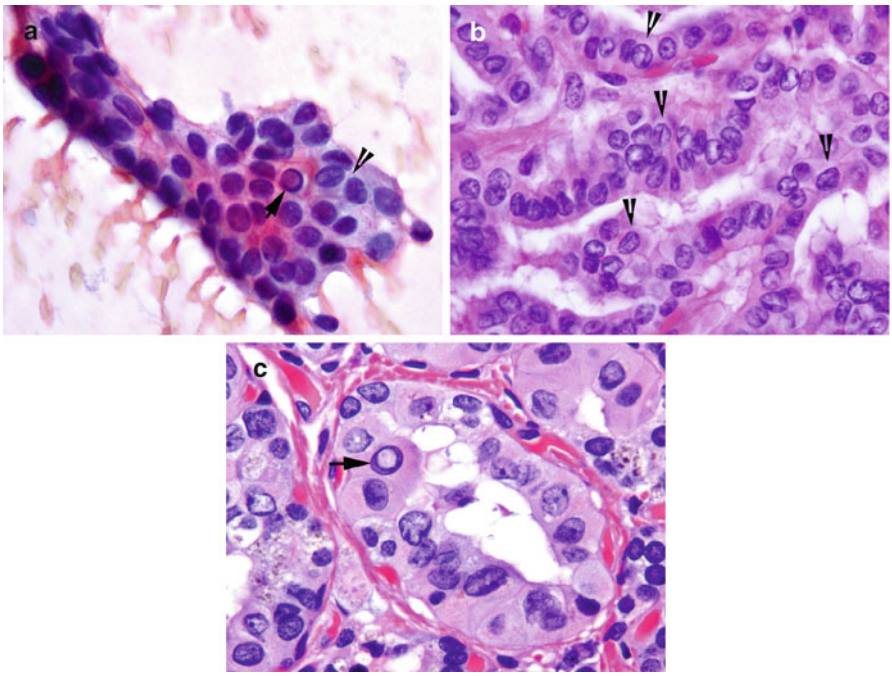

Fig. 11.20 Papillary thyroid carcinoma (43 year old woman with thyroid nodule). (**a**) Shown in the aspirate is a crowded group of follicular cells with nuclear grooves (*arrowheads*) and intranuclear pseudoinclusion (*arrow*). Pap 1000× oil (**b**) Nuclear grooves (*arrowheads*) and (**c**) intranuclear pseudoinclusion (*arrow*) are also seen in histological sections of the lesion. HE 1000× oil

None of these criteria alone is specific for the diagnosis of PC. (For example, nuclear grooves may be seen in chronic thyroiditis, hyperplastic nodules, follicular neoplasms, and intranuclear pseudoinclusions may be found in medullary carcinoma.) The more features of PC, the more certain the diagnosis of PC. False negative diagnoses, which occur in approximately 5% of cases, are predominantly due to PC variants. In one of these, in the FVPC, the tumor is composed of small to medium-sized follicles instead of papillae, and nuclear grooves and intranuclear pseudoinclusions are less common than in conventional PC (Fig. 11.16a). Furthermore, the abundant colloid in the aspirate of the macrofollicular variant of PC can closely mimic a benign follicular lesion. About 10% of PCs become predominantly cystic. In this case, the aspirate contains thin fluid, abundant histiocytes, and often scant carcinoma cells. Many times even these scant carcinoma cells are less typical than in conventional PC. The tumor cells have more abundant vacuolated cytoplasm and less prominent finely granular chromatin. The typical nuclear features of PC are also less prominent in the aggressive tall cell and columnar cell variants, which are characterized by tall cells and crowded clusters of columnar cells, respectively. In the oncocytic variant the carcinoma cells undergo oncocytic change, resembling a Hurthle cell neoplasm. In the Warthin-like variant of PC, the numerous lymphocytes and the oncocytic tumor cells together resemble Warthin's tumor of the salivary gland. Thus, careful attention to nuclear features is essential for all thyroid aspirates to avoid overlooking a PC.

Molecular testing of thyroid FNA samples may improve the diagnostic accuracy and help to reduce the number of cases falling into the "indeterminate" or "atypia of undetermined significance" category. Point mutations of the BRAF and RAS genes or RET/PTC rearrangements are found in more than 70% of papillary thyroid carcinomas [20]. RAS mutations or PAX8/PPAR gamma rearrangements are identified in about 75% of follicular carcinomas [21]. The data on these markers are fast accumulating. The guidelines of the American Thyroid Association already recommend the use of these molecular markers for indeterminate cytology to assist in guiding patient management [22]. In the future, aspirates of patients with PC may be tested for some markers, such as BRAF or RAS, to select the radioactive-iodine-resistant carcinomas and to apply molecular targeted therapy.

Poorly differentiated thyroid carcinoma, including its classic form, the **insular carcinoma**, may arise from either papillary carcinoma or follicular carcinoma. However, the bulk of the tumor no longer shows the features of either of those. Rather, it is composed of cellular islands of tumor cells separated by thin fibrous bands. Therefore, the FNA will usually reveal numerous crowded nests/three-dimensional clusters of relatively uniform, small follicular cells with high nuclear to cytoplasmic ratio. Apoptotic and mitotic forms are often present with necrotic debris in the background, reflecting the high turn-over of this aggressive tumor. A subset of poorly differentiated thyroid carcinomas shows predominantly isolated cells with coarsely granular chromatin. In these cases, the positive thyroglobulin and negative calcitonin and CEA immunostains help to distinguish it from medullary carcinoma.

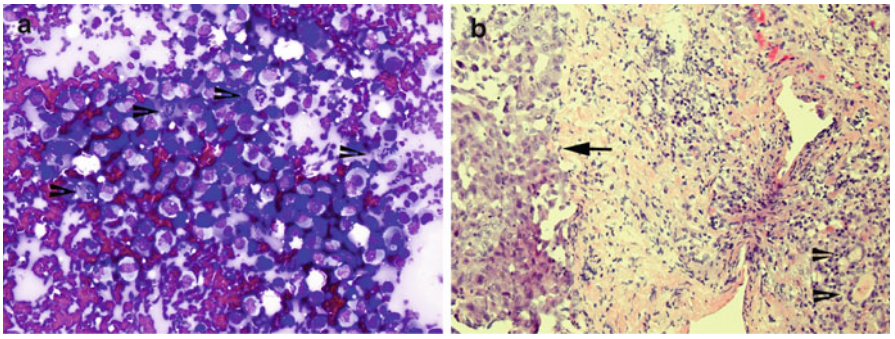

Fig. 11.21 Anaplastic thyroid carcinoma (46 year old woman with rapidly enlarging thyroid mass). (**a**) FNA reveals numerous highly atypical discohesive epithelioid cells with frequent mitotic figures (*arrowheads*). DQ 200× (**b**) Histological section of the lesion shows an infiltrating neoplasm composed of large epithelioid tumor cells with high grade features (*arrow*). These can be contrasted with the residual benign thyroid follicles (*arrowhead*). The tumor cells were cytokeratin positive by immunohistochemistry. HE 200×

The markedly aggressive **undifferentiated/anaplastic carcinoma** carries the poorest prognosis among primary thyroid carcinomas. The FNA yields cellular smears showing round to polygonal and/or spindle-shaped cells with significant size-variation, arranged in groups or dispersed individually in the background of acute inflammatory cells, fibrin, blood, necrotic cells, and debris (the so-called tumor diathesis). Sometimes bizarre and multinucleated tumor cells, plasmocytoid and rhabdoid cells, and osteoclast-like giant cells are present. There are often abnormal ones among the numerous mitotic figures (Fig. 11.21). Along with the loss of differentiation, this tumor loses its immunoreactivity for the usual follicular cell markers: TTF-1 and thyroglobulin. The majority still retains immunoreactivity for pan-keratin, which helps to differentiate the spindle cell-rich form of anaplastic carcinoma from the very rare primary thyroid sarcoma. Clinical correlation and imaging studies showing a thyroid-centered lesion are needed to exclude a metastatic malignancy.

Medullary carcinoma (MC) is a malignant neoplasm arising from the neuroendocrine parafollicular C cells of the thyroid. It accounts for 5–7% of thyroid carcinomas. While 25% of MCs are hereditary and can be the manifestation of a "multiple endocrine neoplasia syndrome", the great majority of MCs are sporadic. The hereditary MC is associated with germline point mutations in the RET proto-oncogene. In sporadic MCs various somatic RET mutations have been identified [23]. Cytologically, MC is characterized by anastomosing clusters or a mostly dispersed population of relatively uniform tumor cells. These can be spindled, plasmocytoid with excentric nuclei, or Hurthle cell-like with finely granular cytoplasm. The cytoplasmic granules appear red with a Romanowsky-type stain. The nuclei typically show the neuroendocrine-type coarsely granular "salt-and-pepper" chromatin with inconspicuous nucleoli. Intranuclear pseudoinclusions, also common in PC, are

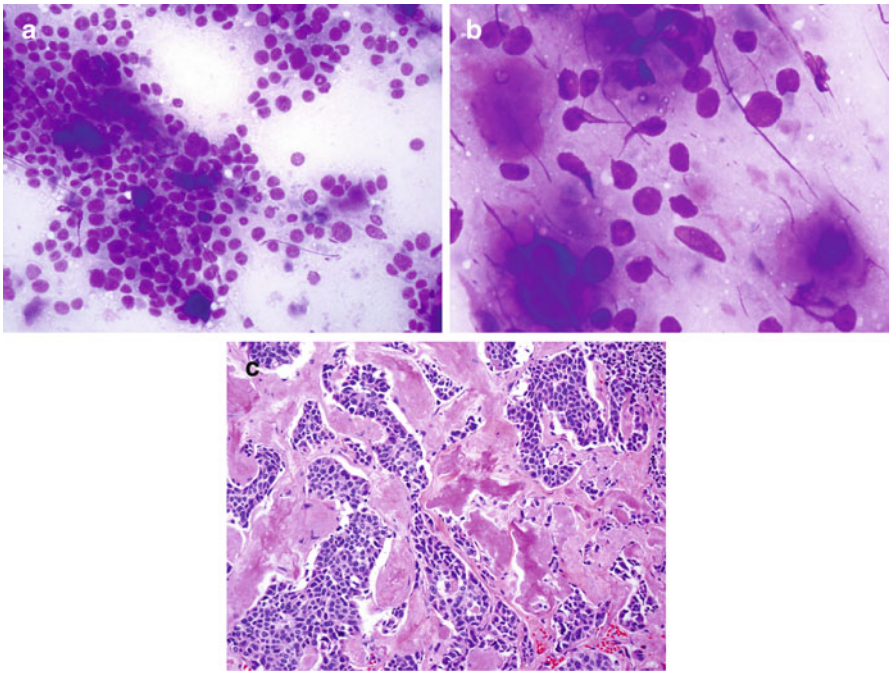

Fig. 11.22 Medullary carcinoma (61 year old man with thyroid mass). (**a**) Cellular smear showing round to elongated nuclei without prominent nucleoli. DQ 200× (**b**) At higher magnification, amyloid with dense, amorphous, waxy appearance can also be appreciated in addition to the bare nuclei of tumor cells. DQ 1000× oil (**c**) A representative section of the mass shows nests and sheets of relatively uniform tumor cells with mostly round nuclei and coarsely granular chromatin next to amyloid. HE 200×

found in at least 50% of MCs. However, careful observation of the coarsely granular salt and pepper chromatin in MC helps to distinguish it from PC, which has pale powdery finely granular chromatin. Up to 80% of MCs contains some amount of amyloid. Amyloid is a fibrous protein aggregate with amorphous dense waxy appearance. It is pink and indistinguishable from dense colloid with a Romanowsky-type stain (Fig. 11.22). However, Congo red stains amyloid orange-red with specific apple-green birefringence under polarized light.

Paragangliomas arise within the paraganglia of the autonomic nervous system, hence they may occur at several H&N sites. The carotid body tumor at the bifurcation of the common carotid artery is the most frequently aspirated. The cellular smears contain variably sized round to oval cells, occasionally with finely granular chromatin and intranuclear pseudoinclusions, in a microfollicle-like arrangement. These features may closely resemble those of a follicular neoplasm or medullary carcinoma of the thyroid. In the case of extrathyroid paragangliomas such as carotid body tumors, the lateral location away from the thyroid helps establish the diagnosis.

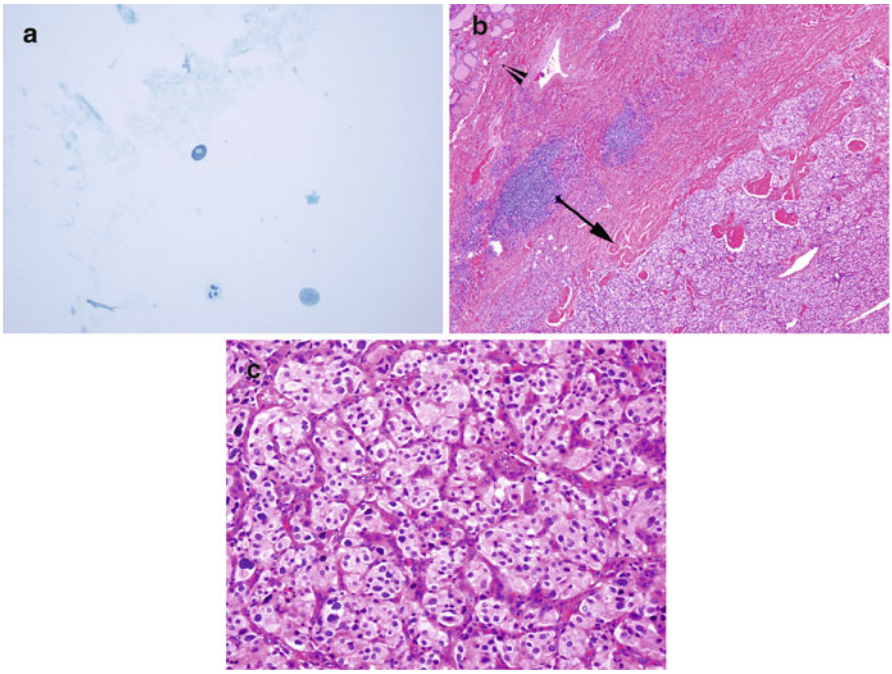

Fig. 11.23 Malignant paraganglioma of the thyroid (54 year old woman with thyroid mass). (**a**) Cellularity varies widely in aspirates of paragangliomas. Sometimes the smears contain mostly blood components and only rare tumor cells or bare nuclei with occasional pseudoinclusions, as in this case. The usual location of a paraganglioma at the carotid bifurcation helps to distinguish it from a papillary or medullary thyroid carcinoma, which must be entertained in the differential. Pap 40× (**b**) However, in this case, the tumor (*arrow*) was arising from the thyroid (*arrowhead*). On immunohistochemical studies, the tumor was found to be reactive with synaptophysin and chromogranin and non-reactive with calcitonin and keratins. S-100 highlighted sustentacular cells. Diagnosis of malignant paraganglioma was rendered based on these features as well as on tumor invasion into skeletal muscle and cricoid cartilage. HE 40× (**c**) A representative section of the mass shows the characteristic "Zellballen" pattern composed of nests of large polygonal cells, separated by richly vascular septa. HE 200×

However, primary paraganglioma of the thyroid has also been described [24] and this rare neuroendocrine tumor may occasionally be aspirated [25], causing significant diagnostic challenge. Negative immunocytochemical testing for thyroglobulin and calcitonin is helpful to distinguish a paraganglioma of the thyroid from a follicular neoplasm or medullary carcinoma, respectively. Separation of benign from malignant paraganglioma is difficult but the tumor diathesis, the more prominent nucleoli, and the mitotic figures favor a malignant process [26] (Fig. 11.23).

Primary thyroid malignant lymphomas, mostly non-Hodgkin's lymphomas, account for less than 5% of thyroid malignances. Secondary involvement of the thyroid by lymphoma is more frequent than primary thyroid lymphoma; about 20%

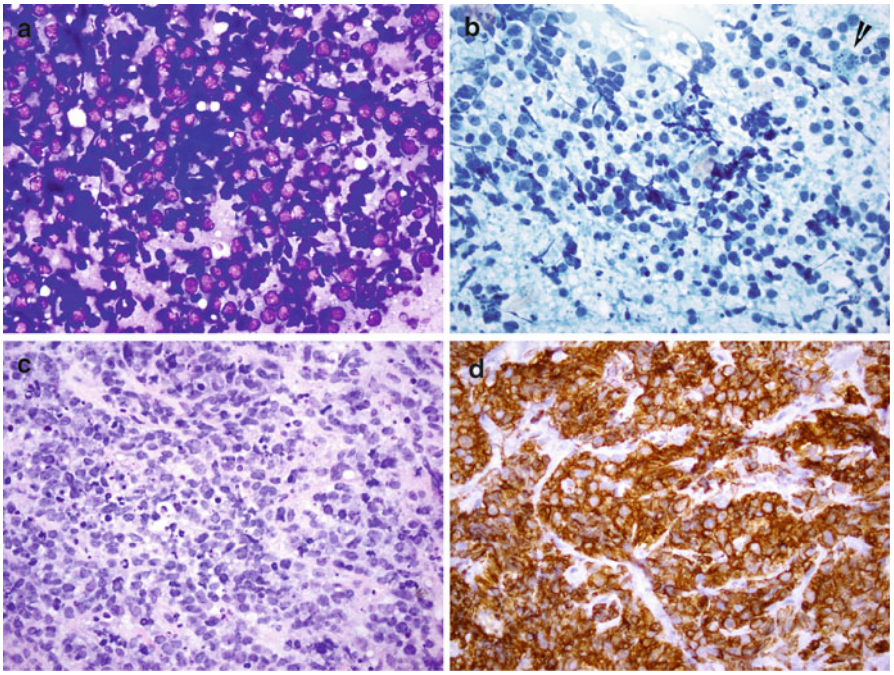

Fig. 11.24 Diffuse large B-cell lymphoma of the thyroid (70 year old woman with thyroid mass). (**a**) The cellular smear exhibits a monomorphous population of discohesive large lymphoid cells. There are many bare nuclei with coarse chromatin which are at least four times larger than those of the rare small lymphocytes in the background. DQ 400× (**b**) A tingible body macrophage (*arrowhead*) is seen beside the monomorphous population of large lymphocytes. Tingible body macrophages may accompany lymphomas with high turnover. Pap 400× (**c**) A representative histological section of the mass shows identical cells with several mitotic figures. HE 400× (**d**) The tumor cells are diffusely positive for CD20 by immunohistochemistry, confirming their B-cell origin. 400×

of patients with disseminated lymphoma demonstrate involvement of the thyroid. Most primary thyroid lymphomas are of B-cell origin (98%). The most common type (70%) is diffuse large B-cell lymphoma (DLBCL), with an aggressive clinical course. The other relatively common type is the indolent extranodal marginal zone B-cell lymphoma (mucosa-associated lymphoid tissue – MALT – lymphoma) comprising 6–27% of thyroid lymphomas. Two-thirds of lymphomas are preceded by Hashimoto thyroiditis. The aspirates of lymphomas are markedly cellular and composed of dissociated cells with coarse chromatin, one or more nucleoli, and lymphoglandular bodies best seen with Romanowky-type stains. Smears in DLBCL show a monotonous population of discohesive large lymphoid cells with moderate cytoplasm, course chromatin, and one or more prominent nucleoli. Flow cytometry or immunohistochemistry reveal CD20 positive cells with immunoglobulin light chain monoclonality (Fig. 11.24).

In MALT-lymphoma, the abnormal B cells appear in three forms: the small to intermediate-sized marginal zone B-cells with irregular nuclei, moderately dispersed chromatin and inconspicuous nucleoli; the intermediate to large monocytoid B-cells with open chromatin and abundant pale staining cytoplasm, and the sometimes dominating plasmacytoid cells. The distinction of this low-grade lymphoma from lymphocytic thyroiditis is sometimes problematic. Definitive diagnosis of lymphoma in cytological specimens may be facilitated by the documentation of a clonal lymphoid proliferation by flow cytometric immunophenotyping or immunocytochemistry, or by molecular techniques such as the polymerase chain reaction-based assay for immunoglobulin heavy chain gene rearrangement [27].

Metastatic tumors to the thyroid are rare, the reported incidence varying from 2.7 to 4%. The most frequent ones are renal, colorectal, lung, breast, melanoma, lymphoma, and H&N carcinoma metastases. The possible diagnosis of metastatic tumor should be entertained when the cytological features of the aspirated malignant cells are different from those of the previously discussed primary thyroid neoplasms. Information about a malignant tumor elsewhere in the body is of utmost importance. Especially when the features of the metastatic tumor are similar to those of a primary thyroid neoplasm: cytological features of metastatic renal cell and breast carcinoma can mimic those of a follicular neoplasm; metastatic papillary lung carcinoma can resemble papillary thyroid carcinoma; metastatic melanoma may be misinterpreted as medullary carcinoma. Negative immunocytochemistry for thyroglobulin and thyroid transcription factor-1 can assist in identifying a metastatic tumor.

11.5 Cytopathology of Cervical Lymph Node Lesions

Cervical lymphadenopathy is not a rare phenomenon. Palpable enlarged lymph nodes (LN) in the neck are often associated with infections but can also be the first sign of cancer. Cervical lymphadenopathy is present in over 30% of patients with H&N cancer when they first seek medical care [28]. FNA has become the primary method for the initial evaluation of LNs when are they suspicious for malignancy [29]. Ultrasound-guided FNA of cervical LNs has a sensitivity of 89%, specificity of 98%, and accuracy of 94.5% to diagnose the most common malignancy, metastatic squamous cell carcinoma [30]. Although previously regarded as limited in its use for diagnosing primary lymphoid malignancies, FNA in combination with immunophenotyping and molecular studies is gaining respect in providing accurate diagnosis of lymphoma. FNA combined with immunocytochemistry/flow cytometry has reached a sensitivity of 95.5% and a positive predictive value of 96.8% in the investigation of lymphoma presenting in the neck [31].

When evaluating the aspirate from a suspected LN, the first step is to confirm that, in fact, a LN was aspirated. The characteristic cytological features of a LN include lymphoid cells, which are discohesive cells with scant to moderate cytoplasm,

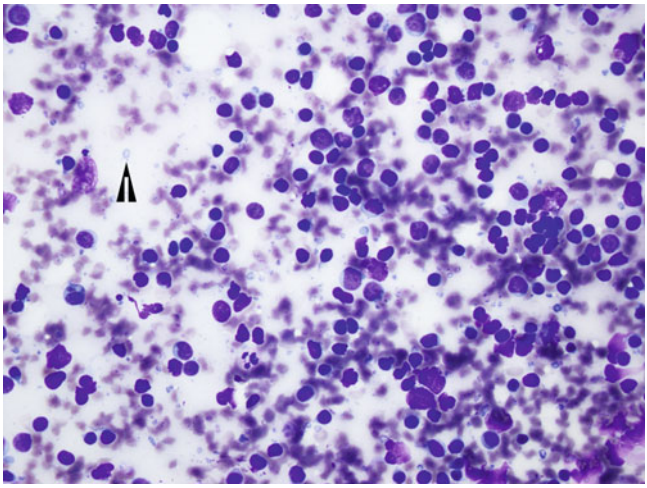

Fig. 11.25 The aspirate from a benign reactive cervical lymph node exhibits a polymorphous population of discohesive lymphoid cells and numerous lymphoglandular bodies (see *arrowhead*). DQ 400×

and lymphoglandular bodies (Fig. 11.25). The latter represent fragments of lymphocyte cytoplasms measuring up to the size of a red blood cell. Lymphoglandular bodies are best appreciated on Romanowsky-type stain as round pale blue bodies with lacy internal structure. The presence of these cells in the background are important in the identification of lymphoid tissue, as non-lymphoid "small round blue cell tumors" such as Ewing's sarcoma or small cell carcinoma may resemble lymphocytes. On the other hand, FNA of a LN, that is completely replaced by metastasis or becomes fibrotic/necrotic due to treatment effect, may not yield sufficient lymphocytes to be recognized as a LN.

Once it is established that the aspirate is derived from a lymph node, a metastatic neoplasm needs to be excluded. In general, FNA of LNs with metastatic neoplasms shows non-hematopoetic (carcinoma, sarcoma, or melanoma) cells in the background of polymorphous lymphoid cells. Most **metastatic carcinomas** exhibit cohesive groups of round-polygonal tumor cells with well-defined cytoplasm. However, metastatic melanoma and high grade SCCA may display a single cell pattern resembling a lymphoproliferative disorder.

SCCA is the most common neoplasm (90%) to metastasize to LNs in the H&E region [32]. The aspirate of **metastatic squamous cell carcinoma** is usually highly cellular. The hyperchromatic tumor cells are arranged in sheets and groups which have irregular borders with loosely attached cells hanging from their edges. The amount of scattered, independent neoplastic cells depends on the differentiation and cohesiveness of the tumor. The single cells often exhibit bizarre forms, including tadpole and spindle shapes. The keratinization is best demonstrated by Papanicolaou stain: the keratotic cells show dense orange color (orangeophilia) due to the affinity

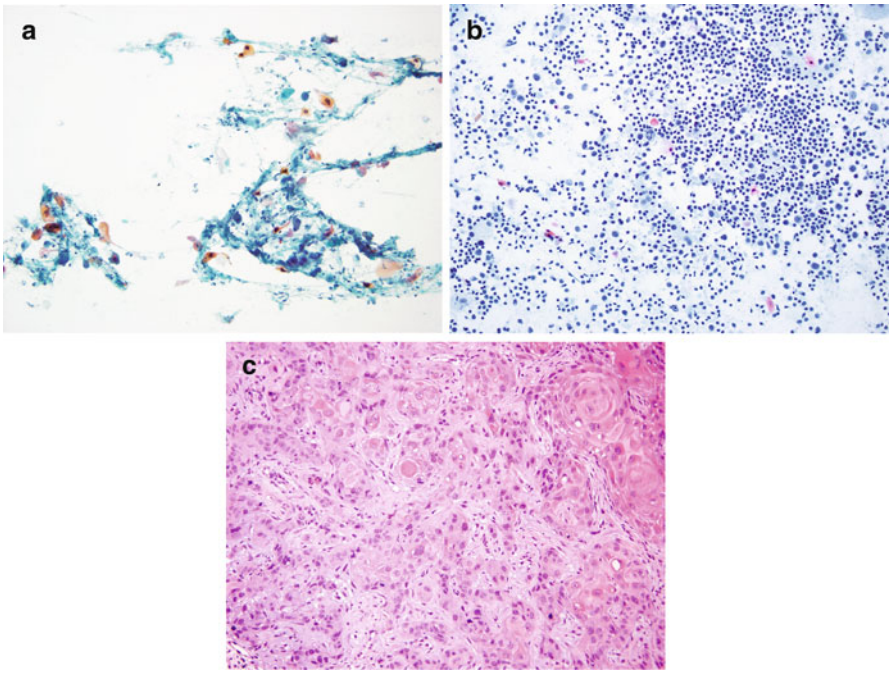

Fig. 11.26 Cervical lymph node with SCCA metastasis (50 year old man with enlarged neck LN). (**a**) The aspirate contains many large atypical cells, including a tadpole-like cell, with orange-colored cytoplasm and hyperchromatic nuclei. Pap 200× (**b**) Another smear shows the polymorphous lymphoid population, reactive to the metastatic orange-colored squamous cells. Pap 200× (**c**) The characteristic whorled pattern of SCCA and focal keratinization can be appreciated in the corresponding histological section. HE 200×

of keratinized squamous cells for one of the components of the Papanicolaou stain (Fig. 11.26). Cystic SCCA metastasis can present a significant diagnostic pitfall: if the metastasis and eventually the entire LN undergo cystic change, the often poorly cellular aspirates will show mostly dirty necrotic content and inflammatory cells with scant anucleate or mildly atypical squamous cells. These findings can easily be confused with an inflammatory process or a branchial cleft cyst. The possibility of cystic SCCA must always be kept in mind since the frequency of cystic SCCA metastasis varies from 9.1 to 21.5% depending on the site of the primary tumor [33]. Knowing that the patient has a primary SCCA, especially if that is in the H&N region, helps to avoid this mistake. However, in about 2–5% of cervical SCCA metastases, the location of the primary carcinoma is never discovered [34].

Some unique carcinoma types may also present diagnostic difficulties when they metastasize to LNs. Metastasis of the Epstein-Barr virus-related **undifferentiated nasopharyngeal carcinoma** may exhibit only scattered large carcinoma cells accompanied by abundant lymphocytes, some eosinophils, and occasionally granulomas [35]. Thus, it can be confused with lymphoma, especially Hodgkin's lymphoma,

if particular attention is not paid to the scant epithelial cells that mark for cytokeratin on immunocytochemistry. Epstein-Barr virus detection by in-situ hybridization in FNA specimens can be used as a supplemental tool to render this diagnosis [36]. **Basaloid squamous cell carcinoma**s and basaloid type salivary gland carcinomas occasionally exhibit numerous single cells with high nuclear to cytoplasmic ratio when they metastasize. They can be differentiated from lymphoma if the focal cohesive groups are not missed and their reactivity for cytokeratin is confirmed by immunocytochemistry. Rare reports of FNA of **metastatic sinonasal adenocarcinoma**, intestinal-type, describe moderately cellular smears with numerous naked, atypical nuclei, and rare signet ring-like cells in the background of abundant mucin [37].

If only lymphoid cells are present in a cervical LN FNA, it must be determined whether these lymphoid cells represent a benign lymphoid process or a malignant lymphoma.

Benign lymphoid hyperplasia due primarily to viral or bacterial infections is a common cause of cervical lymph node enlargement. The hallmark of a reactive LN is the *polymorphous* nature of the lymphoid cells. The mixed population displays a broad size spectrum ranging from small mature cells to large immunoblasts. The small mature lymphocytes with dark chromatin and scant cytoplasm always dominate (Fig. 11.25). Numerous tingible body macrophages can be seen. These are large cells with engulfed particles in their ample cytoplasm. Though tingible macrophages are most commonly found in reactive LNs, they may also be present in any high turnover lymphomas such as Burkitt's lymphoma or large cell lymphoma (Fig. 11.24b).

Certain specific reactive conditions can be distinguished by their unique features: in **infectious mononucleosis** some atypical large lymphoid cells, often with eccentric nuclei and pale open chromatin, are observed. In **cytomegalovirus infection,** numerous immunoblasts and characteristic intranuclear inclusions may be seen.

Some benign conditions exhibit an increased number of epithelioid histiocytes that aggregate providing a granulomatous appearance. These **granulomatous lymphadenopathies** include: infectious diseases (tuberculosis, fungi, toxoplasmosis, cat-scratch disease) with or without necrosis; dermatopathic lymphadenopathy associated with skin rash; Langerhans cell histiocytosis with eosinophils and grooved nuclei; sarcoidosis with non-necrotizing tight granulomas; Rosai-Dorfman disease with large histiocytes containing intact lymphocytes in their cytoplasm. The histiocytic aggregates should not be confused with the cohesive groups of atypical epithelial cells seen in metastatic carcinoma. An exception to the non-neoplastic nature of the granulomatous conditions is the granulomatous reaction associated with Hodgkin's disease.

Classic Hodgkin's disease (HD) is also an exception to the general guideline that polymorphous lymphoid population equals a benign condition. In HD the smears reveal a mixed background population, including lymphocytes, eosinophils, plasma cells, and histiocytes. However, Reed-Sternberg cells or their variants are the hallmark cytological findings in this condition. Reed-Sternberg cells are large cells with several irregular hyperchromatic nuclei and macronucleoli. They are CD15 and CD30 positive by immunochemistry (Fig. 11.27). A variant, the popcorn-shaped L&H cell in the lymphocyte predominant HD, has a different immunophenotype: it

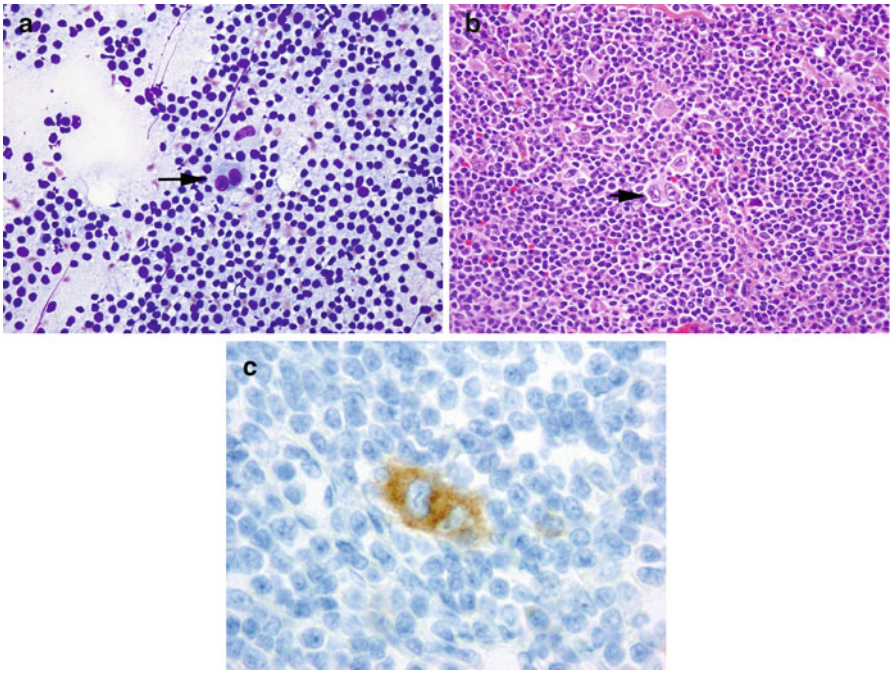

Fig. 11.27 Hodgkin's disease involving cervical lymph node (43 year old man with enlarged neck LN). (**a**) Shown in the aspirate is a typical large binucleated Reed-Sternberg cell with centrally located macronucleoli (*arrow*). DQ 400× (**b**) Histological section of the LN showing a Reed-Sternberg cell (*arrow*) and similar but mononuclear Hodgkin cells with a polymorphous lymphoid population in the background. HE 400×. (**c**) The Hodgkin and Reed-Sternberg cells are immunoreactive for CD15 and CD30 (the latter is shown) 1000× oil

is CD45, CD19, and CD20 positive. HD should always be considered in the differential diagnosis of persistent lymphadenopathy, especially if it is associated with fever, weight loss, and night sweats. Therefore, the cytopathologist must conduct an exhaustive search for the diagnostic, often rare Reed-Sternberg or L&H cells.

Non-Hodgkin's lymphomas are generally characterized by a *monomorphous* population of lymphoid cells. Although there is a variation in cell morphology between different types of lymphomas, within a particular lymphoma, the size and appearance of the cells are usually alike. The diagnosis of a specific lymphoma is based on cell morphology, immunophenotyping, and molecular studies as listed below.

Small lymphocytic lymphoma/chronic lymphoid leukemia: mature, small, round lymphocytes mixed with rare larger prolymphocytes; CD19, CD20, CD22, CD23, CD5 positive, CD10 negative monoclonal phenotype.

Mantle cell lymphoma: small to intermediate sized lymphocytes with irregular nuclear membrane and cleaved nuclei; CD19, CD20, CD22, CD5 positive, CD23, CD10, CD11c negative monoclonal phenotype; characteristic translocation t(11;14) by FISH analysis, reflected by Cyclin D positivity on immunocytochemistry.

Follicular lymphoma: small to intermediate sized lymphocytes with irregular nuclear membrane and notched/cleaved nuclei; CD19, CD20, CD22 positive, CD5 negative monoclonal phenotype, CD 10 positive in 60% of cases; t(14;18) translocation and IGH/bcl-2 fusion by molecular studies.
Marginal zone lymphoma: small to intermediate sized lymphocytes with round nuclei, small nucleoli, broad rim of lightly blue cytoplasm; CD19, CD20, CD22 positive, CD5, CD10 negative monoclonal phenotype.
Lymphoplasmocytic lymphoma: small plasmocytoid cells and plasma cells; CD23, CD5, CD10 negative, surface IgM positive, CD20 variable phenotype.
Lymphoblastic lymphoma: medium sized lymphoid cells with blast-type chromatin and scant cytoplasm; CD1, CD10, CD19, TdT, CD4/CD8 positive.
Burkitt's lymphoma: medium sized round lymphoid cells with nucleoli, narrow rim of basophilic cytoplasm with vacuoles; CD19, CD22 positive, TdT negative, CD10 variable monoclonal phenotype.
Diffuse large B-cell lymphoma: uniformly large atypical cells with irregular nuclear membranes and prominent nucleoli; more often positive for B-cell markers and shows monoclonality if surface immunoglobulin is not lost.

There are rare lymphomas in which the broad size-variation of the lymphocytes resembles a reactive process:

T-cell/histiocyte-rich B-cell lymphoma: an uncommon morphologic variant of diffuse large B-cell lymphoma with less than 10% malignant large B cells scattered amidst a majority population of reactive T lymphocytes and histiocytes. Accurate diagnosis of this entity is difficult and rests with careful immunohistochemical analysis of the tumor cells [38].
In other rare lymphomas the pleiomorphism of the lymphoid cells mimics a non-lymphoid neoplasm:
Anaplastic large cell lymphoma: pleiomorphic large highly atypical cells with frequent multinucleation, horseshoe shaped nuclei, abundant cytoplasm; majority are of T-cell, minority are of B-cell or null-cell origin with variable phenotype; characteristically CD30 positive, may be EMA positive; majority harbors the translocation of t(2:5) resulting in ALK protein dysregulation detectable by immunocytochemistry.

11.6 Cytopathology of Other Lesions of the H&N Region

The cytological features of sinonasal salivary gland-type adenocarcinomas are identical to those described in the section of salivary glands. The cytological features of intestinal-type sinonasal adenocarcinoma, SCCA, undifferentiated nasopharyngeal carcinoma, and paraganglioma were also discussed previously.

FNA of **sinonasal melanoma**s reveals cells identical to those in aspirates from cutaneous melanomas. Namely, FNA yields a highly cellular smear of poorly cohesive plasmocytoid to elongated, occasionally binucleated cells with macronucleoli, intranuclear pseudoinclusions, and frequent melanin pigment that appears as fine, dusty cytoplasmic granules.

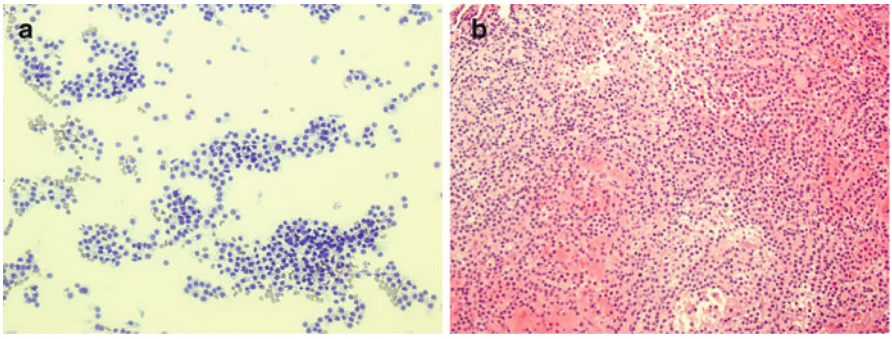

Fig. 11.28 Parathyroid gland (49 year old woman). (**a**) The smear reveals relatively uniform cells with evenly spaced round nuclei and indistinct nucleoli. DQ 200× (**b**) Identical cells are seen in the histological section. HE 200×

There are two malignant neoplasms unique to the sinonasal tract: the aggressive sinonasal undifferentiated carcinoma and the olfactory neuroblastoma, an uncommon neuroectodermal tumor of the superior nasal cavity. These tumors are rarely aspirated. According to scarce reports, **sinonasal undifferentiated carcinoma** yields hypercellular smears with a single-cell-predominant pattern and a background of naked nuclei and nuclear debris. The cells are medium-sized with irregular nuclear contours, small nucleoli, and mitotic figures. **Olfactory neuroblastoma** exhibits similar cellularity, cellular arrangement, and chromatin. In contrast, olfactory neuroblastoma demonstrates smooth nuclear contours, fibrillary cytoplasm, rosette formation, and absent mitotic figures [39].

Jaw lesions, including odontogenic tumors, are infrequently aspirated and FNA experience is limited. The cytological features of **ameloblastoma** are probably the most described. The hypercellular smears have two distinct cell populations: small, hyperchromatic, basaloid-type cells with peripheral palisading, and scattered larger cells with more open chromatin. Occasional fragments of mesenchymal cells with more elongated nuclei and ample, clear cytoplasm are also present. The rare malignant cases exhibit prominent cytologic pleomorphism, cellular crowding, molding and a high mitotic/karyorrhectic index [40].

Parathyroid cysts are rare, representing less than 1% of all neck swellings. They can present clinically as low neck masses and mimic a thyroid nodule. However, FNA can assist in formulating a correct preoperative diagnosis. The aspirate typically reveals clear, colorless and watery fluid that has an extremely high concentration of parathyroid hormone. Ultrasound-guided FNA combined with parathyroid hormone measurement has also been described in the preoperative localization of **parathyroid adenoma**s, with a specificity of 95% and sensitivity of 91% [41]. Cytological features of parathyroid lesions include discohesive cells or bare nuclei, about the size of red blood cells, which are mostly uniform but occasionally show marked variation in size (Fig. 11.28). In addition, some cells may be arranged in a nested pattern associated with capillaries [42].

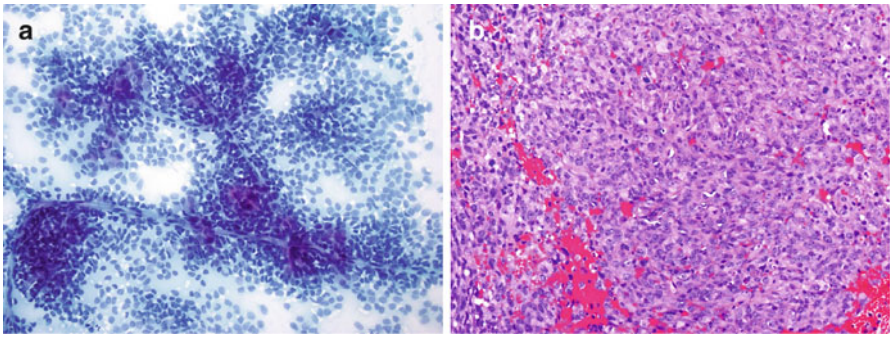

Fig. 11.29 Monophasic synovial sarcoma (35 year old man with oropharyngeal mass). (**a**) The cellular aspirate shows loosely cohesive clusters accompanying blood vessels with single cells hanging from the edges. The cells are oval or short spindle shaped, with scant or no cytoplasm. Pap 200× (**b**) Crowded sheets of these tumor cells with mitotic figures can be seen in the tissue biopsy. Immunohistochemical studies supported the diagnosis of synovial sarcoma, only 3% of which occur in the H&N region. HE 200×

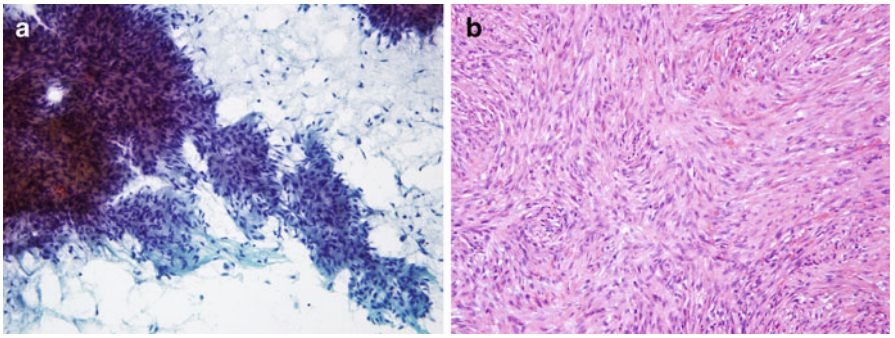

Fig. 11.30 Nodular fasciitis (29 year old woman with parotid mass). (**a**) Cellular smear showing haphazardly arranged spindle cells with wispy cytoplasm, in clusters and as single cells. Pap 200× (**b**) Histological section of the lesion shows haphazard bundles of bland spindle cells with a few typical mitotic figures and extravasated red blood cells. HE 200× This fast-growing benign pseudosarcomatous lesion may, though rarely, develop in the H&N area

A variety of mesenchymal proliferations can involve the H&N region. The cytologic features of the malignant mesenchymal neoplasms (angiosarcoma, leiomyosarcoma, rhabdomyosarcoma, osteosarcoma, chondrosarcoma, malignant fibrous histiocytoma, synovial sarcoma (Fig. 11.29), etc.), the benign mesenchymal neoplasms (Schwannoma, neurofibroma, etc.), and the mesenchymal tumor-like lesions such as nodular fasciitis (Fig. 11.30), are not different from those in other areas of the body. Two lesions stand out because they show preference for the H&N region: chordoma and extracranial meningioma.

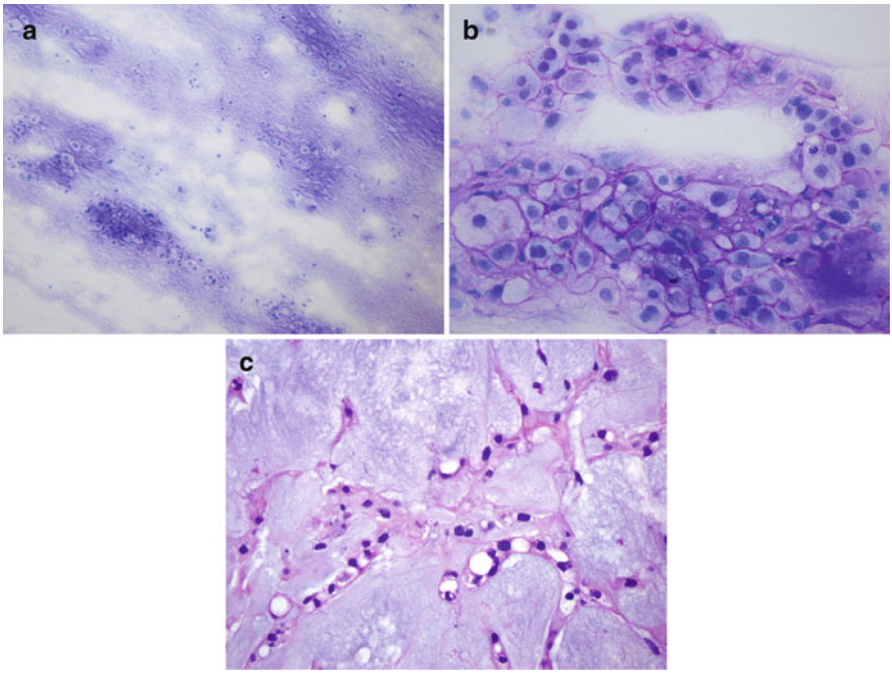

Fig. 11.31 Chordoma (62 year old man with vertebral column mass). (**a**) Shown in the smear preparation is sparse cellularity with prominent myxoid background. DQ 100× (**b**) The cells have rather uniform round-oval nuclei with distinct nucleoli and vacuolated cytoplasm. Occasional binucleate cells are seen. DQ 400× (**c**) Corresponding histologic section shows the vacuolated cells and the myxoid stroma. HE 400×

Chordoma is a malignant tumor that frequently arises from the base of the skull and may extend into the nasal cavity, maxillary antrum, or nasopharynx. The aspirate shows abundant myxoid-chondroid stroma, which has bright purple color with Romanowsky-type stains. Embedded in this stroma are small ovoid cells and large cells with vacuolated clear cytoplasm representing the diagnostic physaliphorous cells [43] (Fig. 11.31).

The rare **extracranial meningioma** has been reported in various H&N sites. The aspirate reveals many oval to spindle shaped cells, either by themselves or in larger groups. The cells have round nuclei, evenly dispersed fine chromatin, and small distinct nucleoli. Spindle-shaped cells in concentric whorles, and psammoma bodies characteristic of meningioma have also been described [44].

Finally, it is essential to discuss lesions which, by cytological examination, can be difficult to be distinguished from a cystic carcinoma metastasis:

Branchial cleft cysts, a result of developmental abnormalities of the branchial apparatus, usually arise at the anterior border of the sternomastoid muscle. They are lined predominantly by squamous epithelium, but minor columnar epithelial cell

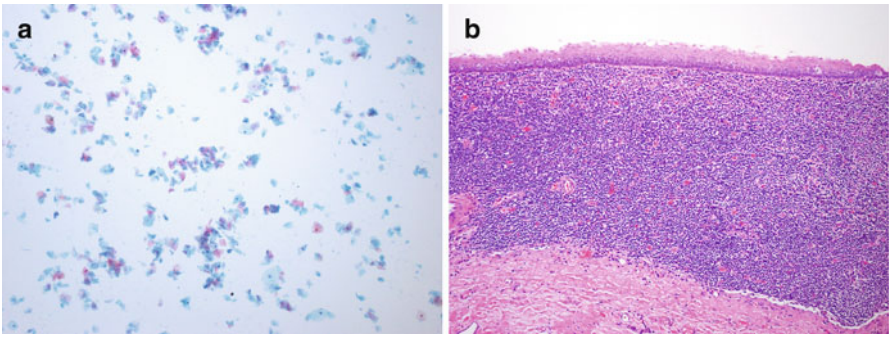

Fig. 11.32 Branchial cleft cyst (25 year old man with neck lesion). (**a**) The aspirated fluid contains mature squamous cells and anucleate squames. No hyperchromasia or atypical nuclei are seen. Pap 100× (**b**) Histological section of the cyst wall shows benign squamous epithelial lining rimmed by benign lymphoid tissue. HE 100×

lining may be present. FNAs of branchial cleft cysts yield thick yellow fluid which containing many anucleate squames, some squamous cells, and occasional columnar cells and lymphocytes. Amorphous debris with neutrophils is commonly seen in the background (Fig. 11.32).

Thyroglossal duct cysts show similar cytological features. These are cystic remnants of the embryonic thyroglossal duct and therefore are typically located in the midline of the neck near the hyoid bone. Although many thyroglossal duct cysts contain thyroid follicles adjacent to the squamous and ciliated columnar cell lining, follicular epithelium or colloid may rarely appear in the aspirate.

Epidermal inclusion cysts are superficial dermal cystic lesions of hair follicular and/or traumatic origin. They are lined by squamous epithelium and contain keratinous debris. When these cysts are ruptured, numerous neutrophils and foreign body-type multinucleate giant cells can be present in the smears, in addition to the anucleate squames and mature squamous cells (Fig. 11.33).

In markedly inflamed branchial cleft cysts, thyroglossal duct cysts, and epidermal inclusion cysts, the benign squamous epithelial cells may exhibit significant reactive atypia. In this case, the distinction from a well-differentiated SCCA that shows little nuclear atypia, may be difficult. The patient's clinical history and the lesion's exact location may provide some guidance. Particular attention should be paid to make sure that features of SCCA such as increased N/C ratio, nuclear hyperchromasia, or nuclear membrane irregularity are not present. On the other hand, clinically benign-appearing cervical cystic lesions may turn out to be malignant. In a study aimed to investigate the incidence of unsuspected carcinoma in routinely excised cervical cysts at a tertiary care teaching hospital, the incidence of unsuspected carcinoma in 196 consecutive cystic neck lesions initially diagnosed as branchial cleft cysts was 3.6% (6 metastatic squamous cell carcinoma and 1 metastatic papillary thyroid carcinoma were found) [45].

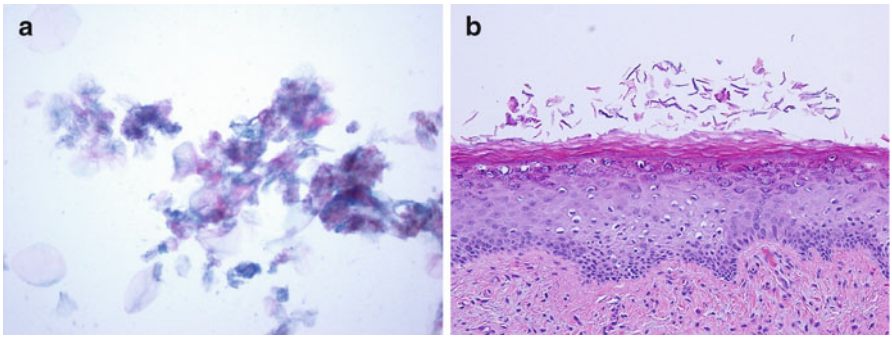

Fig. 11.33 Epidermal inclusion cyst (36 year old man with neck lesion). (**a**) Predominantly anucleate squames are present in the aspirate. Pap 200× (**b**) Histological section demonstrates the squames as they become detached from the surface of the cyst's benign keratinizing squamous epithelial lining. HE 200×

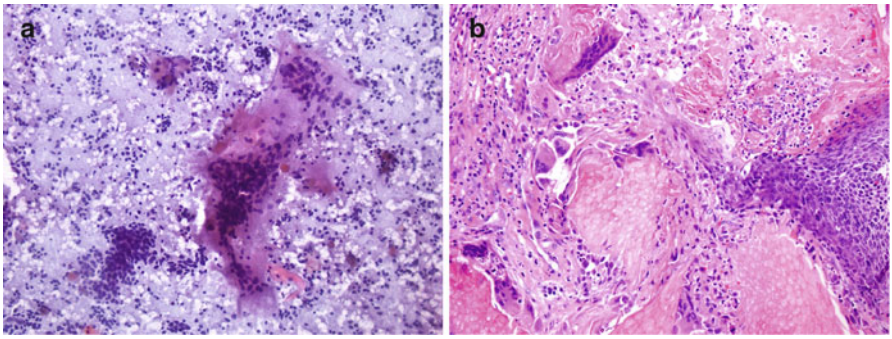

Fig. 11.34 Pilomatricoma (22 year old woman with facial mass superficial to the parotid). (**a**) The aspirate reveals basaloid cells, multinucleated giant cell, and keratinous debris. Pap 200× (**b**) Histological section of the lesion contains the characteristic elements: basaloid cells, ghost cells, keratinous debris, and multinucleated giant cells. HE 200×

Pilomatricoma (pilomarixoma, calcifying epithelioma of Malherbe) is a benign skin adnexal tumor that can be clinically mistaken for a cyst. It is composed of small basaloid cells, keratinous debris associated with foreign body-type giant cells, and ghost cells with abundant pink cytoplasm and an empty space that once contained the now absent nucleus. Therefore, in the aspirate of pilomatricoma, the cytologic features include a pink fibrillary material enveloping clusters of basaloid cells with high N/C ratio and evenly dispersed chromatin, multinucleated giant cells, and sheets of ghost cells which can resemble SCCA (Fig. 11.34). The recognition of the unique constellation of cytological features in the appropriate clinical context helps to distinguish pilomatricoma from carcinoma [46].

As demonstrated in this chapter, cytology is an invaluable diagnostic modality in the evaluation of H&N lesions. Though it should always be used in the context of the clinical presentation, cytology alone can usually distinguish a benign from a malignant process, and often successfully makes the final diagnosis. Its use in the preoperative setting often eliminates the need for surgery and effectively reduces the number of invasive procedures patients must undergo. Its role in the management of H&N lesions continues to evolve and expand as new, progressively more advanced techniques come into widespread use.

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Chapter 12
Squamous Cell Carcinoma of the Head & Neck and Cervix: Overlap and Distinctions

G. Kenneth Haines III

Contents

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"…a rose is a rose is a rose."

Gertrude Stein, 1913

Abstract The practice of medicine would be easier if the mathematical law of identity was as readily applicable in the biologic world. One illness is not the same as another. Within a single illness, cancer, for example, the spectrum of clinical significance ranges from none (low-volume, low-grade prostate carcinoma) to dire (glioblastoma multiforme, an aggressive form of brain cancer). Much of the success of medical research came about through attempts to progressively subclassify diseases into more uniform groups to facilitate their study.

In this chapter we focus on a single common histologic tumor type, squamous cell carcinoma, noting similarities and important differences that occur depending on origin in either the head & neck or the uterine cervix. Although smoking is the primary risk factor for head and neck carcinoma, and persistent infection with high-risk variants of the human papillomavirus (HPV) is essential for the development of cervical cancer, the story is more complex. Subsets of head & neck cancers have recently been linked to HPV infection, and epidemiologic studies consistently link smoking with cervical carcinoma. Distinct differences are beginning to emerge at the molecular level between smoking- and HPV-related squamous carcinoma. These new insights may bring us closer to telling when a rose actually is a rose.

Keywords Head & neck cancer • Cervix cancer • Squamous cell carcinoma • Human papillomavirus • Carcinogenesis

Abbreviations

CIN	Cervical Intraepithelial Neoplasia
CIS	carcinoma in situ
DNA	deoxyribonucleic acid
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
HSIL	high-grade squamous intraepithelial lesion
LOH	loss of heterozygosity
LSIL	low-grade squamous intraepithelial lesion
mRNA	messenger ribonucleic acid
N:C	nucleus to cytoplasmic ratio
URR	upstream regulatory region

12.1 Introduction

One of the most challenging requests I receive in surgical pathology (aside from questions about culturing microorganisms from formalin-fixed paraffin-embedded tissue) is to determine the site of origin for metastatic squamous cell carcinoma. This is not an unusual situation as smokers are at risk for carcinomas of the head and neck, lung, bladder, cervix and other sites. Histologically, conventional squamous cell carcinoma can be generally divided into keratinizing and non-keratinizing types, based on the presence or absence of whorls of keratin, referred to as keratin pearls (Fig. 12.1). There are several immunohistochemical markers that are useful in classifying a poorly differentiated neoplasm as a squamous carcinoma in defined settings. The combination of CK 5/6 and p63 is touted as highly sensitive and specific for squamous carcinoma [1]. Thus, a lung tumor positive for CK 5/6 and p63 and negative for TTF-1 (adenocarcinoma marker) and synaptophysin (a neuroendocrine marker) is reasonably classified as squamous cell carcinoma on core biopsy. The clinical context is important, as other tumors such as urothelial (bladder) and myoepithelial (salivary gland) carcinomas have the same immunoprofile. While immunohistochemistry has made the diagnosis of squamous cell carcinoma more precise, the same cannot be said for identifying the site of origin for a metastatic squamous carcinoma. Even with the wide variety of antibodies currently available, immunohistochemistry is of limited value in localizing a primary site [2]. This difficulty in distinguishing a head and neck squamous carcinoma from one arising in the lung, cervix or other site feeds the notion that all squamous cell carcinomas are alike. As a consequence, findings based on studies of

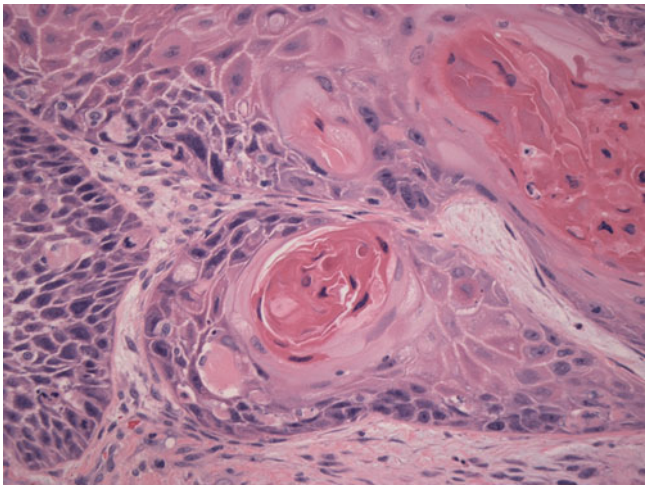

Fig. 12.1 Keratin pearl. In keratinizing squamous cell carcinoma, tumor cells accumulate keratin proteins within the cytoplasm as they mature from the periphery inward. As they die, they leave a rounded aggregate of keratin known as a keratin pearl

squamous carcinoma or precursor lesions from one site, may be applied (often without appropriate validation) to other sites. This chapter will compare and contrast squamous carcinoma of the head and neck and cervix, including their risk factors, molecular pathways, and assessment of precursor lesions. In the not too distant past, this would simply be a comparison between chemical carcinogen (tobacco smoke) and virally (HPV) induced cancer. With the recognition of a subset of HPV-related squamous carcinomas of the head and neck, this dichotomy is no longer tenable. Nature is more complex and subtle than the simplified models that we use to study (and teach) the natural sciences. Hence, medicine and pathology are reiterative processes, constantly refining or correcting what we "know", based on the acquisition of new findings.

12.2 Risk Factors

Squamous cell carcinoma of the head and neck has long been regarded as primarily a disease of middle age to elderly males who were chronic smokers and drinkers. Yet any large clinical practice comes across patients who do not fit that mold—an older female non-smoker or a young person with a minimal or no smoking history. Many of these cases show no evidence of a p53 mutation, suggesting the presence of a different mechanism of oral carcinogenesis [3]. As effective anti-smoking campaigns reduced the incidence of squamous cell carcinoma in some head and neck sub-sites, the incidence surprisingly rose in others, particularly in the oropharynx [4]. Epidemiologic studies identified a subset of such patients who tended to be young (<40–45 years), more likely to be non-smokers/non-drinkers, and whose tumors lacked a p53 mutation. This group of patients was more likely to have engaged in oral sex, raising the possibility that a sexually transmitted disease (HPV) was important in the pathogenesis of these cancers. Immunohistochemical and molecular studies subsequently confirmed the presence of HPV in the majority of these tumors.

12.2.1 HPV

Papillomaviruses are species- and tissue-specific, circular double-stranded DNA viruses. Hence, the human papillomavirus (HPV) only infects squamous epithelium of humans. Most viruses are subclassified by serotype, distinguished by immunologic means based on differences in surface antigens. HPV is different, in that it is classified by genotype—specifically by the genetic sequence of the L1 major capsid gene. More than 130 HPV types have been identified. Those subtypes with specificity for squamous mucosa are referred to as genital, anogenital or mucosal HPV, to distinguish them from others such as the HPV responsible for the common skin wart. The group of genital HPVs is further divided into high- and low-risk types,

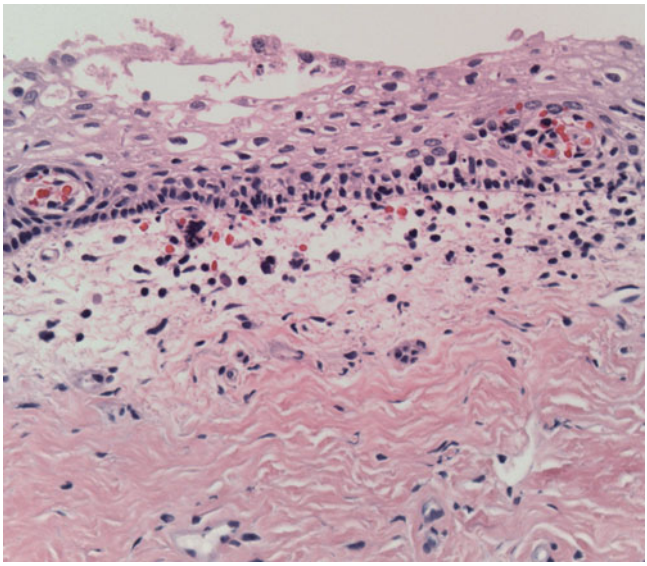

Fig. 12.2 Flat condyloma. HPV changes in cervical mucosa are manifested by enlarged, dark wrinkled nuclei surrounded by a clear space. Such koilocytes (halo cells) become apparent in the middle portion of the epithelium. Note the distinct single layer of basal cells at the bottom of the epithelium, excluding dysplasia

based on their ability to transform (immortalize) cells or their association with cervical cancer. Approximately 15 genotypes are currently classified as high-risk. HPV 16 and 18 are reported most commonly, with HPV 31, 33, 45, 52 and 58 accounting for a significant minority of cases, the last two being particularly common in Asia. Within the low-risk group, HPV 6 and 11 are the most frequent, producing wart-like or flat lesions called condylomas (Fig. 12.2).

Infection with HPV is extremely common, occurring in up to 80% of women [5]. The time of first exposure to HPV in the cervix corresponds to the onset of sexual activity, peaking between 18 and 30 years of age, and declining thereafter. About one third of cervical Pap smears in women ≤ 24 years of age are positive for a high-risk HPV, with 10–12% containing HPV 16 or 18 [6]. Fortunately, most cervical HPV infections do not result in cancer. We will take a closer look at HPV-mediated carcinoma below.

12.2.2 Smoking

Despite protests from tobacco companies and their paid spokespeople, the carcinogenic effect of tobacco smoking is quite clear [7].

Patients who are active smokers at the time of cancer diagnosis have an increased overall mortality compared to those who quit within the year preceding diagnosis,

or who were former smokers [8]. Patients who continue to smoke 2 years after their diagnosis are more likely to die from cancer than those who stopped [9].

12.2.3 Other Risk Factors

Smoking and drinking go together so often it is hard to tease out the effects of one from another. Alcohol causes a dose-dependent increase in the risk of head and neck cancer, particularly of the oropharynx and larynx. Alcohol appears to work synergistically with tobacco, as the combined risk is more than additive [10]. Alcoholism has been associated with a variety of immunologic and dietary deficiencies that may interfere with a patient's ability to kill tumor cells. Further, alcoholic patients with head and neck squamous cancer have lower survival rates than non-alcoholics, independent of patient age, tumor site, stage, grade or treatment [11].

Other important risk factors include chewing betel quid, containing a mixture of betel leaf, areca nut and slaked lime, with or without tobacco or other ingredients. The basic pH generates reactive oxygen species from components of the areca nut, contributing to the mixture's local carcinogenic potential.

12.3 HPV Carcinogenesis

12.3.1 HPV Attachment and Entry

Cervical squamous mucosa is surprisingly resistant to HPV infection. HPV simply cannot infect the mature keratinocytes lining the surface of squamous mucosa. In order for an infection to occur, the mucosa must be eroded, allowing the virus to bind to components of the underlying basement membrane. As immature basal keratinocytes (or stem-like cells) migrate into the area to heal the defect, HPV attaches to a cell surface receptor (likely α-6 integrin), and is transported into the immature cell through endocytosis. As HPV infection and cervical dysplasia are most commonly found in the transformation zone (the interface between the multilayered squamous epithelium of the ectocervix and the single cell layered glandular epithelium lining the endocervix), additional factors must be involved. Cells showing immature squamous metaplasia in the transformation zone may be directly susceptible to HPV infection, or the thin epithelium at this site may simply be more easily eroded, allowing HVP entry as above.

Once in the cytoplasm (referred to as an episomal location) of basal keratinocytes, the virus replicates, producing up to 100 copies of viral DNA, and begins transcribing a set of early (E) genes, including E6 and E7 (discussed below) at low levels. As the infected keratinocyte matures in the middle layers of the epithelium, viral replication accelerates, producing thousands of copies of HPV DNA per cell. At the same time, early gene expression increases and a maturation-dependent promoter drives the

expression of the late (L) genes coding for the structural capsid proteins. Complete infectious viral particles are assembled in the superficial layers [12]. Infection with HPV is self-limited in most women with intact immune systems. However, the infection becomes persistent in 10–15% of patients. It is this subset of women with persistent infection with a high-risk HPV type who are most likely to develop cervical cancer.

12.3.2 HPV Gene Products

HPV contains a circular double-stranded DNA, divided into early (E) and late (L) genes and an upstream regulatory region (URR). Messenger RNA (mRNA) transcripts are polycistronic, meaning that a single strand of mRNA, utilizing several splice donor and acceptor sites, encodes multiple polypeptides. There are two major promoters that induce transcription of viral mRNA. The early promoter (termed p97 or p105, depending on the HPV type) is located upstream of the early genes, and is active in both immature and mature keratinocytes. Thus, early genes are expressed (at some level) in all infected keratinocytes. Expression of the late genes is under the control of a differentiation-inducible promoter (p670 or p742), which is active only in maturing keratinocytes in the mid to upper epithelial layers. The early genes are important for viral replication and maintaining the virus within infected cells, often through interaction with regulatory proteins of the host. It is this interaction of early genes, particularly E6 and E7, with the protein products of the tumor suppressor genes, p53 and pRb that are responsible for most of the carcinogenic potential of HPV.

HPV E6 is a multifunctional protein that acts as a transcriptional transactivator or repressor, interacts with a number of cellular proteins, and is capable of inactivating the tumor suppressor gene p53. While several mechanisms for this latter action exist, the primary method appears to be through the formation of a complex with a ubiquitin-ligase (E6AP, E6 associated protein) and p53. This results in the addition of a small regulatory protein (ubiquitin) to p53, targeting it for proteosomal degradation. In the presence of DNA damage or other cellular stress, intact p53 blocks cell cycle progression, allowing time for DNA repair, and / or induces programmed cell death (apoptosis). The E6-mediated degradation of p53 prevents these protective mechanisms.

While E6 primarily blocks cell death, E7 promotes cellular proliferation through its interaction with the retinoblastoma gene product, pRb, a key regulator of cell cycle progression. Hypophosphorylated pRb binds and sequesters E2F, a transcriptional activator, into an inactive complex. Under appropriate growth signals, pRb is phosphorylated by cyclin-dependent kinases, releasing E2F. The free E2F prompts the cell to move into the S (synthesis) phase of the cell cycle, leading to cell proliferation. E7 binds pRb, preventing its regulation of E2F activity. The E7 has also been reported to bind to a protein in chromosomal centromeres, interfering with chromosomal segregation. This may account, in part, for the aneuploidy (abnormal number of chromosomes) common in cervical cancer [13].

The continuous expression of E6 and E7 is critical for the development and maintenance of cervical cancer. Inhibition of E6 and E7 in the famous human

cervical cancer cell line HeLa, blocks cell proliferation [14]. Repression of E7 expression leads to the regression of in situ and invasive cervical carcinoma in a transgenic mice model [15].

Although E6 and E7 are present in both high-risk and low-risk HPV types, those from high-risk types bind p53 and pRb, respectively, much more tightly than the same proteins from low-risk HPV types. In fact, E6 from low risk HPV does not bind appreciable amounts of p53. Further, integration of viral DNA commonly occurs only in high-risk HPV types, leading to higher levels of E6 and E7 expression than generally found in episomal HPV.

12.3.3 Episomal vs. Integrated

HPV can remain in the cell cytoplasm as an episomal (extrachromosomal) circular DNA, or can be integrated into a host chromosome. For integration to occur, the circular DNA of HPV usually breaks within (and therefore disrupts) the E2 early gene. The point of insertion into the host DNA occurs at fragile sites (hot spots) and in transcriptionally active regions, which may disrupt an important host gene [16]. This integration is associated with an increase in genomic instability, altered viral gene expression and increased stability of viral mRNAs [17]. The disruption of E2 is important in cervical carcinogenesis. E2 normally functions to repress many of the HPV early genes, including E6 and E7, maintaining a low copy number of the viral genome in the immature basal keratinocytes. With the loss of E2, E6 and E7 levels increase, enhancing their action on p53 and pRb. It is important to note that viral integration is not required for carcinogenesis, and when present, is not sufficient to produce cancer. Other factors, such as host immune response and genetic polymorphisms of key regulatory proteins or presence of co-existing risk factors may be determinative.

12.3.4 Cervical vs. Head and Neck HPV-Mediated Carcinogenesis

The scenario of HPV-mediated carcinogenesis in the head and neck region is similar to that of the cervix, with a few notable exceptions. An equivalent of the transformation zone does not exist in the head and neck. The areas where squamous mucosa merges with columnar respiratory epithelium are not the most frequent sites for HPV-associated carcinoma. Instead, the tonsilar crypt epithelium of the oropharynx is a major site of HPV infection and subsequent tumor formation. A second difference between cervical and head and neck cancer is that both high- and low-risk HPV types have been identified in head and neck squamous cell carcinoma, although the former are significantly more common. A third difference is in the morphology of HPV-related squamous carcinomas. Poorly differentiated basaloid squamous carcinoma is

the prototypical HPV-associated cancer in the head and neck. As essentially all cervical carcinomas are HPV-related, these tumors run the spectrum from well to poorly differentiated and keratinizing to non-keratinizing (see below and Chap. 9).

12.4 Smoking Carcinogenesis

12.4.1 Carcinogens in Tobacco Smoke

More than 30 known human carcinogens can be found in tobacco smoke, including polycyclic hydrocarbons and free radical generators. In addition to various cytotoxic effects, these reactive species can directly damage DNA, resulting in the progressive accumulation of acquired mutations.

12.4.2 Smoking-Related Mutagenesis

The development of head and neck squamous cell carcinoma is thought to be a multistep process, with progressive accumulation of mutations leading to invasive cancer. Loss of heterozygosity (LOH) at 3p14 and 9p21 are early changes seen in premalignant oral lesions [18]. Inactivation of CKKN2A (p16), located at 9p12, either by deletion or promoter methylation removes an inhibitor of cell cycle progression. There are several putative tumor suppressor genes in the region of 3p, including VHL (3p25-26) and FHIT (3p14.2) and the DNA mismatch repair gene, hMLH1 (3p21.3). Each of these appears to be involved in a proportion of cases [19]. Mutation of the TP53 tumor suppressor gene at 17p13.1, followed by amplification of the cyclin D1 gene (CCND1 at 11q13) appear to be early changes, commonly identified prior to the development of invasion.

Whole exome sequencing of invasive squamous cell carcinomas shows frequent mutations of genes regulating cell proliferation (TP53, CDKN2A, PTEN, PIK3CA and HRAS), or squamous differentiation (NOTCH1, IRF6 and TP63) [20].

The specific genetic alterations in head and neck squamous cell carcinoma show some racial differences, with losses of the CDKN2A (p16) gene and gain of the SCYA3 gene (associated with both a lymphocytic response to tumor and the presence of lymph node metastasis), more frequently seen in African-American than Caucasian patients [21].

12.4.3 DNA Repair Mechanisms

Given the mutagenic properties of the carcinogens in tobacco smoke, it would be unsurprising that host factors, particularly polymorphisms of DNA repair genes

account for some of the individual differences in susceptibility to the carcinogenic effects of smoking. There are multiple mechanisms for repairing damaged DNA. Some are useful when a single DNA strand is damaged (e.g. nucleotide excision repair (NER) and base excision repair (BER)); others repair double-strand breaks (recombination repair (RR)). The NER pathway plays an important role in removing bulky helix-distorting lesions, primarily nucleotides damaged by UV-radiation and other mutagens. The BER pathway removes smaller lesions, predominantly bases that have been modified by alkylation or other process, interfering with proper hydrogen bonding to their base pair. The data suggest that these have only a minor effect on susceptibility to head and neck cancer [22].

12.5 Key Molecular Pathways

Three key tumor suppressors show major differences between HPV-positive and HPV-negative (i.e. carcinogen-related) squamous cell carcinoma. Mutations or epigenetic silencing is commonly found in the TP53, RB1 and CDKN2A genes in carcinogen-related squamous carcinoma, resulting in absence or loss of function of p53, pRb and p16, respectively. HPV-related squamous cell carcinoma, both of the head and neck and cervix, rarely shows such mutations. Instead, HPV produces proteins that result in the rapid degradation of p53 and pRb. In contrast to the absence or low-level expression of p16 in carcinogen-related squamous carcinoma, p16 is almost invariably overexpressed in HPV-related squamous carcinoma. At this point, it is worthwhile looking more closely at these proteins and some of the key signaling pathways altered in squamous carcinogenesis.

12.5.1 p53

Inactivation of p53 appears to be a critical feature for the development of squamous cell carcinoma. A mutation in TP53 can be detected in 60% of all head and neck squamous cell carcinoma cases; HPV-related inactivation of p53 is seen in an additional 20% [23]. Other mutations upstream or downstream of p53 in its regulatory pathways may account for some of the remaining cases.

P53 is normally a short-lived protein. Under conditions of cellular stress, the protein is stabilized and accumulates. P53 is activated through several stress-specific pathways. For example, double-stranded DNA damage activates an ATM (ataxia telangiectasia mutated)-mediated pathway, while some oncogenes activate p14arf, blocking the p53 inhibitor HDM2. Activation of p53, through phosphorylation of specific serine residues, increases its stability and ability to bind DNA, inducing transcription of target genes. Variations in the sensitivity of different response elements to p53 helps regulate which set of genes are expressed. At low

levels, p53 promotes transcription of proteins involved in cell cycle regulation, blocking cell proliferation. Higher levels of p53 induce transcription of apoptotic proteins [24]. Thus, inactivation of p53 interferes with growth regulation and the ability to respond to DNA damage [25].

12.5.2 pRb

The product of the retinoblastoma gene, pRb is an important regulator of cell cycle progression. Like many proteins, the activity of pRb is regulated by its phosphorylation status. Hypophosphorylated pRb binds to and sequesters the transcriptional activator E2F, preventing the G1 to S phase transition. The E7 protein of high-risk HPV effectively binds pRb (and the closely related p107 and p130 proteins), inducing their degradation. E2F is released and cell cycle progression commences [26]. Mutation of the RB1 gene in smokers can abrogate this regulatory mechanism. However, deletions are seen in only 30–35% of cases, and in fewer than 10% of precursor dysplastic lesions (see below). Alterations in associated pRb interacting proteins may interfere with pRb function despite normal pRb [27].

12.5.3 p16

The immunohistochemical expression of p16 ($p16^{INK4A}$, CDKN2A) is often used as a surrogate for HPV infection in both head and neck and cervix. In normal, uninfected cells, when appropriate growth signals direct the phosphorylation of pRb and subsequent release of E2F, free E2F translocates to the nucleus to induce transcription of proteins necessary for cell cycle progression. In addition, it induces transcription of p16. As p16 protein levels increase, they block phosphorylation of pRb by a cyclin D-CDK4/6 complex, enabling pRb to again sequester E2F and stopping cell cycle progression. In carcinogen-related head and neck carcinogenesis, p16 levels are decreased through genetic or epigenetic mechanisms in a highly variable percentage of cases [28]. Loss of p16 abrogates this negative feedback loop, allowing continued cell cycle progression and resulting tumor growth. In an apparent contradiction, p16 is highly overexpressed in HPV-related squamous carcinomas, yet fails to stop cell cycle progression. These cells are able to proliferate despite supernormal levels of p16 due to HPV E7-mediated degradation of pRb. There simply is not enough available pRb to sequester E2F. Released from this control, free E2F continues driving cell proliferation and the production of more p16. This dependence on E6 and E7 to circumvent host regulatory mechanisms explains why the continued presence of these proteins are absolutely required for the survival of HPV-associated cancer cells.

12.5.4 EGFR and Signaling Pathways

In addition to p53, pRb and p16, alterations in receptors for growth factors, cytokines or other ligands or their associated downstream signaling pathways play important roles in tumor biology. EGFR (epidermal growth factor receptor) is overexpressed in the vast majority of head and neck and cervical squamous cell carcinomas. Upon binding of epidermal growth factor (EGF) or other ligands (e.g. transforming growth factor-alpha, TGFα) to EGFR, the receptor activates signal transduction pathways leading to cell growth and proliferation. With overexpression of EGFR, tumor cells respond to lower levels of growth signals than normal cells, providing a growth advantage. In addition, some head and neck squamous cell carcinomas have a mutated EGFR gene, producing a truncated receptor that is constitutively active. Whether similar mutations are present in cervical squamous carcinoma is not clear [29].

Activated EGFR signals through several pathways, including PI3K/Akt/mTOR, MAPK/ERK and JAK/STAT3. While there are distinct differences between the pathways, they generally integrate signals from cell surface receptors sensing the availability of nutrients and growth factors. Activation of these pathways promotes cell growth and proliferation, and inhibits cell death (apoptosis).

VEGF (vascular endothelial growth factor) is interesting in that it promotes tumor growth through actions on the surrounding non-neoplastic stroma, rather than directly modulating pathways in the carcinoma. Tumor cells produce VEGF in response to tissue hypoxia or EGFR/STAT3 signaling. VEGF is then secreted into the extracellular environment, where it binds receptors on endothelial cells (VEGFR2), promoting the growth of new blood vessels needed to support an enlarging tumor. Identification of specific mutations in a receptor or signal pathway component creates opportunities for targeted molecular therapies, some of which are under investigation or are now used in routine clinical practice [30, 31].

12.6 Precursor Lesions

Precursor lesions to invasive carcinoma are termed “dysplasia”, literally abnormal growth. In practice, this refers to a neoplastic, potentially malignant, epithelial proliferation that has not invaded into the stroma. Dysplasia is often graded on a two-tiered (low-grade vs. high-grade) or three-tiered (mild, moderate or severe) scale, based on the degree of deviation from normal epithelium. We will start with cervical dysplasia, which has been studied most extensively. Concepts and criteria developed in this setting have been applied to other sites, including the head and neck.

As noted, the E6 and E7 proteins of high-risk HPV types maintain cells in a proliferative state and delay cellular maturation. This manifests as increasing thickness of the normally single layer of basal cells and upward extension of mitotic figures beyond the parabasal zone. Thus, cervical dysplasia is often manifested as a delayed maturation, rather than progressive cytologic atypia (larger nuclei with

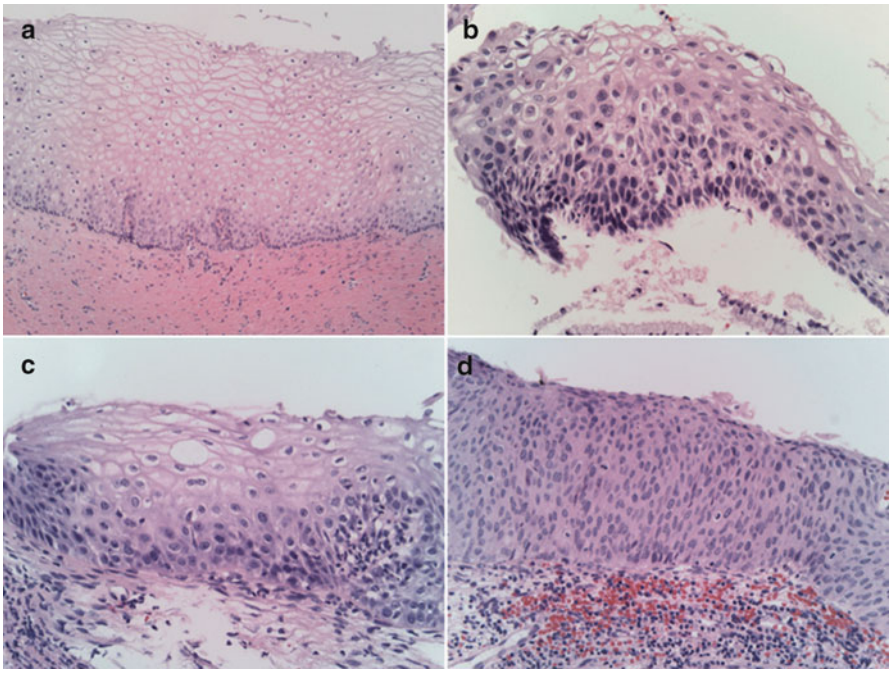

Fig. 12.3 Cervical Intraepithelial Neoplasia (*CIN*). (**a**) Normal cervix. Note the single distinct layer of basal keratinocytes at the bottom of the epithelium. Cells immediately above begin to mature, with paler nuclei and more cytoplasm. (**b**) CIN1. Basal keratinocytes extend a short distance upward into the epithelium. The cells acquire light pink cytoplasm, a sign of maturation, in the lower third of the epithelium. Koilocytes are apparent in the mid and upper levels of the epithelium in this example. (**c**) CIN2. Immature cells with high N:C ratios extend upward in the epithelium. Mitotic figures may be seen in the mid-level. (**d**) CIN3. The cells at the base of the epithelium are essentially the same as those near the top. Only the uppermost layers show evidence of maturation, with flattened nuclei. Mitotic figures are seen in all levels of the epithelium

marked variation in size, shape, staining characteristics). This will be an important point of distinction when considering dysplasia in the head and neck region.

12.6.1 Cervical Dysplasia

Dysplasia in the cervix is quantified using the CIN (Cervical Intraepithelial Neoplasia) system for tissue specimens (cervical punch biopsy, endocervical curettage, cervical cone biopsy, hysterectomy) and the SIL (Squamous Intraepithelial Lesion) system for cytologic specimens (Pap smear, cervical brush, conventional or liquid-based preparations). Under the CIN system, cervical dysplasia is graded as mild (CIN1), moderate (CIN2) or severe (CIN3) (Fig. 12.3). In normal, non-dysplastic cervical epithelium, the basal cells (small cuboidal cells with scant cytoplasm—hence a high

nucleus to cytoplasmic (N:C) ratio) are limited to a single layer. The cells immediately above, the parabasal cells, have distinctly more cytoplasm, giving evidence of cellular maturation. Mitotic figures, rare in normal cervical mucosa, appear in this area. As maturation continues, the cells become larger (cytoplasm much more than nucleus), yielding a low N:C ratio (Fig. 12.3). In CIN1, basal cells comprise more than one cell layer, but maturation still begins in the lower third of the epithelium. Mitotic figures are more frequent than normal but are generally limited to the lower third of the epithelium. In CIN2, the maturation process is significantly delayed, with basal cells filling up to two thirds of the epithelial thickness. There is often, but not always, significantly more nuclear pleomorphism than in CIN1. Mitotic figures are more abundant, and atypical forms may be seen. CIN3 is designated when the immature basal cells involve more than two thirds of the epithelial thickness. When they replace the full epithelial thickness, the term carcinoma in situ (CIS) was formerly applied. As the behavior of CIS and CIN3 are identical, both lesions are now classified simply as CIN3.

This system correlates well with the biologic behavior of the lesion, and is thus useful for managing patients. Lesions meeting criteria for CIN1 frequently regress without treatment and only 20–30% progress to CIN2 or CIN3. Patients with CIN1 therefore are good candidates for observation. Lesions designated as CIN2 or CIN3 rarely regress, and about 20% eventually progress to invasive cancer if untreated. These lesions should be excised (often with a cervical cone biopsy) with assessment of the specimen margins.

The SIL system, or Bethesda system, is applicable to cytologic specimens. Instead of having a full-thickness piece of tissue, where one can see the maturation process from basal layer to the surface, cytology specimens obtain cells only from the surface of the epithelium. While it may be obvious that such tests can detect abnormal cells in a lesion with little or no maturation (CIN3/CIS), the delay in maturation with lower degrees of dysplasia is not fully compensated for by the time the dysplastic keratinocytes reach the surface. While CIN1 cannot reliably be differentiated from a non-dysplastic HPV infection (flat condyloma) on cytology, neither lesion needs excision and can be followed clinically. These are termed “LSIL” for low-grade squamous intraepithelial lesion. This clustering is one reason for using the term “lesion” instead of “neoplasia”. As the treatment of CIN2 and CIN3 is the same, the Bethesda system collapses these into HSIL (high-grade squamous intraepithelial lesion). Figure 12.4 compares a normal cervical cytology with LSIL and HSIL. There are more subtleties and categories within the Bethesda system, but this summary should suffice to consider the assessment of dysplastic squamous lesions in the head and neck.

12.6.2 Oral Dysplasia

While the histopathologic assessment of dysplasia is similar throughout the head and neck region, because of its accessibility, the oral mucosa serves as the model.

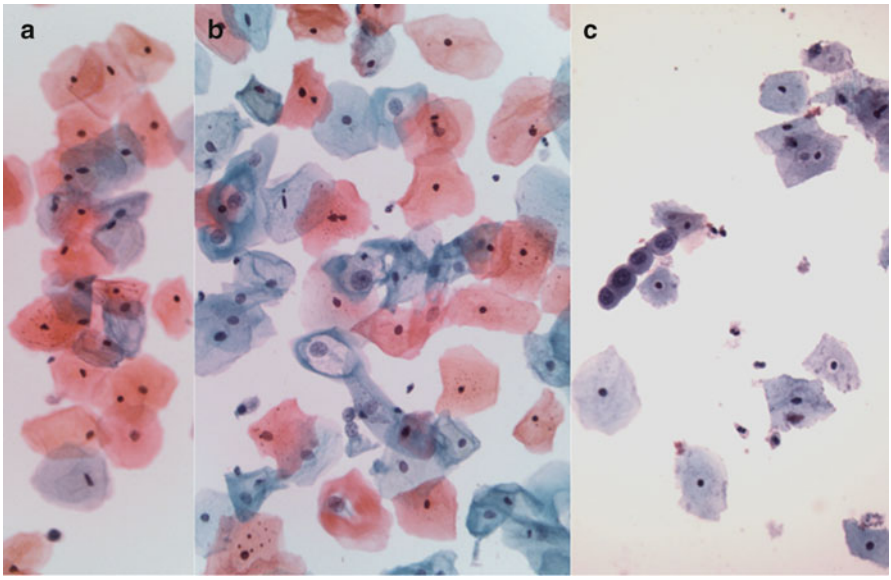

Fig. 12.4 Cervical cytology. (**a**) Normal keratinocytes from the surface of the cervix. Note the uniform small oval nuclei and abundant orange or green cytoplasm. (**b**) LSIL represents either HPV infection or mild dysplasia. Note the enlarged and light-staining nuclei, often with a pale perinuclear halo. Despite the nuclear enlargement, the N:C ratio remains low. (**c**) HSIL shows a marked increase in the N:C ratio as the enlarged nuclei occupy most of the volume of the cell

The 2005 WHO classification system divides "precursor" lesions into 5 categories: squamous cell hyperplasia, mild, moderate and severe dysplasia and carcinoma in situ [32]. The first category, as the name implies, is a non-neoplastic proliferation that strictly speaking, is not a true precursor. It is worth mentioning none-the-less, as one of its forms, basal cell hyperplasia, manifested by an increase in the number of basal cell layers, would be classified as CIN1 in the cervix. Dysplasia in the head and neck, therefore, is more than just delayed maturation. This should be expected, given that most oral cancers are due to carcinogen exposure, which induce roughly twice as many mutations as found in HPV-related cancers [20]. A combination of architectural and cytologic features is used to identify dysplasia in the head and neck. These architectural features include: loss of polarity (nuclei randomly placed within the cell), abnormally shaped rete ridges (The epithelial-stromal interface is often undulating in head and neck sites, compared to the flat interface typical of the cervix. Teardrop-shaped rather than finger-like downward projections are abnormal in the head and neck), increased or abnormal mitotic figures above the parabasal layer (similar to the cervix), and abnormal or premature keratinization. Cytological features of dysplasia include: variation in nuclear or cell size and shape, increased nuclear size, N:C ratio and increased nucleolar prominence. If the cytologic atypia is subjectively mild, the lesion is classified as mild, moderate or severe when the

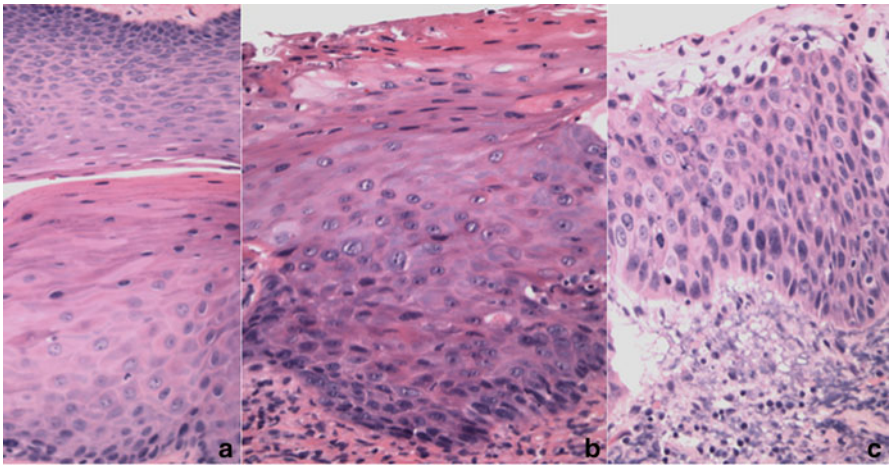

Fig. 12.5 Oral dysplasia. The assessment and grading of dysplasia in the oral cavity is not as straightforward as in the cervix. (**a**) The mucosa on top is normal, with a distinct basal cell layer and orderly maturation of keratinocytes. Note the nuclei at any given level are of similar size and shape. The mucosa at the bottom shows mild dysplasia, with extension cells with larger nuclei up into the lower third of the epithelium. (**b**) Moderate dysplasia shows significantly more atypia than acceptable for mild dysplasia. Note the enlarged atypical nuclei occupy about half of the epithelial thickness. (**c**) In this case of severe dysplasia, cells with atypical nuclei occupy the full thickness of the epithelium. With sufficient cytological atypia, moderate or severe dysplasia should be recognized even when limited to the lower third of the epithelium

architectural changes are limited to the lower third, lower two thirds or extend into the upper third of the epithelium, respectively (Fig. 12.5). In the presence of marked cytologic atypia, moderate dysplasia is upgraded to severe [32]. Detection of markedly atypical cells should always be of concern. In contrast to the cervix, it is not uncommon to see invasive carcinoma arising from a mucosa with atypical cells present only in the bottom-most epithelial layers (Fig. 12.6).

12.7 Invasive Squamous Cell Carcinoma

Squamous cell carcinomas comprise more than 90% of head and neck and 80% of cervical carcinomas. The term "squamous" means scale-like, that is, thin and flattened. This reflects the normal histologic pattern of maturation of squamous epithelia such as skin or the lining of certain mucosal surfaces, such as oral cavity, vagina and cervix. Squamous cell carcinomas from any site have certain properties in common. Well-differentiated examples show a progressive flattening and thinning of the tumor cells as they mature. Squamous cells attach to their neighbor through desmosomes (underlying the appearance of a "spinous" layer in the middle levels of squamous epithelium). As they continue to mature, increasing amounts of

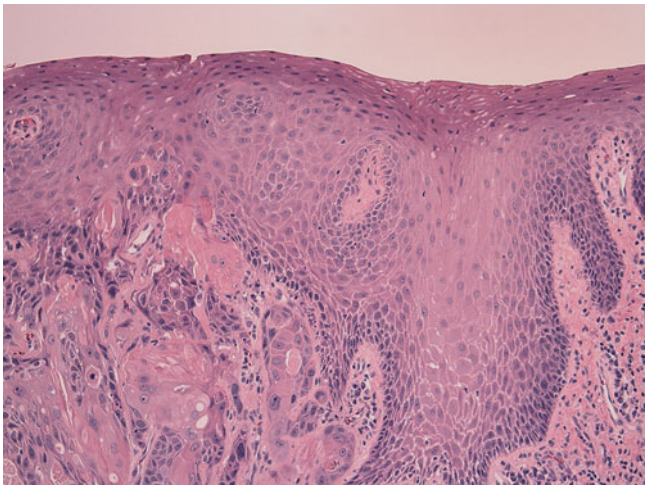

Fig. 12.6 In contrast to the cervix, squamous cell carcinoma of the head and neck can arise from an epithelium where dysplastic cells are limited to the lower third. This is a major pitfall of applying cervical criteria indiscriminately to the head and neck

keratin accumulate within their cytoplasm. As tumor cells die, they may leave behind whorls of extracellular keratin (keratin pearls, Fig. 12.1).

12.7.1 Cervical Squamous Cell Carcinoma

Squamous cell carcinomas arising in the cervix may macroscopically form exophytic papillae, a fungating mass, a flat plaque-like lesion or an irregular ulceration. They may be well, moderately or poorly differentiation, keratinizing or non-keratinizing. They may be composed of large, intermediate or small cells with uniform or pleomorphic nuclei and a high or low nucleus to cytoplasmic ratio. In other words, the gross and microscopic morphology of cervical squamous cell carcinoma overlaps with the spectrum of squamous cell carcinomas seen anywhere in the body. Short of performing immunohistochemical or molecular studies, it is usually not possible to identify these as HPV-associated cancers. Figure 12.7 illustrates an early cervical squamous cell carcinoma.

12.7.2 HPV-Related HNSCCA

Although there is overlap, HPV-associated squamous cell carcinomas have certain features that suggest an HPV rather than smoking-related etiology. HPV-related squamous carcinomas more often arise in the oropharynx than in the oral

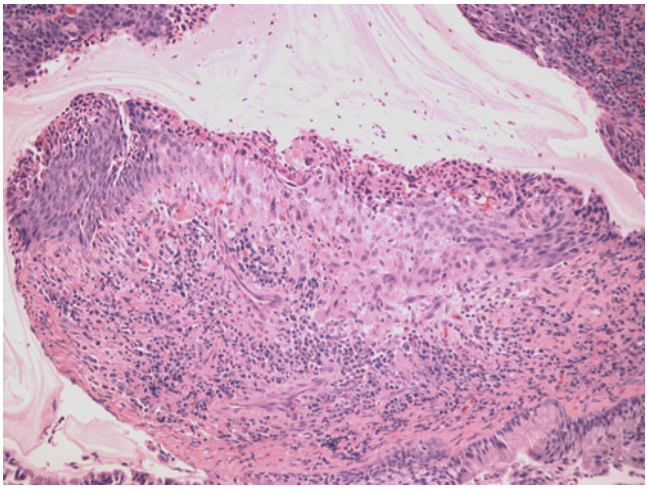

Fig. 12.7 Cervical squamous cell carcinoma. This early squamous cell carcinoma (center of field) is arising from an area of CIN3 (seen best at *left*). Invasive carcinoma often has larger, pinker cells than the small dark cells of the adjacent CIN3. This phenomenon is known as "paradoxical maturation"

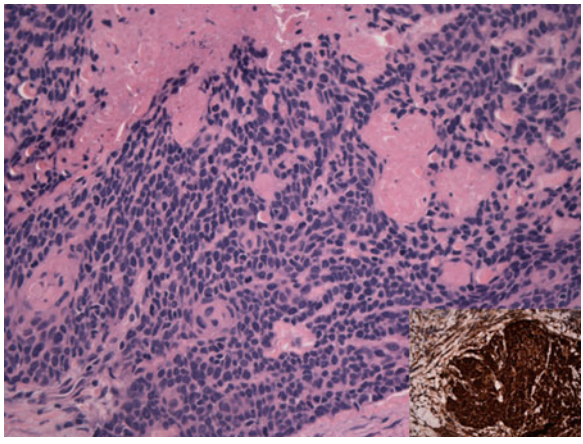

Fig. 12.8 HPV-related head and neck squamous cell carcinoma. These tumors tend to be poorly differentiated and are often of the basaloid subtype, as seen here. These tumors are composed of small cells with small dark nuclei (basaloid cells) and often have large areas of necrosis. The inset shows intense staining of tumor cells for p16, a surrogate marker for HPV infection

cavity or larynx. They tend to be poorly differentiated, often of the basaloid or papillary subtypes rather than of conventional type. The typical appearance of an HPV-related squamous carcinoma is illustrated in Fig. 12.8, and is discussed further in Chap. 9.

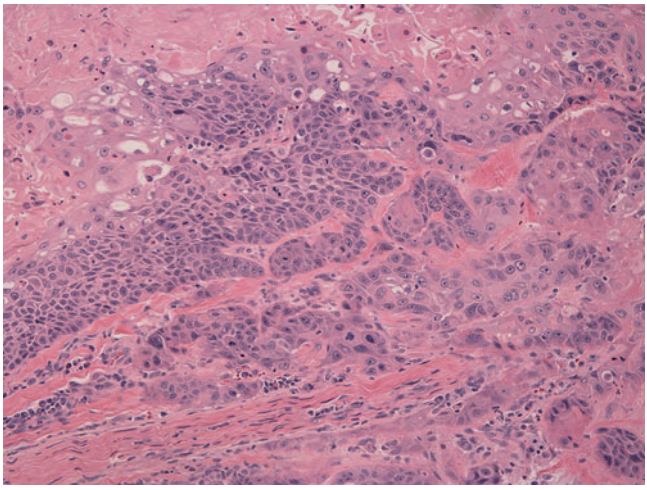

Fig. 12.9 Smoking-related squamous cell carcinoma. These conventional squamous cell carcinomas range from well differentiated keratinizing to poorly differentiated non-keratinizing types. This moderately differentiated example shows significant nuclear pleomorphism, reflecting underlying DNA aneuploidy. As tumor cells mature (*top*), they acquire more abundant pink cytoplasm

12.7.3 Smoking-Related HNSCCA

Carcinogen-related squamous cell carcinomas of the head and neck are more often well or moderately differentiated, compared to HPV-associated tumors, and may be keratinizing or non-keratinizing. They arise more often in the oral cavity and larynx than the oropharynx, but do occur in any head and neck site. A typical example is illustrated in Fig. 12.9. These tumors are discussed more fully in Chap. 9

12.8 Conclusions

It is clear that squamous cell carcinoma is not a single disease. Carcinomas arising from the skin tend to act as locally aggressive tumors, whereas those arising from mucosal surfaces frequently metastasize and cause mortality. Among advanced mucosal squamous carcinomas, attempts have been made to predict response to radiation or other therapies based on morphologic features of the tumor (tumor grade, keratinizing vs. non-keratinizing types) or host response (degree and type of inflammatory response, microvascular density) with limited success. With continued clinical and basic science research, it became evident that there are major differences among squamous carcinomas, even within the head and neck region. With the recognition that HPV-associated squamous carcinomas in this region have differential

responses to treatment, new questions arise. Are there just two types of squamous carcinoma—carcinogen and HPV-associated? If so, why are basaloid subtypes common in the head and neck but rare in the cervix? Only by identifying the alterations at the genetic, epigenetic and protein levels in a given tumor, can we design more specific and effective treatments. We will then know when a rose is a rose, and the era of truly personalized medicine will be here.

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Chapter 13
Viruses and Head and Neck Cancer

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Contents

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Abstract This chapter presents an overview of the viruses thought to be associated with Head & Neck cancers. Human Papillomavirus is the most common and strongly linked virus associated with this cancer. Other viruses, such as Epstein – Barr virus (EBV) and Cytomegalovirus (CMV) have controversial links to Head and Neck cancers. This controversy points to a true lack of understanding within the Head & Neck cancer field, regarding the extent of responsibility for being, or not being, causative agents. It is also perplexing as to why much of the general population is infected with one or more of these viruses, and yet, not everyone in the general population presents with cancer. Furthermore, those which do develop cancer do not always test positive for these viruses.

Keywords Head & Neck cancer • Human papillomavirus • Cytomegalovirus • Acquired immunodeficiency syndrome • Herpes simplex virus

Abbreviations

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy drugs régime used to treat AIDS
BARTs	BamHI-A rightward transcripts
BL	African Burkitt lymphoma
CD28	An important co-stimulator molecule in T cell activation
CD4/CD8+	Types of killer T cells
CMV	Cytomegalovirus
DC	Dendritic cells
EBERs	EBV encoded noncoding RNAs
EBNAs	EBV nuclear antigens
EBV	Epstein Barr virus a γ (gamma)-herpes virus a member of the Herpesviridae or herpesvirus family
HHV	Human herspesvirus
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HSV	Herpes simplex virus
IFN	Type I interferon a type of protein produced in response to pathogens
LMP	Latent membrane proteins
NPC	Nasopharyngeal carcinoma
T cells	Also referred as T-Lymphocytes a sub-group of white blood cells which facilitate cell based immune response mechanisms
TLRs	Toll-like receptors part of human immune system mechanisms
VZV	Varicella-zoster virus an Alphavirus subfamily

13.1 Introduction

Currently, one cannot talk about Head & Neck Cancer without also talking about Human Papillomavirus (HPV). In the past, Head & Neck cancer was subscribed to be a self inflicted cancer, primarily through the use/abuse of alcohol and/or tobacco. We now know that there is a growing population of younger patients that have not used/abused alcohol and/or tobacco, that are presenting with Head & Neck tumors and have HPV associated with their disease. This silent, growing epidemic needs to be acknowledged and the proper amount of resources applied to correct this trend. It is hoped that newly approved vaccines to HPV will be able reduce this growing number of patients. However, these treatment agents will be too late for currently infected patients, and new approaches will be needed to help this patient population in the future. Epstein Bar Virus (EBV) and Cytomegalovirus (CMV) and their association with Head & Neck cancer will also be discussed.

13.2 Human Papillomavirus (HPV)

Human papillomavirus (HPV) is now known to be the cause of skin and genital warts that were reported as far back as the ancient Greeks and Romans [1]. In 1824, the Italian physician Rigoni-Sernmade showed a link between HVP with cervical cancer. [2]. Unequivocal proof that genital warts were transmitted by a virus was shown in 1907 by Ciuffo using cell free extracts. [3]. Richard Shope, in 1932 was able to isolate virus particles from horn-like growths from wild cottontail rabbits and these induced warts to grow on domestic rabbits. They also developed tumors, thus linking a virus with tumors. [4]. Rous in 1934 showed that warts were benign tumors, and that they could become oncogenic [5–7]. The Nobel laureate zur Hausen would go on to show that some HPV subtypes not only caused genital warts, but also caused cancer [8–11].

By the late 1970s and early 1980s significant progress had been made toward cloning and characterizing HPV originating from human tumors. During the early 1980s important work had been accomplished including: (1) Howley's team cloning HPV 1, 2 and 4 from warts[12], (2) zur Hausen's group had cloned HPV 6 from genital warts[13–15], and (3) HPV 11 derived from laryngeal papillomas [16] thereby facilitating further detection and cloning for a variety of different human tumors. Later, zur Hausen's group used HPV 11 as a probe and cloned two of the most prominent, high risk HPVs, HPV 16 [17] and HPV 18 [18], taken directly from cervical cancer biopsies. This significant achievement laid the groundwork for more detailed work on these viruses which clarified the role they play in genital cancers. Immediately following this effort zur Hausen's team showed HPV 16 DNA present in: (1) precursor lesions to anogenital cancers, (2) Bowenoid papulosis [19], and (3) a year later in cervical intraepithelial neoplasias [20]. In 1985 the group also identified specific pathways for integration of HPV and elucidated upregulated expression of E6 and E7 genes involved in cervical cancer [21]. Additional worldwide

epidemiological analysis identified both HPV 16, 18 and the possibility of others as significant risk factors for cervical cancer [22, 23].

Due to the significant experimental challenges faced with early research processes in reconstituting the entire viral infection cycle, such efforts were strongly reliant upon cloning and sequencing for a variety of HPV types derived from naturally occurring infections [24]. A limited number of benign patient lesions were characterized to identify their splicing patterns and structure thereby providing access to viral RNA transcripts. It immediately became apparent from this research that there was a strong dependency of the papillomarvirus reproductive cycle on squamous differentiation of the patent epithelium, and that squamous and glandular carcinomas do not cause viral growth [25–27]. Additionally, upregulated levels of viral DNA and mRNA are confined in both the mid and upper regions of cell strata. Furthermore, capsid antigen was only found in a small portion of superficial keratinocytes. In more advanced dysplasias and cancers, the viral genome is usually absorbed into the host DNA with just a portion of the viral genes uniformly expressed. It would required a more clear understanding of the relationship between viral behavior and virus-patient reactions within normal infections before the appropriate experimental processes and procedures could be developed to model actual infection pathways. By 1992 two groups had created its own organotypic raft culture systems, thereby re-creating the HPV phases of growth [28, 29]. This allowed the molecular mechanisms of the pathogenesis of HPV to be elucidated.

One of the most significant accomplishments in HPV research was the development, and clinical validation of preventative vaccines against primary HPV infections. The vaccines are modeled on Virus-like particles (VLPs) composed of only the L1 capsid protein. VLPs were used, rather than unassembled L1 monomers, to permit conformational epitopes located on the virus particle to be recognized by antibodies. HPV vaccines are type-specific and a degree of cross-reactivity with closely aligned genotypes [30]. Two HPV vaccines are now available for therapeutic use. Gardasil was introduced in 2006 and Cervarix in 2007. Both protect against HPV 16 and HPV 18 which are responsible for 70% of all cervical cancers, as well as other genital cancer types. Importantly, Gardasil also provides prevention against HPV 6 and HPV 11 which are responsible for 90% of genital warts [31]. Both vaccines: (1) appear to have excellent safety characteristics, (2) are strongly immunogenic, and (3) convey type-specific protection against re-infection and lesions in a group of vaccinated women [32]. Generally, HPV vaccines are anticipated to provide protection against HPV induced oral cancers. HPV vaccines are recognized as an enormously significant achievement which is believed to provide a significantly reduction in the mortally of HPV related tumors.

13.2.1 Classification of HPV

Unlike most life forms, viruses are not readily identifiable within existing biological classification systems. Viruses are typically categorized using a number of criteria including: (1) phenotype, (2) morphology, (3) nucleic acid type, (4) host organisms,

(5) mode of replication, and (6) the associated disease state. Two nomenclatures currently exist for the identification and classification of viruses, the International Committee on Taxonomy of Viruses (ICTV) and the Baltimore classification system, which was established in 1971 and named after David Baltimore, a Nobel prize winning biologist. ICTV makes use of serialized ranked taxons, as follows: orders, families, subfamilies, genera and species. The Baltimore system utilizes genome types and replication species for different viruses. The Baltimore system ranks viruses in one of seven groups using the follow criteria: (1) nucleic acid (DNA or RNA), (2) strandedness (single or double), (3) sense, and (4) method of replication. The seven groups are:

1. dsDNA viruses
2. ssDNA viruses
3. dsRNA viruses
4. (+)-sense ssRNA viruses
5. (−)-sense ssRNA viruses
6. RNA reverse transcribing viruses
7. DNA reverse transcribing viruses

HPVs have circular double-stranded DNA genomes and HPV isolates are traditionally described as "types." This was developed because HPVs are not capable of being grown within a traditional *in vitro* cell culture, nor a xenotropic host model, nor do they provide a strong antibody response reaction. This eliminates the possible use of a usual serologic classification system. Therefore, HPVs for the most part are classified according to DNA sequence similarities providing both medical biological attributes [33–36]. This requires a variety of different end-users to adopt a method of classification which can best be used to meet the various needs of the healthcare industry, PV researchers, and the general public. A compilation of most widely used terminology for PV taxa using ICTV classifications is available in the literature [37].

Currently, there are 189 papillomavirus types categorized into 29 genera. Human PVs can be found in five genera: (1) Alpha-, (2) Beta-, (3) Gamma-, (4) Mu-, and (5) Nu- [37], with HPV types being tissue-specific and typically generate either benign or malignant lesions. There are currently more than 120 HPV types classified, with related HPV types categorized by species or genera. Significant types include: (1) α-papillomavirus which infect genital mucosa, (2) β-papillomavirus causing skin infections, with a variety of others grouped in, (3) μ-, δ-, and γ-papillomavirus groups [38].

13.3 The Genotype of HPV Related to Different Cancers and Diseases

13.3.1 Alpha-Type Papillomavirus

There are currently 15 species identified for α-papillomavirus. This HPV type is known to infect the: (1) anogential tract, (2) upper aero digestive tract, and (3) a variety of

different head and neck mucosa. HPV subtypes are further divided into low-risk and high-risk [39]. Low-risk HPV subtypes generate benign neoplasms, for example papillomas. These include HPV 6 and HPV 11 [40]. High-risk HPV which includes HPV 16, 18, 31, and 33 are usually found in the oral cavity or pharynx [40], have capability to stimulate squamous cell immortalization *in vitro* and are typically identified in a subset of malignant neoplasms. All of the aforementioned subtypes are α-papillomavirus. More specifically, high-risk HPV types 16, 31, and 33 are known to induce oropharyngeal squamous cell carcinoma [41, 42], and species 5, 6, 7, 9 and 11 are often associated with growth of cervical cancers and Head & Neck squamous cell carcinoma [43]. Additionally, HPV 16 is most commonly associated with cervical cancer and is estimated to be responsible for 50% of those cancer types, and is member of species 9 [44]. HPV 18 is also involved in cervical cancer causing about 20% of all cases and falls into species 10 [44]. Finally, HPV 6 is responsible for cutaneous genital warts and is a member of species 10 [44]. Most recently HPV 16, 31 and 33, all in species 9, have been associated with increased levels of oral cancer. In head and neck cancers, HPV 16 has been found to be present in greater than 80% of patients presenting with this disease [45–47].

13.3.2 Beta, Gamma, Mu, and Nu Papillomavirus Types

The β-papillomarvirus appears to be distinct in terms of evolutionary origin from the Alpha genus and also are responsible for both immediately apparent and dormant re-infections [48, 49]. The Beta type includes epidermodysplasia verruciformis (EV)-specific types typified in the host by non-genital lesions [50, 51]. Susceptibility is believed to be induced by a genetic mutation [51, 52] with disease expression of both skin cancer and non-melanoma skin cancer (NMSC) throughout most human demographics [53]. Gamma, mu, and nu species are also found within nongenital skin. Gamma can induce cutaneous warts [54], and it appears that mu and nu members can as well [55].

Both oropharyngeal squamous cell carcinomas (OPC) and Oral squamous cell carcinoma (OSCC) cancer types have long been attributed to alcohol and tobacco use/abuse. However, more recently HPV has been acknowledged as a causal link to OPC, especially in carcinomas of the base of the tongue and tonsil. Indeed, this increase in OPC is being observed in a different patient segment within the population, with greater than 60% of the cases in the US involving the presence of HPV [56].

13.4 HPV Epidemiology

It is now believed that HPV is responsible for an increased rate of infection of lymphoepithelium of Waldeyer's ring [57] when compared to intraoral squamous cell carcinoma. HPV 16 has been identified as the principle viral subtype within both of

these OPC [45, 58–65]. These OPC are presenting in young adults, predominantly male Caucasians, but may also present in patients which do not have a history of alcohol and tobacco use/abuse. Two key contributing risk factors appear to be initiating sexual activity at a younger age and greater frequency of sexual partners, both vaginal and oral [60, 66–69]. Interestingly, use of alcohol or tobacco does not appear to correlate to higher potential risk of OPC in HPV positive hosts [60, 70]. HPV also appears to have a causal connection for a percentage of oral cavity cancers. However, these percentages are lower when compared to the relationship which exists between mucosas, for example stratified squamous epithelium and lympho-epithelium of the oropharynx [71].

Data from the USA National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) indicates that the age-adjusted rates for OPC has increased 2–4% each year for the time period 1973 to 2001[72]. Significantly, this is especially true for white males 20–44 years of age, even while the rate of cancers present at other oral sites has decreased [72]. Further review of SEER data from 2001 to 2004, reveals that rates of HPV-linked OPC increased 5.2% each year and the incidence of non-HPV-linked OPC actually dropped by 1.8% annually [73]. It is believed that the drop in OSCC is a consequence of diminished tobacco consumption and the rise in rates of cancers mitigated by HPV infection [74].

The level of HPV DNA attributable to cancers of the head and neck is highly disparate throughout the body of research. Examples of such efforts include, a meta-analysis which indicates that within 35 studies HPV 16 is present in 16.0% [56] of OSCC, and with OPC in 30.9% of the 27 studies conducted [45]. The results for North America for HPV 16 for OSCC are lower, 2–4% [66, 75], and for OPC higher at 63–82% [56, 60, 66, 75–78]. These data may be attributable to regional diversity and variation in methodologies used to detect HPV [58]. More specifically, HPV DNA has been found in oral rinse samples within 3–5% of all adolescents [57, 79], and in 5–10% of adults [80, 81]. However, it is acknowledged this data could be attributable to other oral or related oral pharyngeal infections [82].

13.4.1 Transmission

Current research indicates that oral-genital contact is the principle pathway/mechanism for infection by HPV into the upper aerodigestive tract. It is believed that HPV is transmitted by direct contact through: (1) skin-to-skin contact, (2) mucosa-to-mucosa during sexual activity, and (3) skin-to-mucosa. Research indicates that HPV infection is associated with both oral sex and open-mouth kissing [57, 83, 84]. It is also hypothesized that vertical transmission between infant and mother [85, 86], and auto-inoculation is highly probable but less frequent [87]. Finally, HPV is also thought to be involved in the genesis of other carcinomas, most especially in cervical cancer within women. An example includes HPV 16 and 18 where a strong casual link has been confirmed in about 71% of cervical cancers [56, 88].

13.4.2 Prognosis

Diagnosis for HPV-positive OPCs usually occurs in later stages of the disease and is typified by association with both lymph node, as well as distant metastasis [73, 89]. Regardless of this later stage diagnosis, improved survival rates are being achieved through chemotherapy and radiation treatment protocols along with a lower probability of reoccurrence or second primary malignancies [56, 58, 73, 90–93]. Typical survival statistics include: (1) a 2-year survival window of 87.5–95.0% [56, 94], (2) patients with HPV-positive OPC experience a 28–64% reduction in the risk of death and a 46–73% reduction in recurrence when compared to patients with HPV-negative OPCs [56, 90, 92, 94], and finally (3) HPV-positive tumors with an elevated p16 expression have improved survival versus HPV-positive tumors with reduced or no p16 expression [95–97].

Introducing tobacco exposure significantly changes the survivability and outcome expectations. HPV-positive OPC has lower survival rates than do those patients with HPV-negative OPC. In HPV-positive nonsmokers, the 2-year survival rates were 95% as compared to HPV-positive smokers with 80%, as found in a relatively large comprehensive study [94]. More significantly, a history of smoking in the past, combined with smoking in the present further diminished the possibility of survival. Additional evidence includes those who smoked currently with HPV-positive OPC, had a seven fold increase in the probability of developing recurrence disease versus those with HPV-positive who never smoked. Furthermore, HPV-positive former smokers had a 3.6 fold increase in the possibility of developing recurrence when compared to those who had never smoked [98]. Numerous other research efforts show when discussing HPV-positive cancers, alcohol and tobacco over-use may have an additive [62], as well as multiplicative [81] impact, most especially when considering tobacco use [69, 99].

13.4.3 Prevention

Currently there are two types of preventative vaccines available for use for cervical cancers with a causal link to HPV [100, 101]. The first is a bivalent vaccine which targets high-risk subtypes HPV 16 and 18, the second a quadrivalent vaccine which targets HPV 6, 11, 16, and 18. It has been demonstrated that preventing HPV infection in women can provide a concurrent reduction in carcinoma of the cervix. Additionally, genital warts have been shown to be reduced in males, thereby inferring a possible benefit as well. Each of these vaccines is effective against HPV 16. This is significant due to HPV 16 involvement with OPC, alluding to a possible future role in HPV-associated OPC. However, the long-term impact of these vaccines in preventing HPV-positive OPC remains to be seen in the years ahead.

13.4.4 Clinical Implications

Recent research and demographic infection patterns create the expectation within the healthcare community for an enormous increase in cases of OPC as related to HPV. While early stage detection has improved prognosis for HNC, it remains to be seen how effective clinical examinations are in identifying pre-malignant or early on-set OPC. Among the particularly difficult problems is the visualization within the lymphoepithelium, to discriminate between premalignant and non premalignant regions. Furthermore, clinical examination for cervical lymphoepithelium is a critical factor in diagnosis and detection process. Currently, it remains unknown as to the degree molecular testing may be of use in enhancing the detection process.

Currently, cancer survivors with OPC are receiving treatments with enormous short and long-term toxicity issues, which have significant impact on the quality of life for these patients. OPC seems to respond positively to current treatment régimes with better prognosis. Therefore, a radiation/chemotherapy treatment protocol could possibly be specifically designed to fit the unique needs of patients with HPV-positive OPC to improve and enhance treatment. As part of that protocol, targeted agents and antiviral therapies could also be used. Future treatments may well be based upon HPV status, taking into consideration smoking status with nonsmoking HPV- positive patients benefitting most from an improved treatment protocol. This approach could well decrease the toxicity levels of each treatment program to better fit the survival possibilities for each patient.

Anticipated vaccine immunization efforts are expected to impact HPV presence throughout the general population. It is believed that these activities will assist in HPV-related cervical cancer prevention and therefore, over time, will impact HPV-positive OPC. The degree to which these immunization efforts will actually impact women remains uncertain. It is also expected that as the general population becomes more aware of HPV's causal role in these cancers, there would be a resulting change in sexual behavior patterns and the use of increased safety measures. This increased awareness and related modifications in behavior, may well result in a diminution of HPV-related squamous cell carcinomas.

13.5 Epstein Barr Virus (EBV)

The Epstein Barr Virus (EBV) is a γ (gamma)-herpes virus and considered a member of the Herpesviridae or herpesvirus family [102, 103]. One significant attribute of the herpesvirus category is a complex viral DNA core, enveloped by both an icosahedral nucleocapsid and protein tegument [102, 103]. Herpesviruses are capable of encoding a variety of approximately 100 proteins and which are now known to infect a significant percentage of the pediatric demographic, resulting in more than 90% of all adults being infected with EBV [102]. Viral family types

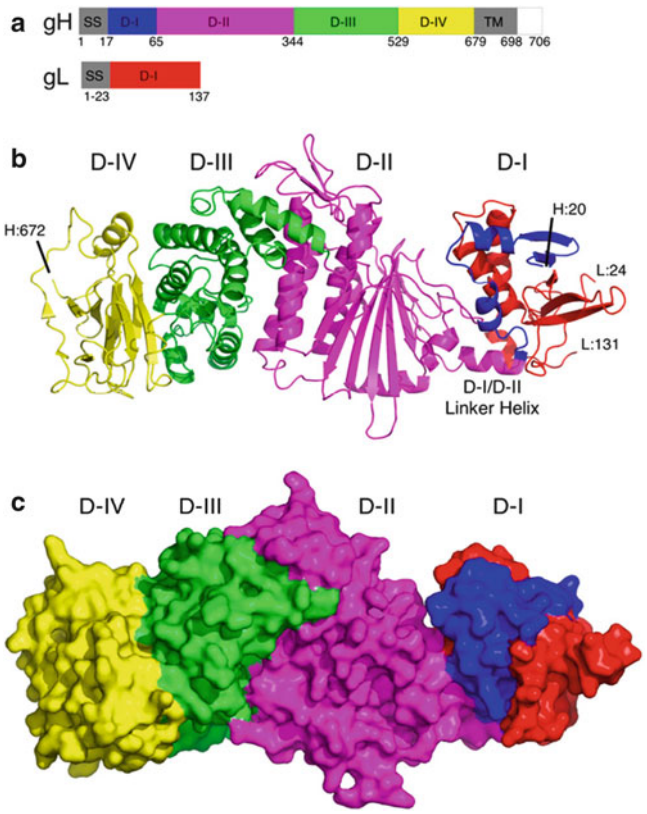

Fig. 13.1 Three varying representations of EBV gH and gL heterodimers. The first (**a**) is a schematic diagram of EBV gH and gL domains. Those domains in color represent the crystal structure depicted in (**b**). Areas not in the structure appear in white or gray. The second ribbon diagram (**b**) depicts the EBV gH/gL structure in color with gH in blue in region D-I, D-II in magenta, D-III in green, D-IV in yellow, and gL in red. The last depiction (**c**) is of the surface of EBV gH/gL displaying molecular configuration and with the same color coding as appears in (b) [116]

include: (1) herpes simplex 1 (HSV-1) and 2 (HSV-2), (2) varicella-zoster virus (VZV) an alphavirus subfamily, (3) EBV a gammaherpesvirus subfamily, also known as HHV-4 [104], (4) cytomegalovirus (CMV), (5) human herspesvirus 6 (HHV-6) and 7 (HHV-7) both in the betaherpesvirus subfamily, and (6) human herpesvirus 8 (HHV-8) [103]. EBV virions are made up of a double stranded, linear DNA genome enveloped in a protein capsid [105]. The tegument is embedded with glycoproteins which are functionally significant for: (1) host range, (2) cell tropism, and (3) receptor recognition [105]. EBV virions usually are 120–180 nm in diameter, with the genome being approximately 100 genes in size (Fig. 13.1) [106–108]. It is now known that there two subtypes of EBV; Type 1 and Type 2 [104], which are differentiated from one another through EBV nuclear antigen (EBNA) loci

EBNA-2, -3A, -3B, and 3C [109]. Type 1 is predominantly found in the Western hemisphere, as well as Southeast Asia, and both Type 1 and 2 are found equally distributed throughout Africa [110, 111]. These subtypes are characterized by a number of criteria include: (1) specific restriction endonuclease digestion patterns, (2) displaying a variety of transforming abilities, and (3) can spontaneously begin the lytic cycle [112–115].

EBV was first encountered in 1958 by the English doctor, Denis Burkitt while working in Africa, who believed it might have involvement in cancer development within children [117, 118]. The cancer later became known as African Burkitt lymphoma (BL) [119]. In 1964 EBV was first described and clarified as "virus-like particles" through electron microscopy when Anthony Epstein, Yvonne Barr and Bert Achong identified its presence in BL [106]. Subsequent studies have made it apparent that a "causal link" exists between EBV infection and; (1) BL [120], (2) infectious mononucleosis [103], and (3) nasopharyngeal carcinoma (NPC) [121–123]. Once infected with herpesviruses, the viruses reside permanently within the host, which remains susceptible to the possibility of lifelong re-infection [102, 124].

13.5.1 Infection Pathways and Biology

The specific infection biology pathway and mechanism for EBV is initiated through latent infection of B-lymphocyte cells (B-cells) which are then cast off through salivary and genital secretions [102]. EBV is believed to then systemically increase the number of B-cells throughout the individual, neither damaging nor destroying B-cells, thereby insuring proliferation and survival of B-cells infected with EBV [125, 126]. There are two distinct infection replication stages for EBV; an active, lytic or acute phase, and a latent state [102, 103]. During the first phase EBV appears to principally target and grow within stratified squamous epithelium of the oropharynx [103]. In the second latent phase, EBV infects B lymphocytes in the upper aerodigestive tract lymphoid organs, resulting in a continued presence within memory B cell differentiation [127, 128]. It is the latent-phase which is believed to support tumorigenic/carcinogenic replication and growth pathways [102]. Host B-cells replicate EBV DNA as an extrachromosomal episome through use of host DNA polymerase [102]. Carcinogenic properties are conveyed through a variety of latent infection gene pathways, primarily of three types; (1) latent membrane proteins (LMP1, LMP2, and LMP2B) [129, 130], (2) EBV nuclear antigens (EBNA1, EBNA2, and EBNA3) [131, 132], and (3) EBV encoded noncoding RNAs (EBERs) [133–135]. EBNAs are believed to play an important part in promoting oncogenic LMP activities [102]. LMP1 for example appears; (1) necessary for cell immortalization and transformation, (2) to upregulate cells which demonstrate improved mobility, thereby facilitating higher tumorigenic activity and quicker disease progression, and (3) suppresses immunogenic responses through downregulation of T-cell response genes, which would normally respond to the presence of tumor antigen [102].

13.5.2 Latency Patterns

Three separate and specific latency patterns are believed to exist and support a variety of disease states, including NPC [103]. This supposition is based on numerous distinct gene expression pattern studies whose results are thought to be caused by differential promoter activity, as influenced by the distinct biology within each host [136, 137]. These three patterns include: (1) Latency type I typically correlated to Burkitt's lymphoma and is evidenced through the expression of EBERs, BamHI-A rightward transcripts (BARTs), and EBNA1 [103], (2) latency type II associated with NPC, EBV–positive Hodgkin lymphoma, and gastric cancer, and characterized through expression of BARTs, EBNA1, EBERs, LMP1, LMP2A, and LMP2B [103], and (3) latency type III linked to post-transplant lymphoproliferative diseases and lymphoblastoid cell lines and evident by the presence of EBNAs 1,2, 3A, 3B, 3C, and –LP, LMP2A, LMP2B, EBERs, and BART RNAs [103]. These bio-molecules appear to be highly important and implicated in EBV mediated tumorigenetic behavior in NPC, including but not limited to: (1) the Wnt pathway, (2) transcription factors NF-kappa B, and (3) beta-catenin [102]. Oncogenes are believed to play critical roles in carcinogenetic growth in NPC and include *BARF1,* believed to be involved in the promotion of growth [102], and the tumor suppressor genes *DCC* and *DLC1,* with recent evidence indicating inactivation of both through methylation biochemical activities, thereby preventing or interfering with anti-tumorigenetic immune response within the host [138]. The precise role EBV plays in the complete tumorigenic pathway of NPC remains to be clarified. However, it is well understood that clonal EBV genomes are present in NPC tissue, providing significant evidence toward clonal growth being the result of one EBV-infected progenitor cell, and therefore a causal link [139].

13.5.3 Immune System Responses to EBV

The innate immune system response is the host's first line of defense against any viral infection, including EBV [104]. This defense mechanism stimulates the release of type I interferon (IFN) early in the infection process. Due to the prolonged incubation period required, this has not been studied *in vivo* in early stage EBV. However, evidence exists for this to also occur with EBV as well [104]. A recent study demonstrates that EBV initiates a strong IFN response and production in isolated human plasmacytoid dendritic cells *in vitro* [140]. Further, viral DNA and proteins are known to be recognized by pattern recognition receptors such as Toll-like receptors (TLRs) which initiate a number of important response mechanisms including: (1) the triggering of an IFN response, (2) mediating the release of natural killer cells, and (3) acting in numerous ways to jump start the adaptive immune response mechanism [104]. Finally, there is data to support the premise that various TLRs are involved in innate immune response to EBV, which includes TLR2, TLR3, TLR7, and TLR9 [140–142].

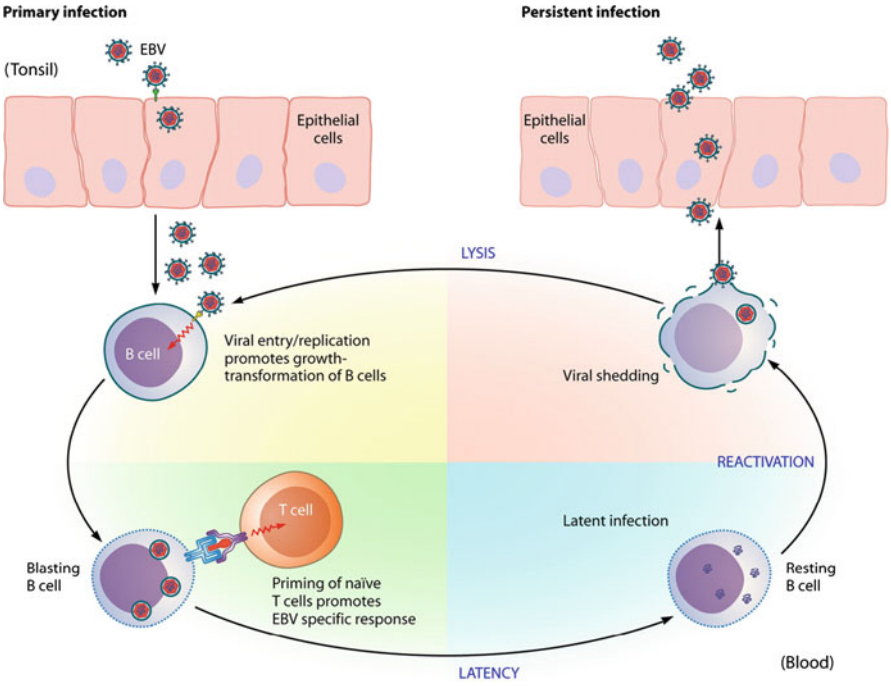

Fig. 13.2 Depiction of apparent pathways for the origin of infection for EBV. The infection typically begins in the oral cavity (tonsils) using a variety of glycoproteins to invade both naïve B cells and epithelial cells. Viral presence results in the introduction of the EBV genome into B-cell nuclei thereby initiating replication of both cellular and EBV DNA polymerases. This is followed by activation of B-cell growth, by EBV genetic materials, which in turn causes growth of blasting B cells, and a concurrent "priming" of naïve T cells. Under normal circumstances: (1) blasting B cells are eliminated by cytotoxic T-lymphocytes, (2) memory B cells activated previously continue lytic replication, and/or (3) EBV may cease protein-encoding gene activity, thereby initiating latency. At a later point in time, the dormancy period may indeed cease through reactivation of B-cells with the resulting cascade effect of viral re-infection and shedding (Reproduced in its entirety with author permission and from an original graphic provided by the publisher, copyright permission © 2011 American Society for Microbiology [104]

The other immune response system in the human body is the adaptive immune response mechanism. This response takes place on two levels: the humoral or antibody response, and at the cellular level with the generation of CD4 and CD8+ T cells, the latter being immensely important in suppressing viral reproduction [104, 143]. CD4 and CD8+ T cells are types of numerous killer T cells, a subgroup of T-lymphocytes, part of white blood cells, all critical in controlling and eliminating pathogens and/or infected somatic cells, tumor cells, and cells with viruses [144]. As a result of the introduction of EBV, usually through the oral cavity, a sequence of events are believed to commence: (1) B-cells initiate growth and differentiation into memory B-cells through the germinal center reaction, (2) the infected B-cells are

then released into circulation, (3) generating detectable amounts of EBV in the blood stream, (4) with a diminished presence of infected B-cells after the original infection, which (5) are thereafter, never entirely removed from the host [104, 145]. Figure 13.2: depicts the most probable EBV infection pathways in healthy carriers.

13.5.4 Demographics and Statistics of NPC

NPC occurs relatively infrequently within North America, and Europe with more or less equivalent adjusted incidence rates of approximately 0.7% of all cancer types, or one per 100,000 population per year, this is also the case for the US [146, 147]. However, this is not true elsewhere in the world, particularly in some parts of Asia where it is an important and significant form of cancer. For example, within certain regions of Southern China the incidence rate is 50 cases per 100,000 per year [148]. In Hong Kong the incidence rate is 25% of all types of cancer, thereby making NPC the leading form of cancer among men 20–44 years of age [149]. In Indonesia the incidence rate of NPC is 6.2 cases per 100,000 per year making it the fourth highest form of all cancers, with 13,000 new cases forecasted for each subsequent year into the future [150, 151]. The causal link between EBV and NPC is well recognized and therefore of particular interest in these regions and other parts of South-East Asia.

13.6 Cytomegalovirus (CMV)

As previously discussed, CMV is a member of the HHV family and has been linked to oral cancer [152]. However, CMV biology and pathology mechanisms are less well understood than many other members of the HHV family. Depending upon the socioeconomic circumstances of any given demographic, between 40 and 100% of all humans may be infected with CMV [153]. It is also of enormous significance that evidence for CMV being a causal link to cancer, and more specifically to head and neck cancers, is associated with a substantial level of controversy [153]. On the one hand, there is important work supporting the development of cancer, and to the contrary, there is substantial research whose results are believed to directly contradict such evidence [153]. Examples in support of causation include a variety of oncogenic viral links: (1) the role of retrovirus and flavivirus (RNA viruses), (2) the function of hepadnavirus, herpes virus, and papovavirus (DNA viruses), (3) Peyton Rous being awarded the Nobel Prize in 1966 for the discovery of viral induced cancer, and (4) Harald zur Hausen receiving the Nobel Prize in 2008 for his work on papillomaviruses in cervix cancer, all well documented [153–155]. On the contrary: (1) evidence for viruses displaying an anti-cancer impact [156], (2) antitumoral effects have also been noted, (3) Vδ2-negative γδ T lymphocytes have been found to be reactive against colon cancer cells killed

by CMV [157, 158], (4) a five hundred percent decrease in the cancer risk for kidney transplant recipients through γδ T lymphocytes induced by CMV [159], and (5) after murine CMV infection, an autoimmune response was described in an murine B-cell lymphoma model [160].

A most recent review and assessment of the accumulated and contradictory data concurs that CMV plays a crucial "oncomodulatory" role within cancer development, but suggests more research is still required to provide conclusive evidence [153]. Furthermore, it is particularly important to continue pursuing the potential of CMV as a possible future therapeutic agent for some types of cancers [153]. Interestingly, CMV has also been found to be among the most virulent and pervasive infections present in immunocompromised individuals, thereby confirming the virus as a prime target for further and aggressive investigation [161–179].

13.6.1 CMV, HIV and Immunosenescence

As is the case with many other latent herpes virus forms, CMV can be active or reactivated after dormancy in individuals, particularly those with: (1) compromised immune systems, (2) human immunodeficiency virus (HIV-1), the retroviral causal agent to acquired immunodeficiency syndrome (AIDS), and (3) among adults aged 65 and older [180]. Chronic HIV is now being controlled more successfully than ever through the use of antiretroviral therapy (ART) [181]. As a result of these efforts, individuals are living far longer and experiencing pathologies and morbidity issues normally associated with much older adults without HIV [181]. Indeed, it is evident that 40 year old patients presenting HIV-positive demonstrate many of the same immune functionality issues as do uninfected 90 year olds [181]. An example includes the presence of equivalent percentages of senescent CD8 T cells found in both demographics [180]. It is also recognized that a large portion of later-stage senescent CD8 T cells are present and indeed specific for CMV antigens [181]. These HIV facilitated modifications and disruptions to the human immune system mimic those chronological changes normally associated with non-HIV positive, older individuals who experience the on-set of human immunosenescence [181].

Immunosenescence describes the process and impact of aging on human immune systems [181]. This phenomenon is systemic in scope and typified by: (1) a reduction in the effectiveness of vaccinations, (2) higher rates of autoimmune issues, (3) an increased susceptibility to infectious diseases, (4) increased tissue damage caused by malfunctioning inflammation response mechanisms, and (5) an increase in the rates of cancers [181]. While this process is inevitable, the progression and specifics of epidemiology vary enormously from one individual to another, depending upon the unique combination of environmental dynamics and genetic make-up of each individual [181]. It also becomes more pronounced with age. Typical modifications on the immune system are known to include: (1) thymic involution, (2) reduction in circulating naïve T cells, (3) reduction in number and functionality of hematopoietic

stem cells, (4) a decreased CD4/CD8 ratio, (5) greater levels of pro-inflammatory cytokines, for example IL-6 and TNFα [182], (6) accumulation of late-differentiated memory CD8 T cells which have experienced important functional and phenotypic modifications, (7) an absence of CD28 expression (CD28 is an important co-stimulator molecule in T cell activation), (8) shortened telomeres (an area within a chromosome made up of nucleotides), and (9) loss of telomerase activity (an enzyme involved in normal DNA sequencing) [181]. Immunosenescence has been shown to be enormously significant to increased susceptibility in the formation of cancers [181].

Epidemiological studies indicate that the on-set of old age and the consequent reduced efficacy and response of the immune system is the single greatest contributing factor to infection and the development of cancer, more important than life style choices, such as smoking [183]. Significantly, there is also recent additional evidence indicating that CMV may possibly be a primary cause of immunosenescence, regardless of age [181]. One suggested route for a possible long-term therapy is the development of a CMV vaccine, administrated in childhood, and which is believed could inhibit later development of large numbers of senescent T cells within the highly susceptible elderly demographic [180].

13.7 Conclusion

The viral association with Head & Neck cancers has been, and most likely will be, an important area of investigation. The sheer complexity of the topic makes this subject matter very hard to address and therefore, progress will most likely be slow. Never the less, from our current perspective, it is a very important topic. It is unclear as to what the impact of current vaccines against HVP will due to change the incidence of Head & Necks cancers, but it is hoped that it will be significant. If this is the case, then perhaps researchers will be encourage to make vaccines to other viruses that are associated with Head & Neck cancers.

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Chapter 14
Head and Neck Carcinogenesis a Product of Complex Evolutionary Forces

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Contents

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Abstract This chapter explores carcinogenesis of the head and neck as a product of biologic forces present in micro and macroenviroments. We attempt to present dynamic complex characteristics of head and neck tissues in a framework that explores ecologic selection as a means to understand and explain the risk for cancer. We contend problems with diagnosis and treatment responses results from an inattention to environmental interactions and their impact upon malignant transformation and reversal to a normal physiologic state. Furthermore an emphasis is placed on Darwinism and ecologic selection that determine functional roles and activities of keratinocytes derived from the proliferative stratum of mucosa in response to changes in head and neck environments. In addition, we consider unique features; such as, microbiome, fluids (e.g., saliva, transudate, exudates), epithelial mucosa biology, and immune responses to provide a broader picture for the influence of evolutionary, chemical, and physiologic changes upon head and neck cells and tissues during carcinogenesis.

Keywords Carcinogenesis • Head and neck squamous carcinoma • Darwinian selection • Evolutionary biology • Microbiome • Oral biology

Abbreviations

HNSCC	head and neck squamous carcinoma
OSCC	oral squamous cell carcinoma
ST	smokeless tobacco
PAH	polycyclic aromatic hydrocarbons
TSNA	tobacco specific nitrosamines
HPV	human papilloma virus
HHV	herpes virus
$NQO	4-Nitroquinoline-1-oxide
MDR	drug resistant gene
ABC	ATP-binding protein cassette
XRE	xenobiotic responsive element
ADH	alcohol dehydrogenase
ALDH	aldehyde dehydrogenase
CYP_{450}	cytochrome P_{450}
GST	glutathione-S-transferase
Rb	retinoblastoma
NF-kB	nuclear factor kappa-light-chain-enhancer of activated B cells
c-fos	cell Finkel osteogenic gene
c-jun	cell JNK related gene
AP-1	activator protein-1
ATF	activator transcription factor
JDP	AP-1 repressor protein
IP3	Inositol-1,4,5 trisphosphate

MAPK	mitogen activator protein kinase
E2F	elongation factor 2
PCNA	proliferation cell nuclear antigen
E6/E7	early HPV proteins 6 and 7
NOTCH1	Notch homolog 1, translocation-associated (Drosophila)
TP63	tumor protein 63
IF6	Interferon regulatory factor 6
ARF	Alternate reading frame of INK4a/ARF locus (CDKN2A)
Nanog	homeoprotein embryonic stem cell transcription factor
AKT	Protein Kinase B (PKB), is a serine / threonine protein kinase
PTEN	Phosphatase and tensin homolog
mTor	mammalian target of rapamycin
CpG	cytosine guanine phosphodiesterase islands
TTP	mpRNA decay factor tristetraprolin
HWE	Hardy-Weinberg equilibrium
RR	relative risk
CI	confidence interval
SNP	single polymorphic polymorphism
ETOH	ethyl alcohol
AA	acetaldehyde
IgA, IgG, IgM	immunoglobulins A, G, and M

14.1 Introduction

Cancer has been described as a disease of genetic changes but we will show in this chapter that a broader more dynamic view of head and neck carcinogenesis is required. There are many reports that describe presentations, distributions and biologic relevance of genetic characteristics for head and neck carcinogenesis. Ultimately these reports focus upon a viral connection (e.g., human papilloma virus) or habit such as, tobacco product or alcohol use. These associations while very relevant to the process of carcinogenesis do not produce a sufficient deep understanding of the processes to prevent, to improve early diagnosis and treatment to improve outcomes for late staged carcinoma.

Moreover there is little mention of other variables such as microbome and oral biology considerations that exert a strong influence upon carcinogenesis. This neglect of a broader assessment of cell and tissues changes in the head and neck results in poorly understood mechanisms that describe aforementioned associations and do not provide a means to determine which patient will respond to which treatment protocol in the most appropriate cancer control manner [1, 2].

Presented herein is an attempt to provide a more complete picture of changes in genetics, chemistry and physiology which contribute to carcinogenesis of the head and neck.

14.2 Oral Biologic Considerations for Modifying Survival of Microorganisms

Oral biology and in other systems in the human body as well as the complete species responds to and is subject to changes in ecology and evolutionary influences. Survival of microorganisms and keratinocytes that compose the mucosa in pharynx and oral cavity further modify risk for carcinogenesis by determining selection in important ecologic niches. These sites also effect survival through chemistry of oral fluids that bath both microbes and tissues and cause modification to cell physiology and tissues. Metabolic regulation of microbes, cells and tissues form an integrated network that is further changed by selective trapping of immune effector cells such as polymorpho-nuclear cells. Subsequent release by microbes of virulence and adhesion factors facilitate biofilm formation and colony formation also contribute to pathophysiologic changes in epithelial and mesenchymal regions of oral mucosa (e.g., epithelium, vascular, neural structures). Below we discuss saliva, viral association, and general considerations for carcinogenesis before we begin discussion of Darwinism-evolutionary survival and ecology changes as important influences for head and neck carcinogenesis.

14.3 Saliva: An Oral Fluid that Modifies Various Microbial and Epithelial Interactions

Salivary proteins include mucin proteins (1,2 MG1, 2), lactoferrin, peroxidases, amylases, carbonic anhydrases, proline-rich proteins, lysozymes, statherins, histatins, glycosaminoglycan, polysaccharides, and immunoglobulin's (e.g. IgA, IgG, IgM). The functional activities of many of these proteins are highly specific and require a precise conformation to interpret function [3–5].

For example proline-rich proteins require S.*gordonii* to be attached to dental surfaces to absorb these proteins or statherins/histatins need to form a α–helix to function [6]. Some of these proteins are also likely participants in formation of bridge networks between sequestered particles from tobacco products and dietary substances in close persistent proximity to dentition, gingiva, epithelial mucosa surfaces and microbes and this association is also expected to increase risk for transformation or at least enhance inflammatory responses to damage tissues.

It is also anticipated but unclear whether oral microbes modified by the presence of tobacco product or diet driven substances will interact further with the array of substances already present in the oral cavity. These include **tobacco smoke condensate constituents** e.g., tars, heavy metals, plastizer particles, nicotine and associated substances polysaccharides, flavorings, surfactants (glycerol-polyethylene glycol oxystearate, polyoxyethylene esters or sorbitol laurate esters, such as polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monoisostearate, etc…); **preservatives**

[e.g., anti-oxidant reducing agents; such as, (Butylated hydroxytoluene BHA)]; butylated hydroxytoluene (BHT), methyl paraben, ethyl paraben, propyl paraben, potassium sorbate, sodium benzoate, sodium bisulfite and mixtures solubilizers); **dietary contributors** (e.g., alcohols, nitrates, volatile aldehydes, nitrosamine, poly-cyclic aromatic hydrocarbon, etc) and **saliva** its self (e.g., amylases, cystatins, mucin proteins, proline-rich proteins or straterins) [3–5].

Among these interactions are selective microbial physiologic changes. For example, contact with saliva which contributes to microbial metabolism, adhesion and colony formation in specific microenvironments in the pharynx and oral cavity. These microbial activities are in a changing balance (loss of symbiosis) with anti-microbial activities linked to saliva function. pH changes (e.g., bicarbonate); immunoglobulin concentration and types; levels of peroxidases, lactoferrin, and presence of immune factors (e.g., defensins, cytokines, interleukins). We also expect a production of concentrated residues of chemicals that will localize in a dependent manner adjacent to pharynx and oral tissues. This will further influence microbial physiology (e.g., biofilm) and change microbial interaction with dentition and epithelial mucosa surfaces. Presence of salivary proteins will also initiate specific metabolic action, for example salivary glycoaminoglycans protein and microbial synthesis of heparan sulfate binding proteins that are used to adhere to oral keratinocyte surface proteoglycans [7–9].

Microbes use salivary proteins not only to increase their adhesion and colony formation but also modify and assist with salivary lubrication of pharynx and oral tissues, swallowing, and taste sensations.

A loss of lubrication resulting from a loss of saliva production of oral mucosa will also increase frictional or irritation damage, and change microbial attachment. Presence of microbial biofilm on pharynx. The pathogenesis of oral tissues increase risk for diseases (e.g., pharyngitis, dental decay, periodontal diseases) [3–5].

Particular attention should be given to the mucin proteins (MG1, 2). These proteins have unique rheological functions to promote adhesion of microbes with a high degree of elasticity, and low solubility. This is expected to be reflected by microbe attachment to surfaces that can be coated by these proteins. However, they have another function which becomes apparent with their loss. Loss of saliva and mucins can occur because of host inflammatory damage in salivary tissues (e.g., sialoitis), proliferation of oral microbial flora in salivary and adjacent tissues and increased host inflammatory response as a consequence of other health issues related pathology from autoimmune diseases, salivary neoplasia, physical or chemical damage to salivary gland, atrophy resulting from aging or use of products (e.g., tobacco, alcohol, recreational drugs (marijuana) that contain genetic damaging chemicals (e.g., N-nitroso aromatic and polycyclic aromatic compounds). Moreover, on a molecular basis, post translation and synthesis modifications of mucin proteins can occur with release of proteases from bacteria or other microbes [10–12]. This offers an opportunity for extension of molecular effects to produce functional changes in mucin proteins.

A loss of mucin proteins and a loss of anti-microbial protection can become evident on calcified surfaces in addition to soft tissues. A loss of mucin protein

changes enamel pellicle which is composed primarily of precipitants of proteins from saliva but also including other fluids (e.g., transudate, exudate, cellular secretions). Enamel pellicle formation, specifically, is a protein precipitate formed from hydroxyapatite salivary proteins (e.g., mucins, and proline-rich proteins), serum proteins and microbial glucans and glucosyl-transferase. This enamel pellicle is promoted as a substrate for clinical oxidation through a bleaching procedure to "whiten teeth" but with modification of enamel pellicle a shift in microbial adhesion could alter distribution of selected microbial populations and assist in loss of dentition as microbial bioflim is stressed to produce more virulent rare microbes not only on the surface of dentition but gingival tissues [13, 14].

In its specific context, enamel pellicle has little direct influence upon soft tissue responses and microbial interactions. Therefore carcinogenic processes at first glance do not appear to be relevant. However, because we are examining a ecologic piece of a larger more dynamic system it is unclear whether long term effects of microbial distribution occur following; salivary mucin protein; enamel pellicle formation and microbial adhesion has on carcinogenesis risk particularly, among young individuals. These individuals are more susceptible to multiple decades of exposure experiences of DNA damage over a lifetime compared to more elderly individuals.

A loss of enamel pellicle manifests as a loss of control for microbial attachment and loss of a diffusion barrier to keep microbes away from the surface enamel and prevent dissolution of calcium-phosphate ions; an initial step for dental caries. There is also as stated before, a loss of effective lubrication which will enhance preferential accumulation of selected microbes and carcinogens as similar processes are developed on mucosal surfaces. The microbial selection comes about because some genera of microbes can metabolize carcinogens (e.g., N-nitroso aromatic and polycyclic aromatic compounds).

Moreover, there is a change in calcium-phosphate balance is also assumed to effect calcium sensitive epithelial responses to phospholipid membrane structures. Phospholipid and associated phospholipase activity activates membrane signal alterations (e.g., exposure to alternative pathway complement lectins (mannose, glucose, other sugars) derived from microbes, mitogens), diacylglycerol activation of protein kinase C and resulting calcinurin-calmodulin enhancement of NF-kB. NF-kB upon binding increases transcription at promoter TATA sites of c-fos, and c-jun oncogenes. These oncogenes function to regulate proliferation, differentiation and apoptosis (e.g., activator protein 1 (AP-1) is a transcription factor which is a heterodimeric protein composed of proteins belonging to the c-Fos, c-Jun, ATF and JDP families) [15, 16]. It is interesting to note that while inflammatory factors play a role in modifying this pathway there is a role for growth factors such as insulin and epidermal growth factors. These factors are associated with growth of transformed epithelial cells [17, 18]. In association with phospholipid/phospholipase signaling there is also an expectation for G protein complex activation that leads to calcium regulation by inositol 1,4,5-trisphosphate receptor (IP_3)r and calcium activation of phospholipase A_2 with p38 mitogen activated phosphokinase (MAPK). p38MAPK stimulates arachidonic acid down-stream effects upon immune products such as, prostaglandin, leukotriene and lipoxins and these immune regulatory factors are

released into the microenvironment through transudates, exudates, and saliva secretions [19, 20].

Another salivary protein family is amylase. Amylases are linked to digestion but these enzymes also have a regulatory role for bacterial adhesion to mucosal surfaces. Physiologically amylases have a broad anti-microbial function in tears, serum, bronchi, and urogenital secretions [3–5].

Another function of saliva is related to lubrication and swallowing. A health human forms about 0.5 mililiters per minute and 500 mililiters in a 16 hour period of the day. Swallowing of saliva is common but it is a avenue for chemicals, and microbes present in the hypopharynx and oral cavity to gain systemic access to organs of the lower digestive tract (e.g., esophagus, stomach, pancreas) [21]. Increased rates of swallowing will be initiated in attempt to increase lubrication of mucosal surfaces usually resulting with increased parasympathetic stimulation.

Saliva also plays a significant role in taste sensitivity because of its ability to modify adhesion of microbes to tongue and flavor receptors [22].

14.4 General Microbial Responses to Exogenous Agents

The oral cavity is known to contain bacteria and yeast (e.g., 700–800) with many more phyto-genetic types [9, 23, 24].

Microbes also interact with oral epithelium routinely:

1. in “planktonic capacity”, with hit and miss interactions that are transient but also in
2. in substantial and persistent forms of bio-films. These types of complexes of microorganisms are stated by National Institutes of Health; as associated with 80% of chronic infections. Moreover, there is a selection of microbes present in the oral cavity because of habits such as tobacco use. For example, a review of the published literature indicates 30 microbes associated with tobacco are also associated with oral diseases which include periodontal diseases and/or oral cancer.

Biofilms are complexes of microorganisms that form and reform matrices to eventually produce protective niches of plaque or calculus on tooth, ‘gum’, and other tissues in pharynx and oral cavity to create continual microbial colonies or communities. In these microbial communities are communication networks based upon metabolism and release of metabolic derivatives called a phenomenon of “quoran sensing”. Dr. Monroe, has described, five phases to this process: Stage (1) Attachment; (2) Irreversible Attachment; (3) Maturation; (4) Maturation II, and (5) Dispersion.

We also recognize that the time allotted to each stage will vary in regards to microenvironment condition; types and number of microorganisms forming each bio-film layer; salivary concentrations of bacterial static and bacteriocidal chemicals; flow dynamics of saliva; mechanical action of the tongue; oral hygiene habits such as brushing technique and dietary content in regards to polysaccharides.

Salivary flow dynamics can also sculpture regions of the bio-film levels and alter concentrations of a myriad of chemicals that influence optiminization of specific colonies. These chemical processes include acidification (pH), oxidation; nitrogen levels (e.g., capacity for conversion of nitrate to nitrite and formation of reactive nitrogen compounds), and presence of metal cations such as iron or calcium which influence cytochrome P_{450} metabolism of microbes [25–30].

14.5 Microbial-Epithelial Interactions a Prelude to Carcinogenesis

Biofilms formed from microorganism are continually changing as new matrices are laid down (e.g., induction of symbiosis) and modified (e.g., induction of parasitism). These bio-films produce protective niches of plaque or calculus on hard tooth surfaces and/or soft oral mucosa with additional incorporation of calcium with accretions from salivary flow from minor salivary glands or submandibular glands. Stated above, accumulations of calcium or phosphate derived from tooth or bone surfaces are a product of an acid pH on the calcified structures with the formation of a metabolic acidosis in adjoining soft tissue mucosa. Metabolic acidosis is identified with an increased concentration of carbonic acid or a decrease in buffering capacity for acid or proton secretion. One way this occurs is by a loss of bicarbonate in saliva. This physiologic disturbance produces a physiologic change in oral mucosa (e.g., attached gingiva) with formation of hypoxia conditions and ischemia. Continual presence of microbial colonies or communities form communication networks based upon metabolic needs and release of derivatives to establish unique centers of "quoran sensing" for each biofilm. There is also an evolution of the biofilm with specific microbial populations. Initial microbial colony formation in a specific ecologic nutritional layer is persistent while other microbes contribute to extending biofilm matrices as microbes adhere and nutritional requirements are addressed for a particular micro-environment.

14.6 Viral Association with Carcinogenesis

It is also notable that oral squamous cell carcinoma is predominantly associated from tobacco smoke product use and other habit linked etiologies (e.g., alcohol product use, poor oral hygiene). These exposures are predominantly found among an older population in comparison to smokeless tobacco product users which are younger [31, 32].

Recognition of this age distinction is important because there is a shift in demographics for head and neck squamous cell carcinomas (HNSCC). Specifically, there is a significant increase of oropharyngeal carcinoma compared to oral squamous

cell carcinoma (OSCC) and this shift is predominant in North America and Northern European countries [33–36].

An important feature found among oropharyngeal squamous carcinomas (e.g., tonsil region) is a high incidence of human papiloma virus (HPV), oncogenic subtype 16, infection compared to OSCC. Oropharyngeal carcinomas are also distinctive in their epidemiology; for example, increased oral sexual activities, numbers of sexual partners and use of marijuana are predominant factors associated with oropharyngeal carcinoma as compared to OSCC. In contrast OSCC is often found among an older population (>35 years of age) that drinks more alcohol, uses more tobacco smoke products and has poorer oral hygiene [37–40].

The inductive capacity of HPV 16 to produce a malignant transformation is still unclear in oral pharyngeal and cavity carcinomas. It is our suggestion and general concept that **poly-microbial associations are likely influencing carcinogenesis in these sites but in different ways**.

For example, smokeless tobacco products damage oral mucosa at the site of placement and we observe this damage in the form of "koliocyctic change" in nuclei and cytoplasam of keratinocytes. This "change", has been associated with a virus exposure. This is likely to be either a HPV or Herpes type virus. This association with the continual placement of this tobacco product is expected to an injured mucosa and contribute to the loss of surface epithelial protection from viruses.

On the other hand use of tobacco smoke products also contribute to loss of epithelial protective mucosa surface as smoke and cigarette, pipe or cigar abrades underlying mucosa with lips and musculature holding the device in place. The physical technique of smoking is one variable, but there are others. These include: how long the smoke is held in the pharynx and oral cavity, velocity of smoke movement, extension of smoke into nasopharynx, esophagus and upper aerodigestive system, flavor of smoke as a stimulant of salivary flow, and presence of a chemical composition that is acting as a nutrient pool for microbe metabolism. Tobacco smoke derived chemicals produce a carcinogenic environment which can coexist with viral carcinogenesis include: nicotine, tobacco specific nitrosamines, poly-cyclic aromatic hydrocarbons, alcohol, sweeteners, simple sugars, phenols, volatile aldehydes, nitrates, fermentation products.

Velocity of particles from tobacco smoke can also produce a damage to cell surface membranes of epithelial cells to stimulate a stress (e.g., physical, oxidative) response to cause release of peroxidation products, and immune generated factors that modify surface glycoproteins and influences adhesion of microbes [41–43]. A clinical appearance of chevron-like keratinization of the epithelium characterized by a pumice-like appearance is often a manifestation of smoke exposure [44].

This inflammatory process that is generated is not expected to be localized but it is expected to be a generalized phenomenon to enhance presence of various microbes. On the other hand, viral attack is expected to be specific targeting of susceptible cells. For example, HPV attack of basal-stem cell like populations of keratinocytes. It is our further expectation that HPV and Herpes family of viruses (HHV) infections are specific to enter keratinocytes and therefore alter host resident and opportunistic colonies of bacterial species that form biofilm.

14.7 HPV and Head and Neck Carcinogenesis

In the oropharynx mucosa as in other epithelial structures there is a compartmentalization of cells. In this context, HPV movement through weakened tight junctions and eventual entry into basal keratinocytes at sites of inflammation is often tied to presence of habits that introduce concentrations of chemicals. In this situation smoking of marijuana and exposure to cannabinoids magnify the effects of heated smoke containing particles that are capable of moving at relatively high velocities.

Inflammatory weakening of epithelial attachment, intercellular bridge-desmosome tight junction, and membrane proteins as stated above is a prelude to HPV activities in keratinocytes (e.g., loss of tumor suppressor function or reduction in expression of desmosome proteins to further weaken epithelial attachment: claudins, integrins, glycol and mucoproteins, phospholipoproteins) [45–47].

HPV (16/18) attachment results from cell surface membrane proteoglycan/mucoglycoproteins, common determinants (e.g., CD24) and enhanced expression of serine endoproteases such as furin convertase [39, 48].

In conjunction, we expect a surface proteoglycan-heparan binding protein complex to facilitate attachment of various microbes, such as *Streptococcus* sp. This genus of microbe can attack oral mucosa and reduce integrity [49, 50].

Metabolic, biochemical and molecular events associated with HPV oncogenic subtypes (16/18) have been described [51–53].

In brief, HPV 16 and 18 subtypes produce L1 and L2 surface late proteins. L1 is a substrate for furin convertase while L2 assists in stabilizing the entry of HPV into the basal keratinocyte. In addition, early proteins during replication of the virion after entry and following incorporation into the genome of basal keratinocytes can occur. These early E6/E7 proteins are localized to p53/retinoblastoma (Rb) protein complexes that also contain proteins that regulate check point control regulation (e.g., p53/p73/cyclin D1/p27 CIPI/p16). E6 suppresses p53 function regulation at G_1 check point and uncouples p73 maintenance of p53 tumor suppressor activities such an apoptosis and genome DNA repair in conjunction with increased telomerase activity. HPV 16 E7 shows homology with the pRb binding sites of cyclin D1 and releases E2F. E7 directly binds to p21, and releases PCNA and other S-phase promoting genes. p16 is in contrast with p53 loss of function; as p16 is increased in expression and correlates with HPV 16 infection. E2F activates cyclin E, and cyclin E accelerates p27 proteolysis of its own inhibitor. The induction of p16 expression is assumed to be indirectly associated with E7, which is upregulated only after prolonged inactivation of Rb, though loss of phosphorylation [54]. E7 suppressors of Rb phosphorylation also depresses tumor suppressor function. In addition there are increases in growth factor transcription for epidermal and keratinocyte growth factors with a stimulation of growth for transforming clones of basal keratinocytes [55–57].

PCR assessment and immunohistochemical identification of p16 are used to identify HPV infection in head and neck tissues [58, 59] with p16 expression

becoming an important clinical indicator of a good prognosis for HPV related carcinoma.

Stated above tobacco use is often associated with oral squamous cell carcinoma in comparison to oropharyngeal carcinoma which is more likely linked to HPV 16 infection among young Caucasian males and to a less extent; females. We expect HPV related carcinomas are not as often associated with tobacco smoke product use because of the microbial population (e.g., fungi and bacteria) located in the oropharynx compared to the common sites for oral carcinoma presentation. These include floor of the mouth, base of the tongue and lateral border of the tongue. In addition, modification of HPV 16/18 capacity to attach and enter into basal keratinocytes is expected to be different at these various sites because of the chemical contributions by microbes present in biofilms. Moreover, the type, number and localization of specific microbial species, for example *Streptococcus* sp. is also anticipated to be modified. *Streptococcus* sp. differ in the oropharynx compared to oral cavity sites because of changes in surface physiology attachment; metabolism; genetics (e.g., increased expression of cytochrome P_{450}s, ADH, ALDH genes) and saliva interaction with specific microbial strains and subsequently keratinocytes [50].

A strong association between risk for oral squamous cell carcinoma and use of tobacco products as been repeatedly documented but this relationship is not clearly demonstrated for smokeless tobacco products or association with HPV [60–62].

However, Rodu and Jansson; in a "summary of relative risk" (RR, approximates confidence interval see equation Evolutionary Influence and Epithelial Responses) for oral cancer and related sites, showed an "increased incidence related to smokeless tobacco (ST) product type" for oral/pharynx/larynx and chewing tobacco; larynx for moist snuff; oral cavity/pharynx/larynx for dry snuff and oral cavity/pharynx/larynx, for unspecified smokeless tobacco products [63]. Unfortunately, in their discussion there is no attempted correlation to specific histopathology presentations that distinguish different forms of oropharyneal and oral squamous cell carcinomas a OSCC. These histopathology differences are important because they can be tissue site specific and the cancers are also characterized by different survival curves, responses to treatment and growth behavior. For example, squamous carcinomas that are infected by HPV 16 in comparison to those that lack this infection grow slower and patients with an HPV related carcinoma have a better prognosis (see [37, 53]).

Evidence for an association between ST and HPV related cancers is presented by Geer et al. in his histopathology description of ST exposed attached gingiva, mucosa [64]. Furthermore, in his analyses: 10% of lesions were HPV associated with ST leukoplakias; 3% with dysplasias, and 20% of OSCC had HPV subtype identification [64, 65]. The validation of this finding will demonstrate a wider distribution for HPV subtypes in the oral cavity and a possible more involved actor in malignant transformation in oral cavity sites.

In terms of current diagnostic histopathology, these lesions are candidates for "koliocytic dysplasia" (SIN: 1–3) but the clinical significance for malignant transformation is still unclear [66].

Lee and Hamling provided additional indirect evidence for this relationship between ST and oropharyngeal cancers by showing a estimate for an association and this association was later confirmed by Rodu and Cole [67] and Rodu and Jansson [63, 67].

Further study is required to validate this relationship between ST use and HPV related oropharyngeal carcinoma. It is our expectation that a validation of this relationship would demonstrate that ST use places adjacent mucosa under provides continual attack on oral mucosa and chemical modification by various microbial species. This process is associated with changes in a previous established symbiotic physiologic relationship between the microbial biofilm and the oral mucosa to produce loss of mucosa functional integrity. Therefore loss of covering, and immune protective activities contributes to an increased opportunity for rare microbes to infect oral mucosa tissues and accelerate a loss mucosa protective functions. The risk for HPV oncogenic infection at these sites are likely a product of the process described at to placement and at the site of placement. Our conceptual understanding is oral microbiota release varying concentrations of carcinogenic agents, modifying oral biologic conditions in the oropharynx and cavity.

In addition identification errors for HPV type has produced an unclear association with risk for oral disease. Typing is dependent upon technique and validation by histopathology using standardized molecular approaches [35, 68].

Recently we have reported on a role for microbial interactions with HPV oral keratinocytes damaged from exogenous epidemiology sources such as ethyl alcohol [50]. Moreover, OSCC exhibits relative low levels of HPV copies compared to oropharynx carcinomas. OSCC present with non HPV subtype 16 infections, and/or increased infection by Herpes type viruses (HHV-4, Epstein Barr virus; Simplex, HHV-1,2) accompanied by persistent presence of oral bacteria (e.g., *Streptococcus* sp.). On the other hand, oropharyngeal carcinomas predominant on tonsillar or, hypopharynx regions; are more likely to contain HPV 16 and other viruses such as Coxsackievirus or John Cunningham virus (JCV) (e.g. polyomavirus). These latter viral associations are interesting because they only occur in the oral pharynx (tonsil region) /base of the tongue (lymphoid area) respectively among younger populations that are immunosuppressed. In addition, JCV has also been identified on normal tongue at enhanced risk for OSCC [69].

In Fig. 14.1 we present an overview of these relationships. We emphasize that infection (microbial component), inflammation (host immune response), and genetics (inherent expression, genotype variations in particular environments) are integrated to produce neoplasia derived from selective clones of basal-stem cells in the oral mucosa that undergoes malignant transformation.

14.8 A General Overview of Models

Selective targeting of gene expression is evaluated in rodent models using knockout, knock-in and transgenic mice in association with a potent carcinogen that exposes the animal to direct carcinogen application in oral pharynx and cavity tissues or indirectly through dietary incorporation of carcinogen (e.g., 4-nitroquinoline-1-oxide) [70–77].

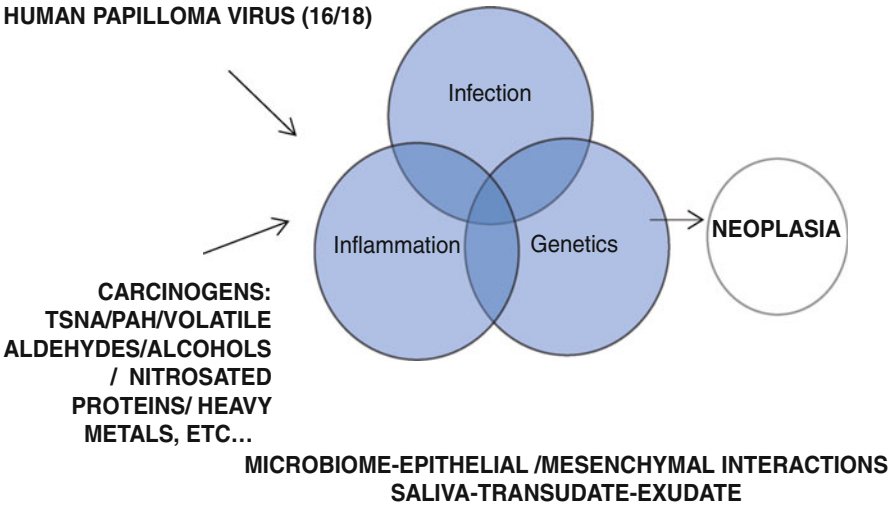

Fig. 14.1 Primary system processes that result in malignant neoplasia. This figure summarizes the interconnection between infection, inflammation (host response) and genetics to produce malignant neoplasia. Selection of malignant clones of cells is under influence of saliva and microbiome because of the variety of chemical and viral carcinogenic agents

Other standard head and neck carcinogenesis models are the Syrian hamster (Mesocrietus auratus), and Wistar rats that are exposed to chemical carcinogen. These models are used extensively to evaluate mucosa malignant susceptibility to chemicals found in ambient air, tobacco products, and other environmental exposures (e.g., Herpes simplex virus, alcohol). Use of PCR and hybridization offers an opportunity for genetic expression analyses (e.g., DNA, RNA, protein). It is recognized all models have similarities and major dissimilarities to human metabolism, physiology, immune reactivity, oral microbiology and anatomy (e.g., buccal mucosa pouch). For these reasons, our ability to correlate findings from an animal model to risk for human transformation among specific cellular sites for basal-stem cell like keratinocytes is not good, and needs to be improved.

Another example, gene expression responses are also used to validate specific DNA damage, and mutation generation associated with head and neck carcinogenesis following application of carcinogen in animal models (e.g., poly-cyclic aromatic hydrocarbon (PAH) or tobacco specific nitrosamines (TSNA) [78, 79]). Although histopathology presentation at tissue and gene levels significantly dissimilar to human cell and tissue changes. Great caution should be used in evaluation of result significance because of the stated differences.

Conceptually these animal models test presence and expansion of mutator phenotypes that are inducible by repeated exposure to one or several carcinogens. That is, they characterize the incidence of "**field cancerization**"**; which is definable by a single mutated stem cell that can expand into additional adjacent expanding**

clones of cells to produce a tumor mass. This process is repeated until a neoplasia forms. Formation of these neoplasias also consists of unstable cells that demonstrate chromosome aberrations in addition to multiple mutations. Therefore we can observe single base point mutations and nucleotide bulky DNA damages in many malignant cells. Furthermore, chemical carcinogenesis does not consistently produce mutation on identical chromosome and gene sites but there is a variability compared to DNA damages/mutation introduced through viral activity. Viral carcinogenesis is constrained by the biologic requirement for viral replication [80].

HNSCC induction lacks a clear distinction between viral and chemical processes however, they can occur simultaneously and are repeated until a malignant neoplasia results from multiple mutations and nuclear instability (e.g., acetylation, phosphorylation and methylation changes).

Animal modeling does have a role in examination of gene- tissue interactions but this approach should not be taken without acknowledgment of important exogenous factors that affect carcinogenesis peculiar to human HNSCC carcinogenesis. This understanding is exemplified as follows:

Models for Head and Neck carcinoma following exposures to tobacco smoke or condensate are used to produce changes in the airway. Associated with this change is the induction of inflammation with a selective cell death. This cell death can take the form of cellular suicide, apoptosis or loss of cell viability through inflammation to produce cell death and tissue necrosis. Bacterial infections; for example, Hemophilus *influenza*, Staphylococcus *aureus* and others, as well as, viral infections (e.g., influenza A virus, synthetic viral PAMP, poly (inosine:cytidylic acid) have demonstrated the induction of cell death through both processes. Furthermore, immunologic cell death attack is a consequence of exposure to tobacco combustible product administration in animal models. Moreover, tobacco smoke condensate, smokeless tobacco, or smokeless tobacco extract (STE), applied directly to oral mucosa produces tumors in animals. In the hamster buccal pouch and the rat lip canal models; tumorigenicity by the fore-mentioned, tobacco vehicles in terms of percentage of animals that eventually demonstrate malignant tumor and extensive length of time for tumor presentations is limited. In the case of the hamster, additional exposure to complete carcinogen such as, poly-cyclic aromatic hydrocarbons (e.g., 7,12 dimethylbenz[a]anthracene) is required to generate carcinoma. Dietary studies or administration of carcinogen through the drinking water; tobacco specific nitrosoamines (TSNA) or injected TSNA also produce systemic organ tissue tumors (e.g., carcinomas and adenocarcinomas).

However, the models cannot recapitulate use and exposures by humans to tobacco products [81].

Taken together the process of oral carcinogenesis in humans compared to animals is expected to differ as to metabolism and activities of chemicals, saliva (e.g., quantity, quality), microbial flora and interaction with adjacent oral mucosa. These variables ultimately have an impact upon quantity, site and significance of chemical carcinogens chemistry or viral entities damage effects on specific DNA, different forms of RNA and proteins. Moreover a central criticism of animal model carcinogenesis in comparison to human exposure experience is lack of exposure to complex environmental compositions that humans are routinely exposed. This is to a degree

considered when tobacco condensates are used in research studies, or exposure to tobacco smoke is studied in animal models. In the former situation smoke exposure in animal models effects upon head and neck tissues, although similar to human experience has several differences that require consideration. For example, a high metabolic respiration rate is found among small mammals compared to humans. This breathing pattern when identified among humans is associated with hyperventilation. A process that causes respiratory depletion of carbon dioxide, and respiratory alkalosis. This is corrected by increasing carbon dioxide; rebreathing into a paper bag, increased synthesis of carbon dioxide and/or decreasing pH. In contrast, metabolic alkalosis will effect local and systemic epithelial physiology with increased bicarbonate levels that influence selective microbial biofilm metabolic quality and quantity as a reduction in mucosa pH is noted. This response also reduces respiratory rate, increases PCO2, and depresses pH. Another variable is the transient velocity time of smoke in animal versus human head and neck tissues. Smoke velocity can cause a drying of oral mucosa, cause a physical injury to epithelial cell membranes; precipitate selective microbial proliferation and incidence of infection; enhance host inflammatory response and ultimately reduce integrity of mucosa for protection against opportunistic microbial attack. In this situation of tobacco condensate placement adjacent to oral mucosa in animals; hamsters or rats shows similarities with human oral mucosa tissue, such as a epithelial architecture and thickness. However, other associations reduce possible significance of any findings. These include: microbial biofilm interactions with oral mucosa; drainage of tissues; host immune activities, and quality and quantity of saliva. Moreover, appropriate concentrations are not used.

14.9 Epidemiologic Consideration for Head and Neck Cancers

Observing cases of HNSCC around the world; males present with 170,900 new cases a year, with 3.2 cases per 100,000; 0.9 deaths per 100,000 in developed countries and 107,700 new cases with 61,200 deaths in developing countries [82].

There is also noted to be a close association with geographic locations that have a incidence of one or more of the following behaviors: Use of combustible tobacco, non-combustible tobacco (e.g., smokeless tobacco products); use of other smoke products (e.g., marijuana); use of alcohol; exposure to human papilloma virus and other viruses (e.g., Herpes family of viruses); sexual activities that increase risk for exposure to viruses, poor oral hygiene (e.g., loss of dentition), and presence of an suppressive immune response often linked to infectious communicable disease [42, 43, 82–86].

This close link to behaviors; some with addictive (e.g., nicotine) habits and DNA damaging agents (e.g., chemical, viral, and other microorganisms) alters the normal function of mucosa as a protective surface.

Therefore HNSCC induction although affected by exogenous environment is also a consequence of individual exposures (e.g., microbiome, habits, diet, sexual/oral activities, etc) in conjunction with inherent genome expressions.

However, as described above, we also recognize considerable efforts are expended to understand genetic function and expression capabilities during formation of mutation sites and as a mechanism for loss of cell growth regulation (e.g., repair: base excision, nucleotide excision, mismatch etc.). Unfortunately a larger picture which examines Darwinian type selection; driven evolutionary-ecologic influences from exogenous factors will provide a more complete understanding for a role for mutation and survival selection of particular clones of basal-stem cell like cells to develop a malignant tumor mass (e.g., squamous cell carcinoma) in the head and neck region [87].

Carcinogenesis is dependent upon interaction with a specific cellular target, receptor or membrane process (e.g., cathrin coated vesicles, transport pump) that is often linked to critical differentiation of the target cell (e.g., AKT/PETN/mTOR). This association is also linked to physiologic regulatory pathways (e.g., oxidative metabolism) for proliferation and eventual transformation (e.g., sufficient DNA damage, lack of DNA repair or faulty mechanisms at both DNA and RNA levels).

In addition, we expect deregulated growth resulting in loss of check point control and a reduction of cells at rest (G_0); with accumulations of epigenetic events that lead to unstable nuclear expression and patterns of gene expression (e.g., methylation silencing of tumor suppressor genes, acetylation of histones, and phosphorylation with selective kinase activities and unbalanced phosphatases activities). It should also be noted that HPV oncogenic subtypes (e.g., 16/18) will induce epigenetic methylation silencing of tumor suppressors such as p53 [88–90]. There, chemical and viral carcinogenesis achieves malignant transformation using a comparable pattern of cell physiologic capture.

Tissues such as oral mucosa seek to maintain "physiologic norms". These "physiologic norms" include oxygen partial pressure/ partial pressure of carbon dioxide, pH, energy stability functional activity of cytochrome P_{450} enzymes, and regulation of cellular structures (e.g., membrane, cytosol, organelles, nuclear structures and process of division). To accomplish this feat tissues and cells are dependent upon the micro-environment and macro-environments. These environments reflect release of a myriad of immune factors, growth factors, extracellular matrix chemicals, hematologic agents, neuopeptides, and electrolytes – ions that flow across membranes. This chapter examines cellular factors that address evolutionary advantage to cell transformation as a reflection of environments.

14.10 Oral Biologic Features that Regulate Head and Neck Carcinogenesis (HNSCC)

Characteristics of HNSCC are not unique to development of HNSCC but share commonalities to other squamous cell carcinomas.

However there are features that are peculiar to head and neck tissues and these include some differences in: anatomy, microbiology, immunology, chemistry, physiology, and tissue conditions (e.g., lubrication, drainage, inflammatory host response).

Anatomic arrangement of mucosa places a large surface area exposed to the outside environment. This level of exposure is also unique because we have the opportunity to repeat examinations of tissues in direct contact with a variety of chemical compositions from diet, ambient air, and habits. This environment creates ecologic niches that maintain and promote the growth of a complex and large microorganism community (e.g., 600 to 800 taxa of microbes). These microorganisms in the course of their survival response to a pharynx/oral cavity environments release chemicals to form a biofilm in a symbiotic relationship with host epithelium. Additional interactions occur that results in a loss of the initial symbiotic relationship but is quickly replaced with another. However, repeated changes in symbiosis can lead to a parasitism among microbes on host oral mucosa tissues. Eventually the integrity of the mucosa is compromised a state of disease with pathologic change in tissues is observed. This interaction between microbes and epithelial surfaces also results in continuous host inflammatory activities that function to control virulence; growth and chemical release by microorganisms [7, 9, 24, 91].

There are also multiple fluids that bath all cells (e.g., microorganisms and eukaryotic epithelial cells) in the pharynx and oral cavity. These tissues have a variety of functions (e.g., saliva, transudate, exudates). These functions as stated previously include immune activities, microorganisms growth regulation, lubrication, assisting with swallowing, taste, and sensation [3–5].

Furthermore, immune reactivity is demonstrated to differ in oral mucosa settings compared to other epithelial surfaces because dendritic histiocyte, Langerhan cells; thymic (T) derived lymphocytes (gamma/delta receptor repertoire), a unique immunoglobulin cadre (e.g., IgA, IgG, IgM) that provides an anti-viral capacity and a selective hypersensitivity capacity [92–94].

Previous reviews of head and neck carcinogenesis, are focused upon inherent genetic expression effects but unfortunately not discussed are oral biology integration events that are in response to habits such as tobacco product use.

However, as noted above, an important observation is the "**field cancerization effect**". This **principal asserts that development of a predominant clinical cancer in the head and neck does not completely describe a level of transformation because there are many other sites of malignant transformation identified by chromosomal or gene changes. These genes are not all somatic and relatively new nucleotide changes can be admixed to older persistent nuclear instability damages. Furthermore, some are non-somatic, but linked to sex chromosomes or are manifestations of poorly organized DNA repair and/or chromatid arrangements during mitosis cells that have not attained clinical relevance** (e.g., cytogenetic abnormalities, loss of heterozygosity, etc.) [95–103].

HNSCC carcinogenesis is more common among older individuals, although as stated above a growing number of individuals are presenting with HPV related oropharyngeal carcinoma at younger ages. However, as also stated above both age groups will present with multiple "hits" to susceptible basal-stem cells (see "two-hit hypotheses": Armitage and Doll, and Kundson hypotheses) that are probable candidates for a **resting cell phase designated, senescence (e.g., G_0).** Oral squamous cell carcinoma (OSCC), non-HPV related carcinomas occurs more commonly over many years compared to HPV related oropharyngeal carcinoma. Stated above, a lack of DNA repair

completeness is apparently compromised in both oropharyngeal and OSCC regardless of differences in time requirements for cancer development. However, it should be noted that HPV related carcinomas in general grow slower, demonstrate a less aggressive behavior, and respond more effectively to treatment compared to non-HPV related carcinomas of the head and neck. This difference in growth is expected to be a product of differences in mutation location and number in conjunction with the other characteristics we have already stated (e.g., microbiome interaction with mucosa, chemistry, physiology between oropharynx and oral cavity tissues).

Different tissues in the head and neck will also demonstrate differences for risk to induce specific malignant transformation type cancers. One often overlooked reason for susceptibility to cancer induction is because of the anatomy of the tissue. For example, hard palate keratinized mucosa is less of a target for carcinogenesis to form squamous cell carcinoma compared to induction of salivary gland carcinomas (1–3% of head and neck cancers; 2 per 100,000 with 18 different histopathologies) (e.g., mucoepidermoid and adenocarcinomas) [104–107]. Palatal mucosa does not contain a submucosa which results in salivary gland and lymphoid tissue closer to the epithelium but also to the oral environment and microbial biofilm. Furthermore, the turnover rate for keratinized epithelium from the hard palate is about 30 days compared to 22 days for the floor of the mouth or 25 days for the attached gingiva mucosa adjacent to teeth. Turnover rate is an anatomic characteristics that effects both microbial biofilm and physiology of the oral keratinocytes.

Moreover, both squamous cell and adenocarcinoma tumors are linked to exposure to environmental chemicals such as poly-cyclic aromatic hydrocarbons (PAHs). A review of the molecular biology markers of these different tumor types also dissociates these carcinomas. It is also evident that response to PAHs or other carcinogens (e.g., TSNA) will involve not only the chemistry of the carcinogen; receptor biology (e.g., aryl-hydrocarbon receptor, nicotine acetylcholine receptor) [108–110]; but also capacity to diffuse through membranes (e.g., vesicles). An example of a non-PAH carcinogen that has these capabilities is acetaldehyde [111].

Once a chemical agent enters into a target cell chemical complexes form. PAHs form a variety of Aryl Hydrocarbon receptors (ARHr) complexes that metabolize and binds several exogenous chemicals such as polyphenols, indoles, synthetic polycyclic aromatic hydrocarbons and dioxin-like compounds. TSNA (nitosoamines/N-nitroso aromatic compounds) also bind to different cytochrome P450s (e.g., CYP 3/4A). In addition, nicotinic receptors complex with various cytochrome P_{450}s are also activated (e.g., CYP_{450} 1A1, 1A2, 1B1, 3A4, etc.). The ArHr complex is a developed translocation complex that combine with transcription factor molecules such as, basic-helix-loop – helix Per-ARNT-SIM. Additional interactions occur with p300/p53/p21/cyclin D1 complexes. These latter molecules are associated with post translational regulation of tumor suppressor proteins. Translocation of fore-mentioned complexes from cytosol to nuclear sites results in activation of the xenobiotic gene responsive system (e.g., xenobiotic responsive elements, XRE) in concert with major drug resistant gene (MDR) expressions (e.g., P-glycoproteins for ATP-binding cassette (ABC) family of drug transporters transcription) and a general phase I, transcription balanced by phase II, glutathione-S-transferase activities to control DNA damage (e.g., oxidative and bulky adduct induction) [112–118].

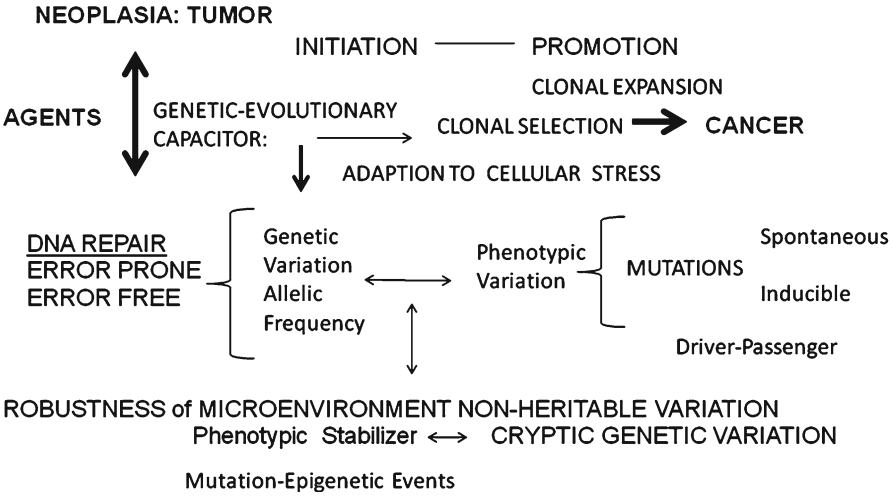

Fig. 14.2 Evolutionary forces that are associated with cancer (HNSCC). This scheme disclosed that initial clonal selection begins with an initiation of DNA damages that result in mutations and then produces promotion of the clone. Some driver mutations are error prone for repair activities, while other are error free or become passenger mutation. Error prone DNA repair offers an opportunity for persistence in a particular microenvironment. This is also a product of allelic frequency variation and eventually phenotypic change to survive in a particular environment as described by robustness and genetic variables

Response to chemical carcinogens is also dependent upon susceptibility genes that can be classified as genes for metabolism such as CYP_{450}s, genes for regulation such as, oxidative damage (e.g., phase II, GST genes) and genes that control a cellular physiologic activity for example, proliferation (e.g., p53, Cyclin D_1) and apoptosis genes (e.g., cysteine proteases- caspases or inhibitors such as Bcl-2, MDM2 families of genes). Individualized responses can occur because the gene expression is regulated by polymorphisms, variants, regulated micro RNA and protein functionality (e.g., microRNA, large coding RNA).

HNSCC mutation lesions contain gene damage that controls DNA repair or tumor suppressor genes such as p53 (e.g., "guardian of the genome"). Although, we contend that mutation identification is insufficient for understanding development of HNSCC under a variety of epidemiologic presentations, ages, and associations [119–124].

Cairns [125] discussed the possibility that carcinogenesis in epithelial tissues as a result of non-competitive factors. In oral pharynx and cavity epithelial mucosa this concept does not appear to apply because selective advantage of a developing clone of transforming basal-stem cells is a product of highly competitive natural selective forces for limited chemical, physiologic, and nutrients as a result of microbe-keratinocyte interaction [125].

We contend models that emphasize somatic gene mutation frequencies do not appreciate carcinogenesis complexity particularly in head and neck tissues (see Figs. 14.1 and 14.2).

Moreover, an initial assessment of ecologic – evolutionary approach to understand HNSCC carcinogenesis has a quantitative difficulty because of the number and type of variables that require examination to understand chemical and physiologic contributions from oral microbiome and mucosa epithelium, immune cells, stromal-mesenchyme and fluids. To examine these relationships is also difficult because there of dynamic changes in chemistry and physiology with small variations have a profound effect on rate of malignant transformation in mucosa. Compounding this problem is the use of animal models or constrained laboratory cultures of bacteria or yeast which provide a short term, and limited view of changes that occur during chemical and viral carcinogenesis.

14.11 Evolutionary-Selective Effects Upon HNSCC Carcinogenesis

The management of potential malignant lesions, regardless of etiology, requires great attention because a risk of malignant transformation is present, although relatively low at about 1%. This means that about 4 persons per 100,000 are at risk of oral cancer [126]. In comparison, a realistic estimate of the risk for oral cancer in patients who use smokeless tobacco use is 0.25–0.5% (e.g., 1–2 persons per 100,000 who use ST products). The risk is expected to be higher among individuals with multiple exposure risks (e.g., 2–3% with 8–10 persons per 100,000 at risk for HNSCC [127]).

We therefore assume a small stem cell population is present in the mucosa as a source of carcinogenic transformation potential. In the case of oropharynx or oral cavity this population remains relatively stable over years of exposure to a variety of mutagenic, carcinogenic, or toxic agents. However, eventual loss of epithelial stability with a loss of normal physiologic activity increases the numbers of progenitor-stem cell like stem cell keratinocyte populations and this leads to a malignant transformation environment.

14.12 Multi-stage Predicators for HNSCC

Decades ago a paper by Armitage and Doll in 1956 began assessment of carcinogenesis by exploring evolutionary biologic influences [130, 131].

In this context cancer is understood as a process of survival of the fittest composed of distinct genetic mutation events that changes cellular function and structures. Targeted for mutation are genes needed for DNA repair, regulation of growth, control of apoptosis and maintenance of nuclear stability. It was expected that a mathematical approach would provide a general scheme that incorporates the fore-mentioned gene mutations into a risk assessment for induction and

progression of cancer at various times of life. Therefore it is expected that mathematical views of cancer progression will meld into our understanding of various selective genetic factors such as, environmental changes; epigenetic events (e.g., methylation, acetylation phosphrylation) geneti; chemical and cell physiology changes to provide a predictive time oriented tool to evaluate specific cell type (e.g., progenitor-stem cell like population) malignant transformation and cancer risk behavior.

Armitage and Doll pointed out that in the 1950s [128] and later [129] suggested that an understanding of carcinogenesis could be gleamed from an assessment of rate of appearance of multiple mutations over generations at particular ages (t) and this is useful when we assess probability of occurrence of each mutation per unit time using stages or generations:

$$\text{"ie., rate=k}p_1p_2p_3p_4p_5p_6p_7t^6\text{"} \quad \text{"k=a constant"}$$

"They stated, logarithm incidence rate (for cancer) will be directly proportional to concentration of a carcinogen". This is in an environment in which mutation appearance is also proportional to a carcinogen concentration and we assume that mutation appearance is equal to incidence of mutation induced cancer. Following this assumption Nordling grouped cancers present in men with an additional assumption that carcinogenic activity and subsequent mutation induction would be unchanged as to number; quality or risk at a particular age. Therefore there was a age dependence liked to type of mutation for a specific cancer. However there was a consideration; "that the entire increase in cancer incidence among adults was not wholly explicable by a mechanism of multiple mutations". Recognized by Armitage and Doll [130] was the inequality between total carcinogenic potential and mutation. Our concern was the determination that "nature of the cellular change is irrelevant to the mathematical analysis". Furthermore, they postulated that changes of state should be stable, specific and discrete for each stage of carcinogenesis (e.g., initiation, promotion). Unfortunately for various human tissue systems these assumptions do not work. For example, complex dynamic interactions between microbial biofilm and epithelium or between adjoining epithelium at different stages of differentiation are not stable and they are relevant in our understanding of HNSCC carcinogenesis.

Another example is concentration of carcinogen derived from a well documented cause of HNSCC, which is smoking tobacco. Concentrations of these DNA damaging chemicals can vary depending on type (filter/non-filter, type of filter) of product, numbers of exposures per day (pack years), or how the product is smoked by the individual. In addition, age, sex, placement location of tobacco product in mouth can also influence exposure to carcinogen and therefore vary quantity and quality of mutations produced. Still other variables include: cultivation conditions, fermentation and processing of tobacco leaf. Moreover, variables of product use, such as, manner of smoking (e.g, differences in inhalation versus expiration); and presence of additives, will also effect carcinogenic risk from this product. Furthermore, the

impact of the product on human tissues will vary depending on genetic susceptibility and additional biologic factors. These include: quantity and qualities of saliva, metabolic activities of microbes, genetic capacity for DNA repair inherent in the individual's genome (e.g., phase I, CYP_{450} activity), and the presence of other chemicals and possible chemical interactions that change binding capabilities (e.g., cross talk between sterol hormones and PAH carcinogens).

These earlier investigators recognized carcinogenesis is a multi-stage process, and they assumed cancers show a uniform and predictable relationship between death rates at any power for any age based and carcinogenesis progression. They further stated this question: is incidence of any cancer at any age "proportional to complex variables"?

This complex and difficult relationship becomes important in addressing incidence of HNSCC, but this contention: early incidence reflects presence of many variables is not found in the presentation of various HNSCCs. The evidence appears to indicate that quantity increase risk but biologic impact is also important. Oropharyngeal carcinoma is often found among young individuals because they will also present with a set of other variables (e.g., habits, sexual activity, pharyngeal infection, oral hygiene). Furthermore, in this situation the time interval to generate the carcinoma is significantly less than the time required for most oral squamous carcinomas to develop in older populations. A higher number of variations in mutation, increased numbers of mutations, and more effective transformation during carcinogenesis for OSCC compared to HPV related oropharyngeal carcinoma is observed.

Mutations found in HNSCC of the pharynx results from a high degree of functional loss of regulation of DNA repair, accompanied by proliferation, and nuclear stability, while losing a capacity for apoptosis. The comparative rapid onset of many oropharyngeal carcinomas is consistent with viral cancer induction (e.g., HPV). Viral entities unlike chemical inducers require survival through replication and is less common among OSCC. In this instance we predict using the Armitage and Doll equations more "hits", and/or mutations for chemical carcinogenesis in comparison to viral (HPV) carcinogenesis but these mutations in OSCC are less capable of rapid transformation compared to viral attack and mutation induction (e.g., HPV 16) in oropharyngeal carcinoma.

14.13 Mutation and Carcinogenesis

In general mutation and DNA damage is caused by chemical/physical agents, viral entities, and inherent random/spontaneous errors. These latter errors can occur at genetic replication sites, cell regulatory regions, and promoter regions for repair genes.

Genetic damage can take the form of a single base, nucleotide, cytogenetic aberration, inversion, reversion, transposition, or multiple/single detections [132]. Therefore the genotypic profile can vary among cancers that have identical pathology diagnoses, and clinical staging. The ultimate manifestation of the cancer condition

is invasion into adjoining tissues, and proliferation of malignant clones of cells that spread from primary to distant locations.

Head and neck carcinogenesis is intertwined in oral biologic principles. Survival of malignant clones of cells is dependent upon a dynamic interaction of unique oral biology factors. These include such examples as, saliva contents and flow; continual changes in microbial biofilm; alteration of microbial-epithelial interaction within oral mucosa tissues; activity of host derived immune factors (e.g., immunoglobulins, other immune factors) and cell types (e.g., dendritic cell population, granulocytes, lymphocytes). The microbiologic ecology, associated chemistry and physiology of epithelial cells also assist in the selective survival of one population of cells over another at various sites in the oral cavity and pharynx. An evolutionary-ecologic process is therefore inherent to carcinogenesis because it creates a phenotypic-genotypic variability required for survival of clones of basal-stem cell like keratinocytes,

Head and neck carcinogenesis is a consequence of multiple DNA damages, "hits" over time to produce persistent mutation and damage among growing numbers of progeny coalescing to form a tumor mass. In comparison to simpler carcinogenesis inductions such as chronic exposure to radiation the fore-mentioned biologic events found among HNSCC are not comparative with radiation induction because the relative risk rates for HNSCS in certain populations with specific exposures and habits are higher and more dynamic. The relative risk induction for cancer described by Moolgavkar [133] using static mathematical models (e.g., Armitage and Doll [130]) is a useful tool to asess the impact between different etiologic factors such as exposure to multiple environmental factors or a single factor.

In response we consider age related incidence rates per 100,000 (about 4 per 100,000 for individuals with multiple exposure risks) for HNSCC as evidence of a dynamic variability associated with the incidence for HNSCC. Stated above there is a age dependence between oropharyngeal carcinoma and OSCC carcinomas even though the rates of these cancers can vary to a degree among specific populations. Variation in rate of incidence for HNSCC can be described as μ_1,μ_2, or both.

In a cell population given by $I(t) \times 10^5$ where I the function of $(t) = m_1 m_2$ (transition rates per cell per year) integrated from 0 to time t in the range of susceptible cells X(s) (e.g., basal-stem cell like, keratinocytes) at time of presentation with HNSCC (age)s. In addition the range includes $\alpha_2 - \beta_2$ which is the difference between proliferation rate and death rate incidence of the cancer. Furthermore, in the head and neck we can expect changes in the environment that will result in appropriate changes in $I(t)$ when μ_1,μ_2,α_2 and β_2 are not constant. This equation therefore is describing promotion effects to a greater degree than initiation in which μ_1 and μ_2 have smaller effects on incidence curves than promoters that influence $\alpha_2 - \beta_2$. In summary this mathematical model is useful to attain an overview of malignant transformation at a select cellular level, for basal-stem-like cells under a set of environmental conditions as previously discussed to provide a description dependent upon the kinetics of growth and differentiation of mucosa.

In addition, previous environmental carcinogenesis processes examined the cancer inductive capacity of a single agent although beginning at time 0, birth. Therefore an assumption is made that "expression for age-specific incidence rates shows risk in

persons exposed to a given dose relative to nonexposed individuals remains constant with time". Moreover, an agent can increase the proliferation of intermediate cells (e.g., a cell derived from a clone of cells undergoing malignant transformation) by a constant amount (i.e., increases $\alpha_2-\beta_2$ without affecting transition rates), then the risk in persons exposed in a carcinogenic environment (e.g., exposure to carcinogen/or carcinogens over time zero to tx in a genetic susceptibility background) relative to those not exposed increases with time. For example, an agent (promoter) affects the kinetics of "intermediate cells", then duration of exposure to this agent is an epidemiologic "effect modifier" (a chemical, environment, and/or gene set that influences the selection and survival of derived cells from expanding malignant clones of cells). In other words, an initiator carcinogen will in the course of carcinogenesis demonstrate a cooperative effect upon promotion; to include not only the initial clone of basal-stem cells but extend the carcinogenic process to other self generating clones (e.g., intermediate cells). This results in more cells in among basal-stem-like cell clones that are at risk for malignant transformation in various stages compared to identical cell types from this compartment in non exposed individuals. In this way promoters affect incidence with small changes in $\alpha_2-\beta_2$ [133, 134].

Therefore Moolgavkar's concept for environmental carcinogenesis has validity with HNSCC environmental carcinogenesis, which is composed of chronic and discontinuing exposures to agents (see above, [133]). However, the promotion process will only proceed within the context of a steady loss of DNA repair gene functional impact upon cellular progeny. The promoted cellular product is expected to demonstrate a high degree of persistent DNA damage of gene sets that regulate: repair, proliferation, apoptosis and nuclear instability (e.g., methylation, acetylation, phosphorylation and other epigenetic modifying pathways and gene regulators).

Moolgavkar and Kundson [134] provided a variation on the Armitage and Doll equations as discussed above. The age-specific incidence rate per 100,000 individuals; is about 2–4 per 100,000 for HNSCC; given by $I(t) \times 10^5$, where *I(t)* approximates $\mu_1\mu_2$ integrated in the range from 0 to t for the definitions $X(S)$ $\{(\alpha 2-P_2)\ (t-s)\}ds$.

Given that: μ1 and μ2 are the transition rates per cell per year, and X(s) represents the number of normal susceptible cells at time (age)s. A expression for age-specific incidence is derived and improves upon the simpler version from the Armitage and Doll model but both describes a "two-hit hypothesis model". These models shape age-specific incidence curves of cancer; in this case, HNSCC to show a dependent kinetics that describes growth and differentiation. These models conceive a resultant product of variables (e.g., microbiome, oral biology, exposure of mucosa, immune reactivity, etc.)

In concert Bozic et al. [135] produced a formula for the number of driver mutations in an environment capable of inducing cancer (e.g., "**Driver mutations = mutations provide a selective growth advantage to the cell. Passage mutations = Mutations that do not alter fitness but occur coincidentally or subsequently to acquisition of a driver mutation". Passenger mutations occur in every cell that has a driver mutation and is typically more numerous**).

According to these definitions low frequency/rare mutations are coincident with driver mutations but this does not disqualify these mutations as significant

contributors to malignant transformation as a function of the total number of mutations in a tumor [135].

The stated purpose by investigators, such as Bozic et al. was to reconcile cancer genetic sequence data with epidemiology and clinical observations for solid tumors. Mathematical assessment uses the concept that tumors are products of discrete times during malignant transformation. Moreover, this process has branching characteristics that results from survival selection of specific cells from specific clones of expanding cells. This process is expected to be a product of a driver mutation which is functional redefined during malignant transformation with the contribution of additional driver and passenger mutations (e.g., driver mutation vs. passenger mutation). Increasing the variable of time results in more opportunities for new driver and/or passenger mutations and additional cell clones at various degrees of transformation for an opportunity to respond to a variety of growth factors; immune factors, and chemical agents. This process is consistent with a "field cancerization effect" which identifies a tumor primary site but also an extension of malignant transformation to distant tissues. This "field' of malignant changes is found in HNSCC. A prediction from this approach and concept is younger patients that present with HPV related oropharyngeal cancers are candidates to have other sites of malignant transformation in adjacent tissue and in more distant oropharynx tissues. However, because HPV oncogenesis subtypes have discrete requirements for infection and replication which limit number and aggressive growth behavior observed in OSCC. This is also consistent with the Knudson two-hit hypothesis because number and type of DNA damage sites produced during viral transformation is limited compared to chemical carcinogenesis [136].

In a recent study a relatively larger number of mutations were found for OSCC compared to oropharyngeal HPV related cancers which validates this relationship described above.

In summary, "Human papillomavirus (HPV)-related head and neck cancers have four times fewer mutations (5 versus 20) than non-HPV-related tumors, which is often found among OSCC. HPV-related cancers also had fewer mutations in the p53 gene". Furthermore, this research found previously unrecognized mutations in NOTCH 1, IRF6, and TP63. Unfortunately these types of studies only provide an analysis at one time point without provision for mutation contributions in these genes during stages of carcinogenesis [137, 138].

Recognized in a "solid tumor" and human genome are "about 40–80 amino acid changes derived from mutations" and solid tumors contain on average 40–100 coding gene alterations which includes 5–15 driver mutations [135].

It is also important to repeat that not all mutations are created equal as to frequency and functional effect upon malignant transformation. Therefore low-frequency or rare mutation events are intrinsically difficult to determine if they are driver or passage mutations.

The formulation; $n=\frac{v}{2s}\log\frac{4ks^2}{u^2}\log k$; provided by Bozic et. al. [135]. Where n = the number of passenger mutations present in a malignant transformed expanding clone of basal-stem cell like keratinocytes as we find in HNSCC.

A proviso offered by this equation is it functions best in tissues such as mucosa which have a low cell division prior to initiation but promoted to create expanding clones of malignant cells.

All models have limitations, one of these is a lack provision for variations in types of driver mutations and numbers of mutations required to reach a threshold for malignant transformation under various conditions. However, there was a test for specificities offered which can be modified for head and neck cancer studies:

For unknown specificities designated (x: mutations with specific known impact on progression of malignant transformation) a calculation can be designed using a kth [(kinetics for expression = expression of driver/passenger mutations s1...k/rate of growth = gr (number of cells/basal cell clones in a "field" of malignant transformation/in at (time interval: months to years)] driver (a driver promotor or passenger mutation) at s_k (specific kinetic activity) and $s_k s$ (multiples of specificities at designated kinetic of growth = k) for any of the tissues of the head and neck using a Gaussian distribution and standard deviation (e.g., somatic mutation number (driver or passenger mutation) is about 142–228 for head and neck carcinoma with driver or passenger mutations classified as: missense mutations, nonsense mutations, out-of-frame insertions or delections [139]).

The central problem with these types of assessments is a lack of attention to the variables we have previously listed (e.g., k (kinetics) numbers of malignant clones of cells rate of growth, and distance between basal cell clones with a driver/passenger mutation) for increased risk for HNSCC. In addition, further lack of knowledge mutation impact during initiation, and promotion with consideration for gene expression of DNA repair, growth, apoptosis and nuclear instability. Furthermore, assessment of a mutation function in relation to ecologic/environment context also require attention (e.g., exposure to carcinogen from microbes or habits) (tobacco/alcohol). Taken together layers of complexity and difficulty in calculating precise interactions are reasons for neglect of this approach. Another source of concern is our lack of evaluation for the Darwinian selective influence upon a driver mutation effect to achieve the integration between mutation inductions and clinical environments occurring simultaneously during malignant transformation. Although a "selective growth advantage for mutations that drives tumor progression was determined to be very small (about 0.4%)" [135]. This result indicates that HNSCC small mutation change that does not limit replication has a profound effect upon cellular response to micro and macroenvironmental conditions and ultimately risk for full malignant transformation. However, mutations can limit development of a HNSCC. This becomes more evident as DNA damages, mutation and/or gene copies/ploidy accumulates in specific basal cell clones. Therefore a contribution of a specific mutation, especially a mutation that is in a driver type that produces a loss of DNA repair, apoptosis, inappropiate growth, and nuclear instability will have a greater impact on HNSCC induction comapred to other mutations/DNA damages that affect other genes not associated with these features.

Armitage and Doll provided another evaluation and explanation using a weight mean of probability from the age ranges related to presentation of cancers, of 0 to age *t*.

In this instance the weight evaluation depends on time of operation of the carcinogen or carcinogenic factor (T: see mathematical definition below) and on order of cellular changes which are products of the functional capacity of this carcinogen factor. The weight value is equal to;

$T_0^{s-1}(t - t_0)^{6-s}$ where: t = age of cancer incidence; t_0=the age subjects are exposed to carcinogenic factor and s = 6 power rule (at least 6 stages to produce a mutation: driver or passenger mutation with impact upon induction of cancer. At a rate per unit time at the 6^{th} log of age (t)+k). The decision to use 6 stages of cellular replication is based on the assumption and experience that 5–6 passages of human oral keratinocytes is sufficient to produce a transformed cell type and a loss of normal physiology characteristics.

The conclusion was that probability for a mutation to appear and to have a consequence for, for example, HNSCC carcinogenesis is proportional to the age mutation number and time of expression, and time of presentation for a specific carcinogen with the expectation that exposure is constant for the time of cancer induction. This mathematical approach shows probable trends and relationships that provide an opportunity to predict a cancer presence. Other diseases (cardiovascular and heart diseases) with a different set of mechanisms also demonstrate mutations that are expressed with increases in age to show association between mutation, time and age are common relationships useful in prediction of a variety of human diseases. The greatest contribution provided by this approach is an understanding and demonstration that cancer is a multistage disease and most often a multistage disease of more than two variables that impact incidence and presentation time. Evidence for this comes from predictive calculations that record age of death and rates for various cancers. Calculations of this type use actuary statistics to make these predictions in combinations with assessment of mutations number and type. This approach provides a enhanced understanding for consequences of specific mutations linked to a definable end point of cancer induction. However, this approach does not assess the biologic effects of specific carcinogens and exposures that initiate and/or promote carcinogenesis and therefore in practical terms shows a specific mutation's contribution to predict cancer progression.

Another mathematical formulation for variable weight strength of a carcinogen has tried to predict carcinogen influence upon specific cancer induction of stages of cancer. However, ability to predict carcinogen exposure effects such as death, is not considered. In addition, a comparison to non-carcinogens predict (e.g., toxin, growth factors, immune factors) that also contribute to mortality; morbidity over time or impact upon biologic systems is unaddressed.

However a mathematical approach can describe in general terms the transformation risk for particular population of cells, such as, basal stem cell like clones in a particular environment, for example, the tonsilar region; compared to the lateral border of the tongue. We assume clonal transformation events are independent. Independent malignant transformation among different clones of basal keratinocytes can be associated with either a micro and/or macro environment and they are at distances which varies from a fraction of a millimeter to centimeters between clones of cells. Cellular distances and in other cases tissue distances between persistent clones of transforming basal keratinocytes influence induction of cancer tumor masses. They reflect responses to DNA damages to these cells at different rates.

Identification of a variety of DNA damages assist in characterization of cancer risk in oral biology environments (e.g., microbiome, saliva characteristics, host immune status). Therefore an independent clonal cell expansion impact upon cancer induction also echoes selective gene set damages. These gene sets describe susceptibility for cancer induction, and are closely tied to DNA damage sites and ultimately growth potential of cells in clones. Specifically, DNA repair, growth, apoptosis, and/or nuclear stability are important gene set targets for DNA damage. These listed activities are also recognized for maintenance of normal physiology and because this process is scattered among transforming clones of basal oral keratinocytes that arise independently and/or simultaneously in oral and pharyngeal tissues, a risk for cancer induction is best described as a "field cancerization effect". Moreover, in malignant transforming cell clones; depressed levels of gene activities and numbers of chemical families that show depressed abilities to regulate pathways and chemical reaction efficiency also occur as clones of cells grow and produce a loss of normal tissue physiologic responses (e.g., protective lining and immune function of mucosa).

Another important feature of expanding malignant transforming cell clones is their different rates of expansion which will influence formation and growth of the primary tumor mass. Stated above, physical distances between malignant clones is not a deficit toward cancer formation because of the "field effect" which identifies a risk for promotion during carcinogenesis and functional activity for driver/passenger mutations. It is expected that a cancer inductive environment is facilitated by a close-proximal location of malignant clones of cells. Therefore, a lack of physical distance between clones of malignant cells would tend to form a tumor mass earlier and with a greater density but knowledge of specific chemical or physical requirements that accelerate or reduce this process is not known. Moreover, it is suspected that survival of aggressive growing clones of cells will predominant in the tumor mass that presents in the oral cavity (e.g., $n + 1{-}mXt^n$, where $n + 1 =$ is a rate limiting step for keratinocyte transformation, m = necessary set of DNA damages required for transformation to occur over time (*t*)). Time remaining for transformation is equal to $n + 1{-}m$ at a rate of time to an nth power (n−m). A test of this concept would be to assess genotypic expression linked to susceptibility for HNSCC at various times of life from the identical site and evaluate growth rate of clones of basal cells that form in the growth front of the primary tumor mass in comparison to the growth rate of basal cells clones at a distance from this tumor mass (e.g., deep sequencing, arrays) [140].

The often observed phenomenon of one predominate primary tumor does not negate the assumed presence of multiple basal cell clones dispersed throughout the "field of cancerization". In these situations the most aggressive growing basal cell clones in time ($t{:}t_1$)are identified in the primary tumor mass which may or may not been exposed to carcinogen/environmental stresses at a greater frequency (*f*) (number of carcinogens (n)/in time (T) interval is context with cellular impact: e.g.: s1s2.... etc (mutation type and number). The above characteristics of exposure therefore govern aggressive growth behavior. These growth characteristics often are associated with further loses of normal physiologic regulation

and complementary changes in micro-environment (e.g., inflammatory change, microbiome interactions).

A complementary selective process can be discerned and describes the independent malignant cell clone rates of growth (e.g., r_1, r_2....etc for each clone of cells) of oral basal keratinocytes. It is assumed a possible summation of growth rates from each surviving clone of malignant basal cells will result in knowledge of growth rate of the primary tumor mass. However, we suggest a HSCC/OSCC tumor mass growth rate is dependent only on the growth of a few clones of malignant basal cells. This assumption is further influenced by ecologic selective forces and stresses that contribute to the elimination of clones of basal cells at various stages of tumor mass formation while other clones of cells predominate then disappear. This process directly influences risk for metastasis of the primary tumor mass, while distinguishes the growth of the predominate tumor mass. Other variables, of nutrition, vascularity, microbial interaction, and immune activities (e.g., a_1;b_1;c_1... etc) will therefore also change the rate of growth and eventually effect metastatic potential and survival.

An extension of this association between clones of basal cells and their growth rate and rate of growth of primary tumor mass is response to treatment of the tumor mass. Rate of growth of clones of basal malignant cells influence tumor cell density and in conjunction with the fore-mentioned additional variables affect distant and local tumor growth spread capability (e.g., metastasis). In addition, rate of growth indirectly characterizes resistance to therapy because these clones of cells were previously selected for survival by DNA damaging agents which had similar chemical effects to therapeutic agents in regards to activation of DNA repair. Although carcinogen chemicals can suppress effective DNA repair to a greater degree.

The rate of formation of a tumor mass (e.g., HNSCC/OSCC) is therefore proportional to the rate of growth, and number of malignant basal cell clones, and/or the distance between these groups of cells at growth edges of the forming tumor mass. It is further recognized that large tissue distances between transforming cell clones can reduce tumor mass induction because of lack of physical proximity but this distance between basal cell clones also facilitates elimination or reduction in toxic and DNA damaging agents and/or dilute chemical toxic effects through a selective survival response. For this reason, greater should be given to progenitor-stem cell like basal cell clone that grow independently and have unique characteristics that produce a solid tumor/carcinoma such as, HNSCC.

14.14 Environmental and Exogenous Chemicals Linked to Mutation

Many mutations that are generated are not self promoting but persistent in a basal cell population. However, specific mutations can be eliminated through apoptosis or tissue turnover which removes from the proliferative compartment specific cells

with specific characteristics. During this process two types of mutation creation pathways occur; one is spontaneous, and the other is inducible. Spontaneous mutations are generally subject to replicative events linked to mitoses (e.g., transcription, translation, both at the DNA and RNA level) and metabolism of oxidative substances. In addition, translesion DNA synthesis can prevent a mutation by error-free incorporation opposite a site of DNA damage, defined as an adduct. It is the error in repair, at the adduct site by replicative or translesional DNA polymerases that is the source of the mutation [141, 142]. Therefore for a mutation to contribute to cancer induction requires an error-prone replication, mispairing, and an environment conducive for expansion of a mutated clone.

We assume that spontaneous mutations occur more frequently and in environments in which inducible mutations are controlled and/or infrequent. However in environments with relatively high concentrations and number of exposure periods for direct DNA damaging; inducible agents change the balance with spontaneous mutation rates become relatively less frequent than inducible or high rate mutator site presentations. It is also expected that inducible mutations that activate a series of base and nucleotide repairs will also repair spontaneous mutation sites more readily because they are largely less complex oxidative adduct damage sites in comparison to bulky adduct DNA sites commonly associated with inducible chemical carcinogens and repair through nucleotide excision repair (e.g., poly-cyclic aromatic hydrocarbons, nitrosamines) [141–144].

Persistence of mutations is based on survivability of a particle clone of cells and ability to form a tumor mass. Elimination of these clones can be associated with apoptosis (e.g., programmed cell death) or elimination of the mutation through an error-free translesional synthesis. Depending on the timing for elimination of mutator cell clones there is expected to be greater or lesser effects upon the genotypic profile without any demonstrable change in phenotype (e.g., single base point mutation). Several mutation sites that persist at error prone repair sites will result in mutations that may involve several nucleotides. This situation creates more extensive changes in genotype and phenotype and progressive inefficiency of DNA repair and this result in a cascading effect with growing numbers of mutations at error prone repair sites. In summary, mutations can be persistent, or short lived, and involve a single base site or multiple bases. Most mutations are not directly linked to malignant transformation and elimination has little effect upon cancer risk. It is expected there is usually present a small persistent numbers of mutation sites that undergo mispairing and exhibit relatively extensive (e.g., size, number of nucleotides) expression during malignant transformation. It is increasing clear that mutation generation by itself is not sufficient to induce head and neck cancers based on the growing numbers of cases around the world.

We also recognize that a malignant clone of keratinocytes is therefore more than a product of a single gene proliferative survival response (e.g., oxidative, bulky adduct DNA damage, mismatch/insertion/delection/inversion changes) but persistent mutations are critically linked to type, amount, and efficiency of DNA repairs and the cellular environment of mucosa tissues [145, 146].

Evolutionary biologists describe population variation in regards to mutation frequencies. Populations are stated to contain high mutators and low mutators and the variability of presentation of mutations is mathematically described. For example:

$$"R = bM / pbM = 1/p." \text{ (Carins, Mutation and Cancer 1998)}$$

Where independent variables are: a,b,p, and M. This equation therefore describes the frequency for a high mutator (e.g., usually 10^{-4}–10^{-5}/per gene/cell division [147]). A high mutators can also be a driver/passenger mutation as previously described. Furthermore, it is expected that high mutator activity (defined by *p*) will manifest as persistent errors during replication and translation that occurs during the synthesis of DNA, RNA, various small and large coded and non-coding DNA and RNAs, polymerases and repair enzymes. Furthermore, an increase in *p* produces an *R* value that approaches 1. An estimate of R = 50 has been offered where p = .02 [activity of a high mutator expression at a frequency (activity/time)]. This indicates frequencies of high mutator (e.g., multiple mutations) phenomenon are relatively low [148].

We conclude a persistence of a clone of basal stem cell like clones of cells with a high number and error prone DNA repair of mutations are in the minority in normal cell systems such as head and neck mucosa as compared to a higher frequency among HNSCC, containing transforming malignant mucosa where these types of DNA damage mutation sites are linked to a high risk for cancer.

Specifically, in the head and neck mucosa tissues, in the lateral border of the tongue, floor of the mouth, and base of the tongue, areas of where we expect to find a few clones of basal-stem cell like cells that have a high degree of mutation while the majority of keratinocytes from the supra basal keratinocytes contain few mutations sites that are either persistent or transferable to daughter cells. In the context of environmental exposure this means a selective attack upon particular basal-stem cell like keratinocytes, produces an efficient DNA repair. In addition, mutated cells can persist in G_0 phase in the cell cycle and assist with regulation of penetrance of a mutator genotype. Turnover rate will also affect persistence of a mutator clone. In general non-keratinized/ parakeratinized mucosa keratinocytes (ventral surface tongue, buccal mucosa, floor of the mouth, lymphoid mucosa) are more prone to turnover than keratinized mucosa keratinocytes (e.g., hard palate) and presumably have less cells in G_0.

Presence of mutations is thought to be evidence for a carcinogenesis process. The initiators of mutation for head and neck cancer are associated with diet, habits, environment exposures and can be described in general using the equations provided above. I have also described the presence of different types of mutations and influence these mutations has upon growth potential and other critical processes that regulate physiology of basal stem cell like keratinocytes.

Another factor not discussed in reviews of Darwinism effects during head and neck carcinogenesis is complex microbiome that interactions with epithelial mucosa. Microorganism interaction with mucosa requires assessment particularly as noted above in discussion of mutation influence upon cell clones growth [149].

14.15 "Field Cancerization" and Environmental Factors for HNSCC

Mucosa from pharynx or oral cavity contains a heterogenous population of basal-stem cell like keratinocytes that provides a target population for malignant transformation. This occurs as we previously discussed a "field cancerization" process that is composed of basal-stem cell like clones at different stages of transformation. Differences in growth among expanding and contracting cell clones are a result of variable levels of chemicals and/or microbes that induce DNA damage, and mutagenesis. Cellular variation presents itself in the form of increased genetic number (e.g., copies of genes) and types of DNA damage sites. In the head and neck genetic damage is strongly influenced by biofilm quantity and type. Changes in microorganisms distribution and microbe composition, quantity and quality of saliva that bath microorganisms and epithelial mucosa, and host immune activities also contribute to the functional presence of DNA damages in mucosa. Additional contribution to physiology and integrity of the mucosa and ultimately resistance to DNA damage is associated with microbial influence. Furthermore, specific preferential locations for HNSCC inductions such as, lateral border of the tongue, base of the tongue and floor of mouth for OSCC and tonsil region for oropharyngeal carcinoma are not only products of genetic susceptibility to particular DNA damages, but also a product of microbial biofilm interactions with mucosa at these sites because of mucosa peculiarities. These include turnover rates of epithelium, concentration of DNA damaging agents (e.g., exposure to chemicals, and/or viruses). These relationships inevitably, leads to a mosaic of genetic mutation variability with increased risk for malignant transformation as DNA damages persist.

For example, base of the tongue will be more directly affected by tobacco smoke than gingival mucosa and the hundreds of mutagens, toxins and carcinogens present in the smoke [150].

In the case of viral infection evidence for a selective localization of particular viruses in cooperation with bacterial and fungi present in the pharynx compared to the oral cavity is considered plausible [151, 152]. In broad biologic terms microbial inclusion in the process of malignant transformation shows another aspect of Darwinian selection. First in the survival of specific species of microbes, but also in activity of host immune response to these microbes. Persistence and capability of immune cells to infiltrate mucosa tissues and interact with epithelium undergoing change after exposure to DNA damaging agents also contributes to a malignant transformative environment.

Another association for evolution selection effects during and HNSCC carcinogenesis, is presence of heritable genes that regulate susceptibility to chemical and/or viral HNSCC induction. Examples include: individual polymorphic variability of genes for: alcohol dehydrogenases; cytochrome P_{450}, and genes for, glutathione-S-transferases (e.g., phase I xenobiotic genes, phase II antioxidant genes), which regulate oxidative, xenobiotic metabolic responses and reactive oxygen substances.

Although, daughter cells often have identical mutations to the parent basal cell we suggest phenotypic change is a result of genotypic variation and mutation and continual selection of one daughter cell for survival over another in changing micro and macro-environments. Taken together these general attributes signify increased fitness of malignant transformed clones of basal-stem cells to produce a HNSCC in selective microenvironments but selection occurs with a high degree of precision. This is evident by the small calculated number of mutations that drive HNSCC progression which is about 0.4% of the basal cells capable of malignant transformation. This small effect shows the need to reach a critical number for mutation expressions (e.g., driver mutator effect) and critical number as noted above to form a tumor mass that can demonstrate metastasis.

Moreover, response by basal/stem cell keratinocyte populations to chemical and/or viral agents can be regarded as a biologic evolutionary driven stress induced tissue adaptation to chemical and/or viral activities. This process modifies cell capabilities and shifts phenotype and cellular capabilities to induce loss of tissue integrity.

We suggest by viewing carcinogenesis as a form of natural selection process gone wrong we can better understand growth behavior and risk for additional primaries or new secondary neoplastic sites in response to treatment.

Oral mucosa from oropharynx (e.g., base of tongue, tonsillar area) or cavity (e.g., lateral border of tongue, floor of mouth, buccal mucosa) contain basal-stem cell populations that have germ cell qualities to produce offspring, such as, progenitor populations of cells. These cells maintain an adaptable replicative compartment of cells and help with structure and integrity of oral mucosa by contributing to a "normal" state of cell replacement. Exposure to agents that cause genome damages expands the progenitor basal compartment and this expansion participates in the maintenance of epithelial phenotypes with appearance of differential gene allelic variations. Following induction of DNA damages a propagation of changes in cellular "offspring", numbers, phenotypes and genotypic allelic variations begin to reduce normal tissue integrity through proliferation of malignant clones of keratinocytes that lack normal physiologic cell to cell interactions and communications. In turn micro and macro-environments act upon proliferative expanding clones of basal-stem cells to facilitate survival of selective progenitor populations and contribute to persistence of phenotypes with a potential for malignant disorders and characteristics (e.g., morphology, metabolic physiology, cellular signaling, nuclear stability).

Similar to germ cell responses to environmental change; gene selective forces exhibit an initial non-random gene damaged expression pattern that results from DNA damages introduced by virus and chemicals. Although, noted above, chemical DNA damage is less constrained than viral associated DNA damage. In time degrees of malignant transformation can be evaluated by examination of combinations of expression (e.g., microarray displays) among unaffected genes, and altered damaged genes that affect DNA repair, proliferation, apoptosis, nuclear stability and regulatory gene functions of cells. Damage to these latter genes is also likely to be random and rarer compared to damage to tumor suppressor genes or the other foremention cell systems because large changes in these genes will cause a loss of viability. Basal-stem cell keratinocyte populations comprise a heterogeneous cell

population with non-random DNA damaged genes responsive to an increasingly selective environment (e.g., ecologic niches) influenced microbial presence and saliva/other fluids. In contrast to germ cell selection which seeks new independent offspring, in this situation reproductive capability is limited to proliferative activity of cells that are integrated into the available structure and form of the mucosa and these cells have comparative very limited independence to germ cell progeny.

Furthermore, in a parallel manner to generation of germ cells, the somatic gene expression in keratinocytes, characterizes the cornerstones of oral mucosa structure and integrity through a gene expression that regulates differentiation in epithelial lineage. Therefore DNA damage to somatic genes leads to loss of mucosa integrity and increased opportunities for viruses and bacteria to enter between desmosome, tight junctions and alter stability of intercellular bridges by mutation of somatic genes that regulate these sites (e.g., claudins, integrins, G proteins, etc.). Further damage to basal-stem cell like clones and daughter basal keratinocytes produces a "snow ball" effect that can accelerate this process, if there is a lack of tissue restraints (e.g., physiologic, immune, microbial epithelial interactions). We suggest to monitor carcinogenesis, use of makers for basal-stem cell like cells, that record changes in oxidative stress, metabolism and risk for cellular damage and mutation (Bozic 2010).

14.16 Progenitor Cell Populations Targets for Mutation

The target cell in head and neck mucosa for creating persistent and critical DNA damages among daughter basal keratinocytes is characterized by stem cell properties and genotypic and phenotypic changes of a less differentiated keratinocyte (e.g., cytokeratin, capacity for proliferation). The progenitor compartment of head and neck mucosa (e.g., gingival, buccal, floor of mouth, base of tongue, mucosa of tonsillar region) is not homogeneous but consists of two functionally distinct subpopulations of cells: *a small population of progenitor cells that cycles very slowly and second stem cell like cell with frequent division and production of basal daughter cells*. This process maintains proliferative potential and homeostasis of the tissue [153–155] and it provides an opportunity for daughter cell selection and further modification of characteristics of basal cell progeny under the influence of the environment (e.g., virus, chemical, microbe).

There are specific stem-cell markers, and they include adhesion molecules, such as the β1-integrins, β-catenin, aldehyde dehydrogenase (ALDH) and cytokeratins 15 and 19 (12–15) [156–159]. It is through the basal cell population that amplification and proliferation of keratinocytes occur to maintain mucosa stability and homeostasis by maintaining number of cells that differentiate, and enter mitosis while maintaining characteristics for survival (e.g., keratinization, immunologic).

Calculations for mutated stem cells by Dr. Carins [87]; has provided an estimate of about 10^{10} stem cells in the body, we would estimate a fraction of these are present in head and neck mucosa (e.g., 10^{3-4}). This estimate is based upon a relatively

low rate of turnover in mucosa of the head and neck compared to other tissues which is 34 days for epidermis to 4 days for the small intestine with the values for oral and esophageal epithelium at about 21–22 days. There are also regional differences in patterns of epithelial maturation associated with different turnover rates. For example, non-keratinized buccal epithelium turns over faster than keratinized gingival epithelium. A relatively higher turnover rate is found among kertinocytes from the less keratinized mucosa surfaces and this appears to be a protective response to exposure to DNA damaging agents. This is also important because different types of carcinomas may occur in parallel with this turnover rate and appears to link risk for a specific carcinoma to mucosa integrity and physiology (e.g., turnover rate/ basal cell compartment proliferative capacity). For example floor of the mouth (e.g., turnover rate = 20 days), and lateral border or ventral surface of the tongue are non-keratinized surfaces and common sites for squamous cell carcinoma while cancers of the hard palate (e.g., mean turnover rate = 24 days) tend to be salivary gland adenocarcinomas [160]. Relatively non-keratinized mucosa lining base of the tongue and tonsillar region are also subject to oropharyngeal carcinoma formation. Another feature not usually noted for these oropharyneal and cavity tissues are cellular circadian rhythms, with most cells being in the mitotic (M) phase at 2,100 h [161]. Dr. Cairns has further estimated there are about 1,014 stem cell divisions in a lifetime which he states is not adequate for a sustainable mutation rate (e.g., about 10^{-7} per gene/ per cell division) to be maintained and transferred to daughter cells to create a malignant transformation. He concludes, "we should be looking for some other driving forces" other than mutation, "that can be linked to (or triggered by) cell proliferation" [87].

14.17 Gatekeeper and Caretaker Gene Activities

Mutation and DNA damages to genes become critical if they target cell cycle regulation and DNA repair capacity (e.g., "gatekeeper vs caretaker genes"). An example of a **gatekeeper gene is an "oncogene" while a "tumor suppressor gene" tries to put the brakes on this process.**

Both oncogenes and tumor suppressor genes are tied to allelic variation-frequency because in the case of oncogenes a single allelic mutation can be significant with loss of regulatory control of a cell cycle phase. Inactivation or loss of tumor suppressor gene function is a product of a loss of allelic regulation and with both alleles mutated and/or additional disruption of pathways with an amplification of a depressed regulation of multiple pathways (e.g., ARF/ Nanog/AKT/PTEN/mTor) [162, 163]. Other factors such as MDM2/MdmX will suppress also p53 regulation through degradation (e.g., ubiquinition) but this can be controlled by ARF to increase p53 activation and this will reduce pluripotency (e.g., Nanog factor [164]).

For example a loss of tumor suppressor function (e.g., allelic mutation) of p53, **"guardian of the genome",** normally prevents the accumulation of mutations by inducing check-point control, and inducing cell cycle arrest. About 50% of all head

and neck cancers contain inactivated tumor suppressor p53 or mutations in alleles of p53 [165]. Importantly, cells with mutations can be eliminated through p53 associated apoptosis, and accumulation in senescence.

Particular loss of tumor suppressor activity results in a loss of a barrier to pluripotency and cellular dedifferentiation that inevitably leads to increase risk for unregulated malignant clone development [166].

To control head and neck carcinogenesis it is crucial we understand the process of **phenotypic variation** which should not be confused with **pluripotency**. **Stem cell populations have a high degree of**pluripotential**activity which permits differentiation to ectoderm, endoderm mesoderm or neuro-ectoderm.** In contrast, **phenotypic variation usually maintains germ cell line origin (e.g., ectoderm) although offering an opportunity for progression of dedifferentiation** to an initial ectoderm/epitheloid cell transformation or metaplastic change to a mesoderm/mesenchymal cell type. In this context of head and neck cancer we suggest an example of dedifferentiation from a squamous cell carcinoma to a carcino-sarcoma. This tumor is often more aggressive; observed at later stages of development and has a poorer response to treatment.

It is further suggested that there is a likely range of DNA damages that includes not only mutation events that target "gatekeeper" and "caretaker genes" but DNA damages that include **epigenetic modifications. These can include methylation regulation of cytosine bases in cytosine guanine islands (e.g., CpG sites) that assist in regulation of expression, but also are accompanied by changes in acetylation of histones and phosphorylation of various purine bases that can silence tumor suppressor genes** [167, 168].

14.18 Senescence and HNSCC Carcinogenesis

Moreover, we recognize a change in cell growth among basal keratinocytes is associated with exposure to DNA damaging agents and accumulation of senescent cells in localized areas of the mucosa consistent with intermittent expansion and persistence of transformed basal cell clones of keratinocytes. It is possible that increases in numbers of senescent cells will promote selective advantage because of specific microenvironment changes [169].

A possible perplexing situation is found among HPV related oropharyngeal carcinomas which often occurs among young (e.g., 20–40 years old) sexually active males and to a lesser degree females which theoretically should not produce an accumulation of senescent cells [85]. However, it is increasing evident that human papilloma virus (HPV) infection is particularly associated with oncogenic subtypes that induce senescence in epithelial cells (e.g., mucosa). In addition, inflammatory products such as mpRNA decay factor tristetraprolin (TTP) induces senescence in HPV transformed epithelial cells (e.g., mucosa) by targeting ubiquitin ligase (E6-AP) [170, 171].

14.19 Mutations and Genetic Manifestations

It is also evident that phenotypic variability is further modified by genotypic expression exerted by a selection of the fittest cells and/or microorganisms in specific ecologic niches. This selection is at times under **genetic drift** control, **a product of random sampling, which also contributes to phenotypic variability**.

The head and neck environment therefore creates new avenues for cell change and provides multiple ways to attain a squamous carcinoma phenotype which is in part dependent on a genotypic profile (e.g., mutation, loss of heterozygosity, DNA/gene copy number). Phenotypic and genotypic changes and variability is expected to be crucial in formation of transformed malignant keratinocytes as noted above because these changes in basal keratinocytes are associated with changes in potential growth/proliferation, puripotentiality, and differentiation.

It is also our contention that the genotypic profile of an individual at birth sets into place a "***cryptic genetic variability***" (e.g., inherent genomic profile) which can become a predominant force as basal-stem cells transform and proliferate in a dynamic head and neck environment [172].

Phenotypic variation has been used routinely by pathologists to grade and differentiate histopathology for potential malignant disorders (PMD) of squamous intraepithelial neoplasias (SIN) but this approach which has been institutionalized by the World Health Organization (WHO) using a consensus approach does not address the dynamic evolutionary-ecologic activities present in the head and neck system which are referred to above [173–175].

For decades there has been recognition that a crucial requirement to produce a malignant epithelial cell is mutation but unlike germline mutations that will affect a population of individuals we are interested in somatic mutations that affects relatively few cells forming the proliferative cellular zone of epithelial mucosa (e.g., basal keratinocyte compartment). This thought is not new because it was described as early as 1916 [176]. Historically many observations of cancer cell invasive capability were linked to chromosome aberrations; use of radiation to further enhance bizarre chromosomal changes, and genetic X linked mosaicism to demonstrate clonalism. In the 1940s chemical carcinogens (e.g., nitrogen mustard, nitrosamines) were demonstrated to be mutagenic to DNA in bacteria and this began the era of chemical carcinogenesis. It was also recognized that mutagens do not necessarily act as carcinogens. Based upon this historical perspective there has been a lack of attention to broader selective influences for cancer inductions that have been referenced above.

14.20 Darwinism and Mutation

Thought has been directed to an association between evolution and cancer by examining selection of somatic cell types as a result of fitness (e.g., survival of daughter cells generated from transformed clones of basal-stem cells) and robustness.

Robustness effects mutations among organisms with small phenotypic effects and robustness reduces the amount of heritable genetic variation on which selection can act but robustness also increases opportunity for evolution in selected genotypes in particular microenvironments.

Robustness is a process of adaption to environment change and this characteristic is also a derivative of as opportunistic microbes introduce stress into a oral biology system which increases risk for mutation and selective cancer induction. Robustness is important to maintain mutation induction rates at low levels sufficient to facilitate microbial and host tissue interaction to permit an evolution of mutual benefit. Microbial and oral mucosa interactions also results in control of growth and differentiation of selected clones of basal cells [177]. This relationship is particularly become important after exposure to DNA damaging agents; such as, tobacco, which contains hundreds of toxins, mutagens and carcinogens there is a rapid dissolution (**degeneracy**) of a symbiotic relationship and a re-establishment of a new symbiotic interaction. However, an increased level of parasitism; a by product of degeneracy, increases with continual repetition of this process.

In this context microenvironmental change is a product of complex integrative relationships between microbes, saliva, and epithelium to form an oral biologic system (e.g., symbiotic state). This system can be further characterized by degeneracy. **Degeneracy is correlated to complexity but has attributes of redundancy and independence**. Figure 14.2, shows our scheme of associations between carcinogenesis mutation and evolutionary selective forces. These processes assist in the transformation of basal cell clones as mucosal microenvironments change.

Each component of the oral biologic system is complex. However, each is a functionally integrated system that is capable of acting as a segregated entity but is best understood as an integrated components. Degeneracy because of its redundant features can describe associations of oral biology (e.g., microbes and epithelium) that are robust and assist in maintenance of cell viability, while in the presence of tissue mutations. Degeneracy is also a continual characteristic of oral biologic environments because of repeated exposures to DNA damaging agents such as, PAH, TSNA or other generators of DNA damage and mutation.

14.21 Hardy-Weinberg Equilibrium and Head and Neck Epithelial Mucosa

There are several important equations that describe **Hardy-Weinberg equilibrium (HWE) and disequilibrium to attain information regarding evolvability of organisms in selected environments**. These equations could be generated by selecting a dominant gene with low allelic frequency and high levels of phenotypic persistence in the face of oral biologic dynamics. Unfortunately stability of genetic microbial or mucosal expression cannot be defined until influences listed above are considered as special factors of significance to affect HWE.

HWE is recognized (e.g., $f(A_iA_j) = 2p_ip_3$, where A and p define heterozygote genotypic variations in a population). Moreover as transformation develops and additional copies of genes and

$$\text{"}k_1,\ldots,k_n \quad \in N : k_1 + \ldots.. + k_n = c\text{"}$$

increased polyploidy occurs as recognized during malignant transformation:

$$(\text{e.g.,"}(p_1 + \ldots. + p_n)^c = \sum (k_1 \ldots.., kn)\, p_1^{k1} \ldots p_n^{kn}\text{"})$$

in a *N* distinct set of alleles in c-ploids, genotypic frequencies are expressed in a HWE but this approach does not recognize variations in oral biologic microenvironments. Therefore calculations for deviations are required through additional integration. However, idealized versions can be used to mine over-all trends and association with the proviso that these equations do not describe adequately the dynamics in Head and Neck environments.

Allelic frequencies that described HWE are also depicted using graphs and diagramed but the association are not comprehensive (e.g., de Finetti diagram [178]).

In summary, HWE assessment does not provide sufficient dynamic calculations to have an accurate predictive value to determine survival effects between microorganisms and epithelial mucosa and is not appropriate to quantify the myriad of variables described above. Therefore additional integrative mathematics is needed to quantity more closely real world dynamics. In conjunction with the previous described models by Armitage, Doll, Kundson, Moolgavkar, and Bozic, a broader view of carcinogenesis can be developed.

14.22 Evolutionary Influence and Epithelial Responses

Selective microbes survive in biofilms that create oral biology ecology system.

Survival of any micro organisms must then be judged as a test of fitness. Degrees of fitness for particular environments are largely based on a number of traits and genetic variations for specific genes required by microorganisms to adapt to dynamic micro and macro-environments. Attributes for survival success includes attachment and colony formation.

Fitness of specific microorganisms to maintain a presence in oral pharynx and cavity is therefore a consequence of persistent colony formation in a biofilm and product of genotype and phenotype change.

Among microbe genotype-genes trait, or frequency of allelic variations and effect metabolic activities that regulate aldehydes or alcohols from various sources such as diet, or habit (e.g., tobacco use). Therefore microbial genotype helps to shape survival under specific environmental conditions.

Phenotype change is also recognized among microbial species as they form biofilms and adhere to oral mucosa tissues or dental surfaces. Examples will include chemical surface changes that will change texture of colonies such as smooth to rough or color.

Therefore continual presence of selective species of microbes indicates not only a genotype selection for fitness and reproduction but a selection based upon genotypic frequency for selective microbial phenotypes.

In summary the **fitness landscape** first conceptualized by Sewall Wright in 1920s is expected to produce **a stable local maxima for each microbe and total microbial population** (oral microbiome) until another selective change is introduced (e.g., diet, exposure to chemicals from habits). In the oral pharynx and cavity this occurs with great rapidity and a loss of symbiosis is gradually replaced by parasitism among microbes and a shift in oral mucosa physiology. In the oral mucosa a loss of integrity and increased opportunity for microbial infection occurs. This results in damage to DNA among basal keratinocytes and further risk for malignant transformation. Dr. Wright used F-statistics to determine heterogeneity in various species populations. In regards to oral biology, this approach would be difficult to use because we lack genotypic identification at some time (t_0) and further identification of specific genotypes under appropriate ecologic conditions at $t_0 - t_x$, which includes s generations that characterize genotypic variation = $s(t_0 - t_x)$ for microbes in specific biofilms, and basal keratinocytes at sites of interactions.

However, persistent presence of selective microorganism and basal keratinocytes clones appears to offer an indirect approach to examine survival fitness as a product of ecologic system selection such as genetic drift and genotypic variability because of rapid proliferation and response to environmental changes.

In general, genetic variability based on chance as an independent genetic event or a product of several events in the oral environment is testable but many genetic analysis studies are weakened because they use only one time point of sampling. Moreover, a sampling error of selection is present each time cytology or cell biopsy harvest is used because we only identify for example, microorganisms that are common in a particular biofilm, or keratinocytes abundant in a selected tissue site compared to another site. A correction for this error is obtained by an internal control and repeated sampling and analysis of identical samples.

Unfortunately previous and current published studies have not attempted to describe the oral microbiome or basal keratinocyte populations in terms of their frequencies for a single gene invariant expression (e.g., allele). This approach would assist in determinations of genetic drift and possible specific roles during carcinogenesis for HNSCC [179].

A multiple sampling process would also enhance our capability to determine genetic drift for an individual's oral biology and increase precision to detect allelic variation. In a non-oral context, genetic drift is determined by examination of offspring sampled from known genotypes of parents and evaluated as to chance or degree of probability for an assessment of an individual's survival and reproduction capacity. Our suggested variation would include genotypic analyses of at least one genus and species of microbe (e.g., Streptococcus), that has a high degree of

survival on several oral tissues. Oral basal keratinocyte survival can also be repeated evaluated for genotypic change related to differentiation (eg., cytokeratin) or immune activity because these are characteristics linked to oral epithelial survival. A **population's allelic frequency**; is used to determine a fraction of the copies of one gene shared among offspring to determine genetic drift in a population of know parental genotypes. In out context, analysis for example of parental strains of specific genus or species of microbes or genotypic variation among basal clones of keratinocytes. Relative risk has been previously noted to be an important criteria for expanding basal cell clones and their response to DNA damaging agents. Therefore RR1 for a specific basal cell clone under environmental conditions that contribute to an increased RR2 is identified with a RR3 from a microbial biofilm. These need to be integrated over time intervals (t_0-t_x) to further define "RR" as follows:

In conjunction with **relative risk which is a risk assessment for an event relative to exposure**. ("$\text{Relativerisk(RR)} = \frac{\text{pexposed}}{\text{Pnon-exposed}}$") There is a probability for individuals.

It is assumed RR > 1, the event of HNSCC is more likely to occur in persons with exposure to (s_1, s_2, ... etc.): HPV onogenic subtypes and/or tobacco, alcohol uses, poor oral hygiene, sexual transmission of virus, use of non tobacco combustible or smokeless tobacco products.

Where: confidence interval "$CI = \log(\text{RR}) \pm \text{SE} \times z$"

$Z\alpha$ = standard score for a chosen level of significance with a standard error

Relative risk differs from odd ratio but it can approach values when the probabilities are small. For example, a habit with a high relative risk for HNSCC (e.g., tobacco) approximates for smokers with $\frac{\text{HNSCC} \times \text{non-smokernoHNSCC}}{\text{SmokernoHNSCC} \times \text{non-smokerHNSCC}}$

In this context HPV (16/18 subtype) exposure produced in one publication: 64% of patients with oropharyngeal seropositivity for HPV-16 oncoprotein E6, E7, or both. In addition, HPV-16 L1 seropositivity with oropharyngeal cancer with a history of heavy tobacco and alcohol use showed an odds ratio, 19.4; 95% confidence interval (CI), 3.3–113.9, and without such a history a calculation for odds ratio, 33.6; 95% (CI), 13.3–84.8 [180]. These types of CI and odds ratio calculations shows a high degree of impression since they are analyses that lack comprehensive assessments of the variables and characteristics noted above.

In the oral pharynx and cavity the parental genotypes of specific bacteria are not accurately assessed unless as stated above repeated sampling and harvest selective error is corrected.

It is also recognized that host epithelial cells are important for microbial survival which is in response to epithelial specific genotypic allelic variation. Therefore the true capability of an oral biologic genetic drift to change microbial and epithelial interaction is difficult to assess and complex. A limited capability for genetic variation is defined by the concept of degeneracy, which was described above as a characteristics which is inherent in the continual changes and conditional responses modified by environment among microbes and mucosa epithelial cells.

Degeneracy characterizes a structurally distinct system and components, such as those cells and tissues found in the oral biology system present in the oral pharynx and cavity. Both human biologic components of the oral mucosa and microbiome are responsive to changes in microenvironment (e.g., conditional interchange) and contribute to genetic trait selection among oral keratinocytes and microbes. The significance to selection process is ultimately persistence of microbial species in biofilm and survival of oral keratinocytes with low levels of RR for malignant transformation [181].

Stated previously, genetic drift in the oral biology system is subject to random effects from exogenous environment, diet or habits etc. that affect selective gene expressions among basal keratinocytes. For example, genes that metabolize polysaccharides and produce bio-matrix to establish adhesion which ultimately determines which microbes survive and are harvested for identification.

Another problem that occurs with a lack of repeated harvest and identification of microbes is difficulty to determine an adaptive peak for microbial species and basal keratinocytes. There is also the possibility that microbial and keratinocyte genotypic identification is in part dependent on a "**founder's effect**" particularly at selective oral mucosa sites such as areas of infection or neoplasia. The "**founder's effect**" helps to describe presence of cell survivors and the **opportunity for additional selective cell populations to proliferate from the larger oral microbiome** [182].

Another feature of an oral biologic system that results in selection of microorganism and influences interaction with oral mucosa is robustness. Robustness was referenced above as a characteristics that acts to stabilize cellular responses to facilitate survival.

Oral microbiome and basal keratinocytes are similar to other cell compartments from other biologic systems that develop mutations. Mutation rates among oral microorganisms particularly among identified species at sites of high risk for HNSCC is largely unknown but mutated genes in selected microbial species can be examined to determine survival and adherence to various mucosa surfaces [183]. Bacterial models are used for example, Escherichia coli develop mutation induction in response to specific toxins. In oral biology a high rate of exposures to similar toxins is documented to produce loss of viability among keratinocytes. In other biologic systems exposed to similar toxic effects investigators have tried to use **prey and predator based systems such as Lotka-Volterra** to better understand mutation persistence, survival and robustness.

Furthermore, we can characterize this relationship by examination for diversification among microbes and epithelium. Although mucosa diversification is restricted to basal regions. Unregulated diversifications result in dyskeratosis and inappropiate differentiation. Therefore there are limits to growth among microbes in biofilm and basal keratincotyes. Limit of growth, diversification is a derivative of resistance or sensitivity genes/alleles. Eventually it is expected an evolutionary and convergent stable relationship with a steady of prey and predator action and reactions for each bio-film and region of interaction with mucosa will occur. However it cannot persist for long periods of time, oral environments are continually disrupted and unstable as a consequence of diet, saliva dynamics, microbial composition, host inflammatory response and complex variables present in dental and gingival

microenvironments, and therefore it is highly likely that diversification and mutation are directly linked following exposure to a variety of chemicals, or product of oral cavity dynamism [184]. Another view of this relationship previously described was a symbiosis and parasitism following formation, degeneracy and reformation of microbial interactive biofilm with mucosa.

In the oral environment while it is expected microorganisms of specific requirements will overgrow in particular environments the formation of symbiotic microbial biofilm presumes a control of prey and predator interactions required to maintain the biofilm and to optimize adherence of a variety of microorganisms. These environments are trade-off products of adaptive dynamic competitive Lotka-Volterra systems (e.g., prey-predator) after exposure to disruptive chemicals from habits such as tobacco or alcohol product exposure. In the oral environment, chemicals from microbes, saliva, host oral mucosa and habits such as tobacco products can also provide an adaptive response for microbial biofilms.

Persistence of the many microorganisms and basal keratinocyte histopathologic configurations exhibited in different tissues gives evidence that oral biology systems are robust and these oral biology systems permit a high degree of variability of survival traits needed by microorganisms to adhere to and persist and basal keratinocytes to maintain homeostatic interactions with adjacent stroma and microbial biofilm. Although permanence of any specific biofilm is questionable but a disruption of one leads to a formation of another because of the constant dynamics present in the oral environment and relative numbers of sites are expected to relatively constant [185]. Together the end result is a robust oral biology system in which mutation generation is dampened sufficient for survival under highly variable conditions such as those linked to tobacco use.

In the oral mucosa adaptive response, with a high level of degeneracy, is curtailed because of biologic limitations to sustain survival/viability in a comparatively homogeneous population of epithelium and mesenchymal stroma.

It is also recognized that too high a level of mutation among microbes or epithelial cells would destabilize interactions between these different biologic systems and deny microbes survival and host tissue of a means to regulate opportunistic microorganism to prevent infection. Furthermore, introduction of non-resident microbes selectively fill an ecologic need for their survival but they disrupt stabilized bio-films and this results in interactions with oral mucosa and host cells (e.g., immune cells) to produce damage to host tissues as virulence factors are released.

14.23 Genetic Variation- Polymorphism

Quantity, flow dynamics and quality of saliva, diet of individuals, habits, exposure to environmental chemicals, and inherent genetic susceptibility of individuals based upon polymorphic variations among genes (e.g., single nucleotide polymorphisms) will also affect mutation generation, type and quantity of DNA damages and allelic mutation variations not only in microbes but also oral keratinocytes. Particular gene polymorphisms of aldehyde dehydrogenease or alcohol dehydrogenase (ADH,

ALDH) exemplifies metabolic requirements and susceptibility to diseases such as cancer but also ethnicity (ancestry) related gene variability can influence this association. Furthermore, single nucleotide polymorphisms (SNPs) and rare variants describe an individual's relationship between diet, habits and activities of microorganisms in specific metabolic capabilities. For example, in both *Streptococci* sp and oral keratinocytes, ethyl alcohol (ETOH) is metabolized by alcohol dehydrogenase to produce acetaldehyde (AA) and then to acetyl–coenzyme A or acetate by aldehyde dehydrogenase. Only the Streptococci sp. capable of metabolizing alcohol to produce acetaldehyde and then acetate can attach to oral keratinocytes to generate large numbers of colonies [186–197].

In humans, alcohol and AA levels in the oral cavity may vary to a great degree depending on complex variables such as initial concentration, rate of exposure, metabolic activity of microbes and keratinocytes, salivary flow, and levels of serum proteins required for adherence of *Streptococci* sp [190–192]. It has also been noted that genes for alcohol dehydrogenase and aldehyde dehydrogenase, as well as associated enzymes, will ultimately effect differentiation of oral epithelium depending on the type of gene polymorphism present [193–197].

14.24 A Measure of Fitness and Survival

Microbes and epithelium interaction results from survival of the fittest activities. **Fitness can be described by a probability and an array of xphenotypes in a specific environment**. Absolute fitness has little relevance because we do not have sufficient quantitative information regarding selection. Relative fitness which is a average number of surviving progeny from a set of microbes species or clones of oral keratinocyte basal-stem cell like cells could be normalized for a specific genotype and genetic load (e.g., "$L = (W_{opt} - V)(W_{opt})$ where W_{opt} never = V but a fitness = 0 is where v = 0 and L = 1") for a microbial species and/ or epithelial clonal population (optimum) with a description of penetrance for selected genetic expression. However, this approach is presently unreliable without a more complete knowledge of oral biologic dynamics in microenvironments.

Furthermore, while natural selection can push fitness towards an optimum peak this is an unlikely occurrence particularly in oropharynx and oral cavity biologic systems because of continual turnover of microbe species and degeneracy in biofilm and epithelium. Therefore, the fitness (genotype load) is derived from a frequency of adaption for a RR1, RR2.... etc. in a t_0-t_x. However, precise quantification is not available. A lack of testable assumptions with a high degree of precision or accuracy implies further that an evolutionary randomness is operational in the oral pharynx and cavity and this is consistent with genetic drift although natural selection because it remains active to provide a direction to permit microorganisms and epithelial basal stem cells to adapt to changing conditions through reproduction and hereditary transfer of selected traits.

Population size also will influence survival of microbes and epithelial basal cells but to different degrees because each population has a absolute requirement for perpetuation in a specific microenvironment.

Among some microbial populations with narrow ecologic/nutrient requirements or selected clones of transformed epithelial basal-stem cell population size is limited and this could depress genetic drift if high allelic frequency for a survival gene was small. For this reason genetic drift is expected to affect frequency of more alleles in small populations and fewer alleles in larger populations. This selection direction can be particularly active in an environment of high allelic frequency in a small population of basal keratinocytes or microbial populations for selected genes (e.g., allelic variation in ADH or ALH genes). It is expected small select subsets will enhance survival advantage in specific ecologic niches (e.g., oral mucosa, gingival pocket, surface lymphoid tissues under exposure from ethyl alcohol or volatile aldehydes).

It is also recognized that some mutations in this situation of small discrete populations of microbes and/or keratinocytes are at a disadvantage because they are in a time dependent competition with other mutations to contribute to survive. For example, some mutations affect genes with similar allelic frequencies and enhance survival while others will reduce survival while still others have no influence on survival under certain conditions. Persistence of mutations and/or allelic variations are therefore affected by the population's ability to reach a survival threshold with genetic drift. An additional consideration is genetic linkage established mutations that contribute to survival selection and population size (e.g. recombination rate vs. genetic diversity vs genetic density at coding and noncoding sites for specific genes).

It is our expectation that a small but predominant population of microbes relative to numbers in the biofilm will target basal-stem keratinocytes and interact with mucosa. This is expected to exemplify a loss of symbiosis, increased degeneracy of the biofilm with a high degree of allelic variation as a rapid population collapse occurs following exposure to a carcinogen. Subsequently, as random selection becomes active and markedly increases select microbe populations metabolism of carcinogen becomes evident through accumulation of DNA damage sites in epithelium. Microbes also interact with mucosa that exhibit loss of integrity and exposure of basal keratinocytes to sustained DNA damage. A population bottleneck is also expected to be observed with an apparent reduction in either microorganisms and/or basal keratinocytes to contribute to genetic variability and enhanced fitness leading to reduced expectations for survival. This process is also linked to a loss of allelic variation among genes with important regulatory/differentiation/proliferation functions.

Ultimately there is a reduction in genetic diversity in either the microbial and/or epithelial populations if carcinogenic exposure persists. It is also expected that with a shrinking population further allelic fluctuations and increased randomness in daughter generations occurs which will increase the functional contribution of each mutation. However in both microorganism and epithelial transformation clones we expect to observe a high proliferative activity under appropriate microenvironments to reverse downward selection pressures. In oral mucosa this is evident by hyperplasia and hyperkeratosis which produce clinical leukoplakias and/or erythroplakias.

Microbial colonies are examples of persistent inhabitants in selected tissue sites such as, gingival pockets and/or supra-gingiva epithelial regions. Often these sites are in contact with dentition and attached gingiva, free gingiva and/or papilla which will select particular epithelial mucosa for interaction while other regions are not directly affected. The extent of this interaction will be dependent upon type, number, activity, and location of microorganisms in biofilms. Moreover biologic cross-talk composed of metabolic products increases survival potential and influences attachment/interaction with epithelial mucosa. It is also important to note presence of a variety of factors that promote or suppress survival of selected microorganisms can also exist in isolated bio-film communities.

Ultimately, as a tumor mass develops its own physiologic system a direct competition with "physiologic states of health" occurs. Modifications of cell, tissue and/or organ physiology systems will secure a competitive edge for a developing mass of independent basal cell clones of cells (e.g., transforming growth factors, epidermal growth factors, keratinocyte growth factors, cytokines, interleukins, differentiation factors linked to protein kinases, proteases, phosphatases, etc.) [198–200].

These tissue modifications provide opportunities for indirect assessment and an avenue to increase our understanding of microbiome and mucosa interactions and to develop novel avenues for cancer screening, early diagnosis and regulation of cancer growth. For example, infection rates and levels of virulence of microorganisms, and inflammatory host responses can be used as a surrogate for malignant transformation. To accomplish this analysis transudate, exudate, saliva or cytologic harvest of microbes and/or keratinocytes provide assesses to cellular DNA, RNA and proteins. Proteins can be detected using standard Western immunoblotting, or picomolar quantities detected and quantified using enzyme linked immunoabsorbent assays (ELISA). RNA and DNA expressions can be determined using a polymerase chain reaction hybridization using probe sequences. More novel approaches under development; include optical tomography, with selected fluorescent detection and ablation with target energy sources such as lasers, or microwaves for early screening diagnosis, and treatments [201–203].

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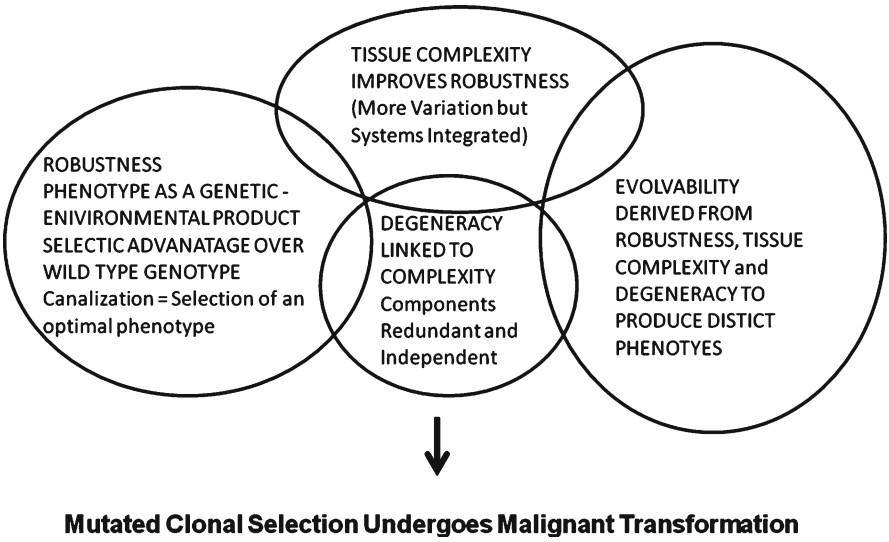

Fig. 14.3 Complementary characteristics for evolutionary changes to induce malignant cells. This figure depicts the relationships between complexity of genotype and phenotype changes in a microenvironment in conjunction. Specifically complexity is also characterized by degeneracy and robustness to obtain a clone of cells that have sufficient variability to survive as microenvironments change. The product of these relationships is evolutionary modifications of genotype and phenotype to produce a malignant clone of cells that can expand and form a tumor

In Fig. 14.3 we present our understanding of the interrationships between various characteristics that predict evolvability and susceptibility for malignant transformation.

This Fig. 14.3 also discloses that following mutation induction, changes in microenvironment, and genotypic and eventually phenotypic changes for malignant phenotypic expression occurs.

These features discussed above demonstrate the complexity of Head and Neck carcinogenesis as products of evolutionary-ecology. chemistry, and physiology alterations that are supported by mutations of DNA repair, cell cycle regulatory, and differentiation linked genes. This complexity was unrecognized when the "war on cancer" began ("National Cancer Act of 1971". National Cancer Institute. http://www.cancer.gov/aboutnci/national-cancer-act-1971/allpages).

Glossary

Fitness Adaptive optimum phenotype and is the contribution of progeny to next generations. Fitness can also be described by a probability and an array of x phenotypes in a specific environment.

Cryptic Genetic Variation Genetic variation that does not contribute to range of phenotypes under standard environmental conditions but becomes important under changes in environment.

Evolvability ability of cell or individual to respond to natural or inducible selection. This dependent upon complexity, degeneracy, and robustness. A product of phenotype and genotype in an environment.

Robustness Invariance of phenotype as a product of genetic and environment.

Pleiotropy effect of a single genetic locus to produce multiple phenotypic variations for enhanced survival.

Field cancerization a single mutated stem cell can expand into adjacent expanding clones of cells and produce a tumor mass. This principal asserts that development of a predominant clinical cancer in the head and neck does not completely describe a level of transformation because there are many other sites of malignant transformation identified by chromosomal of gene changes that have not attained clinical relevance.

Senescence cells in G_0, resting phase.

Driver mutations mutations provide a selective growth advantage to the cell.

Passage mutations Mutations do not alter fitness but occur coincidentally or subsequently acquired a driver mutation. Passenger mutations occur in every cell that has a driver mutation.

Gatekeeper gene is an "oncogene", regulator of cell growth, differentiation and nuclear stability.

Tumor suppressor gene put the brakes on cancer induction process.

Pluripotential_stem cell populations high degree of activity which permits differentiation to ectoderm, endoderm mesoderm or neuro-ectoderm.

Phenotypic variation maintains germ cell line origin (e.g., ectoderm) although offering an opportunity for progression of dedifferentiation.

Epigenetic modifications These can include methylation regulation of cytosine bases in cytosine guanine islands (e.g., CpG sites) that assist in regulation of expression, but also accompanied by changes in acetylation of histones and phosphorylation of various purine bases that can silence tumor suppressor genes.

Genetic drift a product of random sampling, which also contributes to phenotypic variability.

Hardy-Weinberg equilibrium (HWE) and disequilibrium information regarding evolvability of organisms in selected environments to determine selection of the fittest in a particular microenvironment.

Fitness landscape a stable local maxima for each cell and population until another selective change is introduced.

Allelic frequency determine a fraction of the copies of one gene shared among offspring to determine genetic drift in a population of know parental genotypes.

Relative risk a risk assessment for an event relative to exposure compared to a normal environment.

Founder's effect cell survivors with an opportunity for selective populations to proliferate from a larger population.

Lotka-Volterra prey and predator based systems.

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Chapter 15
Nutrition and Head and Neck Cancer

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Contents

Abstract This chapter supplies insight into nutrition in the consideration of its role in multiple aspects of Head and Neck Cancer. While generally promoted in the context of cancer prevention, there are nutritional and dietary aspects to cancer causation, diagnosis, therapy and survivorship. There is clearly a bidirectional relationship where the nutritional status of a patient contributes to their cancer risk and response as well as the occurrence of a Head and Neck Cancer contributes to the likelihood of poor nutritional status of a patient. Hence, nutritional interventions

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are warranted across the "life cycle" of Head and Neck Cancer. The reader will gain knowledge on the existing nutritional guidelines and the state of the science supporting the associations of nutrition and cancer highlighting important considerations specific to Head and Neck Cancer.

Keywords Diet • Nutrition • Food • Micronutrient • Nutritional assessment • Malnutrition

Abbreviations

ACS	American Cancer Society
AICR	American Institute for Cancer Research
AND	Academy of Nutrition and Dietetics (formerly – American Dietetic Association)
BIA	Bioelectrical Impedance Analysis
EN	Enteral Nutrition
HNC	Head and Neck Cancer
MNA	Mini-Nutritional Assessment
MST	Malnutrition Screening Tool
MUST	Malnutrition Universal Screening Tool
NA	Nutritional Assessment
NCI	National Cancer Institute (in NIH – United States National Institutes of Health)
NRI	Nutritional Risk Indicator
NRS-2002	Nutritional Risk Screening-2002
NS	Nutritional Support
NST	Nutrition Screening Tool
NT	Nutritional Therapy
PEG	Precutaneous endoscopically guided gastrostomy
PG-SGA	Patient-Generated Subjective Global Assessment
PN	Parenteral Nutrition
PNI	Prognostic Nutritional Index
QOL	Quality of Life
SGA	Subjective Global Assessment
TPN	Total Parenteral Nutrition

15.1 Introduction

Nutrition and diet play a significant role in an array of issues associated with head and neck cancer. First, dietary and nutrient constituents have been studied as important etiologic factors in the causation of head and neck cancers. Indeed,

international comparisons suggest associations between population dietary patterns and the incidence of head and neck cancers despite the prevalence of known risk factors including smoking and alcohol intake. Substantial reports from cohort, case-control and ecologic studies which focus on dietary factors as etiologic contributors to the development of this subset of cancers exist in the scientific literature. The general principles published to guide nutrition and lifestyle choices by the public aimed at cancer prevention have direct relevance to head and neck cancers. In addition, nutritional chemoprevention may actually afford protection against the onset of head and neck cancers among high risk populations with known exposures to associated carcinogens (i.e., tobacco). It has been observed that individuals with head and neck cancers often present at diagnosis in various states of malnutrition. Such nutritional status is thought to reflect both poor dietary practices prior to the onset of cancer as well as the debilitating and wasting effects of carcinogenesis. Subsequent demands of surgery, radiotherapy, and chemotherapy necessary in the treatment and management of these cancers also introduce major nutritional challenges that impact prognosis, morbidity, and quality of life. Nutritional factors are often subtle and overlooked but in reality represent important challenges in the prevention, treatment, and optimal management of head and neck cancers.

15.2 Nutritional Factors: Causation and Prevention

Although smoking is unequivocally the strongest risk factor, diet and nutrition are also likely implicated in the etiology and prevention of cancers of the head and neck. It has been estimated that 35–55% of cancers and approximately 15% of oral and pharyngeal cancers can be attributed to factors associated with dietary factors [50]. However more recent review is less definitive in arguing that diet is a large contributor to cancer and its prevention [4]. However an inverse association between head and neck cancers and fruits and vegetables, being stronger with vegetables than fruits, has been shown in a prospective cohort study [18].

15.2.1 Etiology

International epidemiologic studies that examine dietary patterns and chronic disease have observed both favorable and unfavorable associations with population diet characteristics and cancer risk. Most notable is the Mediterranean Diet [46]. Those populations adopting food choices that essentially reflect the Mediterranean diet have been observed to have measurable health benefits. For example, the incidence of oral cancer in Greece is less than would be expected based on the high prevalence of tobacco use and alcohol consumption. A case-control study of the possible relationship of diet and newly diagnosed oral cancer patients in Greece suggested that

low incidence of oral carcinoma reported in Greece may be explained in part by the higher consumption of the food groups and micronutrients that appear to protect against the disease [39].

A diet rich in vegetables, fruits and fiber (irrespective of its source) has been associated with a decreased risk to cancers of the head and neck region [30,37,39,52]. Toledo et al. [53] have suggested that the anticarcinogenic effect of fruits and vegetables might be associated with the action of their micronutrients and phytochemicals on the tumor cells. Vegetables and fruits do this by either preventing the activation and/or increasing the detoxification of the carcinogens [27,52]. Even thought there are antioxidants in a vegetarian diet [52], fruits have been reported to have a more consistent inverse relation with oral cancer [37]. Among meat and meat products, Cross et al. [9] noted the relation between red meat intake and the elevated risk for cancers of the esophagus and liver whereas poultry (skinless and non-fried) and fish have been associated with reduced risk of cancer [13]. Of the micronutrients, carotene, thiamine, riboflavin, potassium, magnesium, iron, vitamin D and C, iron, folate and higher intake of Alpha-tocopherol (most active form of Vitamin E) have all been associated with a decrease in the risk of cancer [7,32,38,39].

The anticarcinognic effect of dietary agents are by various mechanisms and occurs either during the cancer/tumor initiation and or during the promotion/progression processes, which include preventing cellular damage by carcinogens due to the presence of antioxidant enzymes and cellular detoxification, reduce cell proliferation rates, and inflammation as well as stimulate normal cell differentiation, cell to cell adhesion and apoptosis [27,54]. From their study of the chemopreventive effect of anthocyanins (a naturally occurring polyphenolic compound found in fruits and vegetables) in rats, Wang et al. [54] suggest that the chemopreventive effect may be because anthocyanins (a) inhibit cell transformation; (b) reduce inflammation and (c) induce apoptosis in cancer cells. Other anticarcinogenic agents and their anticarcinogenic mechanisms include isothocyanate, present in vegetables like cauliflower and broccoli and interferes with the metabolism of nitrosamines; sulphite, present in garlic and inhibits cytochrome p; glutathione-S-transferase enzyme, inactivates alkylic carcinogenic compounds; antioxidants like selenium; ascorbic acid inhibit tumoral promotion; and retinoids prevent both tumoral promotion and progression [27].

"A Global Perspective" is added by the 2007 report of that name from the World Cancer Research Fund and American Institute for Cancer Research [55]. Their review of evidence for mouth, pharynx and larynx convincingly supports alcoholic drinks increasing risk; non-starch vegetables, fruits and foods containing carotenoids as probable for decreasing risk; mate as limited suggestiveness for increasing risk; and limited/no conclusive evidence for effect by cereals, starchy roots, tubers, plantains, dietary fiber, legumes, meat, poultry, fish, eggs, milk and dairy products, total fat, animal fat, plant oils, coffee, tea, frying, grilling or broiling, barbecuing/charbroiling, protein, vitamin A, retinal, thiamin, riboflavin, niacin, folate, vitamin C, vitamin E, calcium, iron, selenium, body fatness, and energy intake. Their review for nasopharynx cancer differs with a probable increased risk for Cantonese-style salted fish. For cancer of the oesophagus they conclude convincing evidence for alcoholic drinks and body fatness.

Table 15.1 American cancer society guidelines on nutrition and physical activity for cancer prevention [31]

Recommendations for individual choices
Achieve and maintain a healthy weight throughout life
Be as lean as possible throughout life without being underweight
Avoid excess weight gain at all ages. For those who are currently overweight or obese, losing even a small amount of weight has health benefits and is a good place to start
Engage in regular physical activity and limit consumption of high-calorie foods and beverages as key strategies for maintaining a healthy weight
Adopt a physically active lifestyle
Adults should engage in at least 150 min of moderate intensity or 75 min of vigorous intensity activity each week, or an equivalent combination, preferably spread throughout the week
Children and adolescents should engage in at least 1 h of moderate or vigorous intensity activity each day, with vigorous intensity activity occurring at least 3 days each week
Limit sedentary behavior such as sitting, lying down, watching television, or other forms of screen-based entertainment
Doing some physical activity above usual activities, no matter what one's level of activity, can have many health benefits
Consume a healthy diet, with an emphasis on plant foods
Choose foods and beverages in amounts that help achieve and maintain a healthy weight
Limit consumption of processed meat and red meat
Eat at least 2.5 cups of vegetables and fruits each day
Choose whole grains instead of refined grain products
If you drink alcoholic beverages, limit consumption
Drink no more than 1 drink per day for women or 2 per day for men
Recommendations for Community Action
Increase access to affordable, healthy foods in communities, worksites, and schools, and decrease access to and marketing of foods and beverages of low nutritional value, particularly to youth
Provide safe, enjoyable, and accessible environments for physical activity in schools and worksites, and for transportation and recreation in communities

15.2.2 Prevention

Strategies for the prevention of head and neck cancers incorporate the information gained from investigative studies which have determined risk factors into recommendations for individuals diagnosed with cancer, those at high risk of the condition, as well as the general public. With sufficient knowledge, it is possible for authoritative agencies to develop and make available reliable guidelines that direct appropriate health care practices and lifestyle choices to individuals and health professionals.

Agencies with reliable information on nutrition and cancer prevention include: The National Cancer Institute (NCI) www.cancer.gov; the Academy of Nutrition and Dietetics (AND) www.eatright.org; and the American Institute for Cancer Research (AICR) www.aicr.org. The American Cancer Society (ACS) www.cancer.org periodically publishes Nutrition and Physical Activity Guidelines to convey that status of the science on "reducing the risk of cancer with healthy food choices" for use by individuals and communities in the United States. The most current guidelines were released in January 2012 [31] and are presented in Table 15.1.

15.2.3 Chemoprevention in High Risk Populations

Cancer chemoprevention has been defined as the use of natural, synthetic, or biologic chemical agents to reverse, suppress, or prevent the progression to invasive cancer [49]. Diet and nutrient constituents may be viewed as potential chemoprevention agents with respect to cancer prevention and control given the findings from numerous studies demonstrating diet cancer associations. As well, animal and human studies suggest that specific nutrients may be administered as nutraceuticals to prevent or treat cancer. Some potential chemopreventive agents include vitamins and minerals (folate, vitamin E, vitamin D, calcium, and selenium), phytochemicals (curcumin, genistein, indole-3-carbinol, and L-perillyl alcohol), and synthetic compounds (retinoids) [20].

This proactive intervention has potential applications for primary, secondary and tertiary prevention with respect to head and neck cancer. Primary prevention strategies would target high risk groups such as smokers, former smokers and/or individuals reporting current or past excessive alcohol use or those known to possess genetic mutations that predispose them to developing cancer. Secondary prevention would involve individuals who have known premalignant lesions such as oral leukoplakia aimed at preventing progression to cancer. The focus of tertiary prevention would be to prevent the onset of second primary tumors which is often the case with head and neck cancers.

Although on the surface the chemoprevention concept appears to be very appealing, considerable research is essential to assure efficacy and safety of protocols in humans. For example, a randomized trial of antioxidant vitamins to prevent second primary cancers in head and neck cancer patients showed that alpha-tocopherol supplementation produced unexpected adverse effects on the occurrence of second primary cancers and on cancer-free survival [1]. Additional and extensive research that develops the clinical application of chemoprevention and cancer is imperative.

15.3 Nutrition Concerns at Diagnosis and Treatment

15.3.1 Nutritional Assessment

Nutrition assessment (NA) and/or Nutritional screening has become an integral and important part of the pre-treatment, treatment and post-treatment phases of cancer. NA tools are used to assess the cancer patient's nutritional status thus helping to identify those patients who are more at risk to develop malnutrition and/or post operative complications. These help the healthcare professional to plan nutritional interventions based on the nutritional status of the cancer patient, thus maximizing the treatment outcomes, reducing the number of complications that may arise either during or after the treatment as well as improving the quality of life (QOL) of the cancer patient [10]. While there are many subjective and objective NA tools that are presently available, depending on the resources available, institutional guidelines

and the need of the patient, there have been questions about the reliability of the objective nutritional parameters (anthropometric, biochemical and immunological) that are being used mainly because of the non-nutritional factors that may effect the result of the NA [2].

One of the most frequently used assessment tool is the *Patient-Generated Subjective Global Assessment (PG-SGA*). This is an economical and easy to use NA [14], which is based on the Subjective Global Assessment (SGA) and was developed specifically for cancer patients [36]. The PG-SGA has questions about the presence of nutritional symptoms and short term weight loss in addition to the medical history (completed by the patient and includes weight and dietary intake changes, gastrointestinal symptoms present for more than 2 weeks and changes in functional capacity) and physical examination (completed by a health care professional for notice of a loss of subcutaneous fat, muscle wasting, ankle and/or lower back edema and abdominal swelling) portion of the PG-SGA [2,17]. The scored PG-SGA, which is an improved version of the PG-SGA, incorporates a numerical score, depending on the symptoms the patient is given points (0–4) and the points are summed to a total score to provide a global rating for the nutritional status of the cancer patient [2,17]. The main benefit of the scored PG-SGA is that it allows to track changes in the nutritional status over short periods of time [24] and has a sensitivity of 98% and a specificity of 82% at predicting SGA classification [2].

One NA that is used to predict postoperative complications among head and neck cancer patients as well as the need for nutritional intervention is the *Prognostic Nutritional Index (PNI)* [19,23,43,47]. In contrast, the *Nutritional Risk Screening (NRS-2002),* introduced by the European Society of Parenteral and Enteral Nutrition [28] is used to identify cancer patients who are at risk to develop malnutrition as well as those who are malnourished and includes an emphasis on the elder patient.

In addition to the above mentioned NA tools there are many more available to the health care professional. These include the Malnutrition Universal Screening Tool (MUST) [51], Malnutrition Screening Tool (MST) [25], The Maastricht Index or Nutritional Index [11,33], and Mini-Nutritional Assessment (MNA) [3].

15.3.2 Malnutrition

Development of malnutrition in cancer patients is multifactorial and may arise due to the cancer itself as well as the side effects of anticancer treatment. However the degree of malnutrition may vary depending on the patient's nutritional status at the time of diagnosis, site of the cancer, presences of co-morbid diseases and illnesses and the different treatment modalities that might be utilized [29]. Malnutrition is associated with a reduced response to treatment procedures, more number of post operative complications, decreased rate of survival and also affects the patients QOL [10] and outcomes have been shown to be influenced by nutritional impact symptoms present before treatment [29]. Malnutrition in the HNC patient's has been estimated to range from 20% [48] to 70% [42].

Issues contributing to nutritional challenges of treatment of HNC include taste dysfunction. A review by Porter and colleagues [41] provides exploration into the etiology, physiology and treatment. They suggest essentially all patients experience altered taste sensation, especially if receiving radiation therapy. Recent work by Ehrsson et al. [15] demonstrates weight loss among HNC patients even with participation in a nutritional surveillance program.

15.3.3 Nutrition Therapy

The aim of Nutritional Therapy (NT) is to help in achieving and maintaining optimal nutritional status of the cancer patient. The goals that NT has to accomplish as quoted by NCI are "Prevent or reverse nutrient deficiencies, preserve lean body mass, help patients better tolerate treatments, minimize nutrition-related side effects and complications, maintain strength and energy, protect immune function, decrease the risk of infection, aid in recovery and healing and Maximize quality of life." (http://www.cancer.gov/cancertopics/pdq/supportivecare/nutrition/HealthProfessional/page4#Section_61).

The Cochrane Collaboration has conducted a review of "enteral feeding methods for nutritional management in patients with head and neck cancers being treated with radiotherapy and/or chemotherapy" that was published in 2010 [34]. There is very limited evidence concerning methods of enteral feeding for head and neck cancer patients. Only one clinical trial was identified and it did not support a specific method.

Hayward and Shea provide a practical review of the nutritional needs of HNC patients [21]. The issues they capture and suggest management strategies include mucositis, dysphagia, xerostomia, thickening of saliva, alterations in taste and smell, nausea and vomiting, constipation, and decreased appetite. A more recent review of the topic has been provided by Epstein and Humann [16]. The two reviews convey much of the same material but are particularly noteworthy for the complementary perspectives, nursing and dentistry respectively.

In HNC patients, the preferred mode of providing nutritional therapy, in the presence of a functional gastrointestinal (GI) tract, is through oral intake [43]. However, there will be patients unable to ingest enough to meet nutritional requirements and will need supplemental delivery methods such as Enteral Nutrition (EN) [43]. Here depending on the anticipated duration for which EN is needed either a nasogastric tube can be placed (if EN is required for less than 4–6 weeks) or a Precutaneous endoscopically guided gastrostomy (PEG), if EN is required for more than 4–6 weeks [43]. Whereas Parenteral Nutrition (PN) is indicated among those HNC patients whose nutritional status is still critical even after getting oral and/or EN for more than 10–14 days [43]. PN is also known as "Total Parenteral Nutrition", "TPN" or "Hyperalimentation". Here the nutrition supplements are given directly into the vein via an intravenous tube/catheter. The main advantage of EN is the presence of few complications [5,45] and is more economical than PN [35, 43] whereas in PN it is possible to replenish specific nutrients in cancer patients.

While there are a number of nutrition formulas available in the market, the more recent "enriched" formulas which have specific nutrients, most important of which are arginine, glutamine, nucleotides and omega-3 fatty acids [8,43,48], have taken the center stage. Various studies about these enriched formulas have found that they help to reduce the post-operative infection rates and complications, reduce oral mucositis among patients who received radiotherapy, increase serum protein levels and the long-term overall and disease-specific survival [6,8,12,26]. However in their review Heyland and colleagues [22] noted that in critically ill cancer patients the use of immuno-nutrition is not associated with fewer infectious complications and that the mortality rate was higher in this group compared with elective surgical patients.

NT and NS have been documented to improve the nutritional status as well as add to the ability to tolerate treatment and its side effects in cancer patients. However, indiscriminate use in well-nourished and/or mildly malnourished cancer patients, who can get adequate nutrition via oral intake, is contraindicated.

15.3.4 Nutrition and Survivorship

An individual who has been diagnosed with cancer and through the remainder of that person's life is a cancer survivor. Those afflicted with head and neck cancers are no different. Currently, there is great interest and an emerging literature on understanding the cancer survival experience and recognizing ways to improve the quality of life among survivors [40]. Although considerable investigation has focused on diet as an etiologic factor and nutritional issues during treatment, little is known about the diet and survival experience of head and neck cancer survivors. A step toward filling the void on head and neck cancer survival is an ACS guide focused exclusively on nutrition and physical activity guidelines for cancer survivors which does address important issues relevant to the respective cancer sites [44].

15.4 Conclusions

The generally accepted nutrition and cancer guidelines have importance for the primary and secondary prevention of head and neck cancers. Chemoprevention through nutraceutical interventions has promise for future protocols to prevent and treat. The fact that so many individuals diagnosed with head and neck cancer present with extensive malnutrition poses enormous challenges to achieve optimal outcomes with these patients. In summary, nutrition is currently a critical factor in all phases of head and neck cancer continuum and will continue to be so in the future management of this disease.

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Chapter 16
Treatment Planning Considerations

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Contents

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Abstract The modern management of head and neck cancer is remarkable for its multidisciplinary nature. Clinical and scientific advances have made treatment options in surgery, radiation oncology, and medical oncology much more effective in addressing both primary and recurrent disease. Nonetheless, the pre-treatment workup and planning may overwhelm the patient, whose decisions heavily influence the type of therapy as well as the outcome. This chapter reviews the elements of treatment planning that impact the patients and their families. Important aspects of the initial examination, imaging, and diagnosis are reviewed. Communication with ancillary providers such as audiology, dentistry, and speech pathology help prepare the patient for treatment and subsequent rehabilitation. Expectations for cure, realistic options for salvage, and the benefits of palliative care may also affect the choice of treatment. While some topics remain controversial, therapy should remain centered on the patient and family, balancing the likelihood of cure with preserving their priorities and quality of life.

Keywords NCCN • AJCC • Airway obstruction • Fine needle aspiration • Comorbidity • Prosthodontics • Pain management • Hospice • Palliative care • Salvage • Quality of life

Abbreviations

AJCC	American joint committee on cancer
CUP	Carcinoma of unknown primary
CT	Computed tomography
DNR/DNI	Do not resuscitate/do not intubate
SDH	Succinate dehydrogenase
EBV	Epstein-Barr virus
FDG	18F-fluorodeoxyglucose (used in PET imaging)
FNA	Fine needle aspiration
HNSCC	Head and neck squamous cell carcinoma
IMRT	Intensity modulated radiation therapy
MEN	Multiple endocrine neoplasia
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NPC	Nasopharyngeal carcinoma
NSAID	Non-steroidal anti-inflammatory drug

PET-CT Positron emission tomography-computed tomography
QOL Quality of life
TSH Thyroid stimulating hormone

16.1 Introduction

The treatment of head and neck cancer can often be a bewildering process. In addition to coming to terms with their diagnosis, patients and their families must navigate through differing opinions, various treatment options, as well as numerous specialists and ancillary providers. The complexity of diagnosis and therapy can often leave patients uncertain about their care and hesitant to ask questions that may affect their choice and course of treatment. On the other hand, this multidisciplinary approach helps maintain best practices and constantly evolving standards of care.

This chapter introduces a roadmap that patients typically traverse when planning their treatment. Initial diagnosis and staging, including imaging, special testing, and the role of the tumor board are explained. Preoperative planning that facilitates treatment such as medical and anesthesia assessment, audiology, dentistry, speech pathology, and nutrition are also reviewed. The importance of patient counseling through treatment planning is paramount: each patient's expectations are different, as is his or her willingness to accept the significant side effects of various treatments, including the possibility of hospice and palliative care. The decisions made during the treatment planning stage ultimately have a large impact on therapy, patient satisfaction, and outcome.

16.2 Diagnosis and Staging

16.2.1 History of Illness

When a head and neck malignancy is suspected, a flurry of diagnostic information is generated to help decide management. Despite considerable advances in imaging and histopathology, the most fundamental component relevant to treatment planning remains the history and physical exam. Information about the onset and progression of symptoms, such as dysphagia, dysarthria, hoarseness, nasal obstruction, and hearing loss provide clues to the location and stage of the disease. Predisposing factors such as past medical history and performance status moreover play a large role in determining the likelihood of patients withstanding the rigors of treatment. For instance, patients with severe comorbidities and poor performance status are less likely to recover well from surgery, or be able to complete a full course of radiation or chemotherapy [1, 2]. Such patients may be counseled to undergo alternate therapies such as a nonsurgical treatment, or less toxic chemotherapy agents that balance an chance of cure with the possibility of completing treatment [3].

Social and family histories also play an important role in the head and neck patient workup. The ethnicity, occupation, and lifestyle are crucial factors in predicting

Table 16.1 Common molecular markers in head and neck cancer

Marker	Disease type	Implication of positive result	Comments
HPV or p16	Oropharyngeal HNSCC, CUP	Oropharyngeal HNSCC – suggests better response rate and prognosis CUP – suggests base of tongue or tonsil origin	CUP – may help define radiation fields
EBV	NPC, CUP	NPC – elevation after treatment suggests recurrence CUP – suggests NPC	CUP – may help define radiation fields
SDH	Paraganglioma	Suggestive of paraganglioma syndrome (paraganglioma and pheochromocytoma)	SDHD mutation – suggests multifocal disease SDHB mutation – suggests malignant disease
RET	Medullary thyroid cancer	Suggests higher risk of MEN IIA/IIB	Testing recommended for family members if patient tests positive
EGFR	HNSCC	Suggests more aggressive disease and poorer prognosis	Overexpressed in 90% of HNSCC; targeted by cetuximab
BRAF	Thyroid cancer, skin melanoma	Suggests more aggressive disease and poorer prognosis	Targeted by vemurafenib

HNSCC head and neck squamous cell carcinoma, *CUP* carcinoma of unknown primary (marker obtained from neck mass), *NPC* nasopharyngeal carcinoma

the likelihood of certain pathologies. For instance, Asian patients with a persistent middle ear effusion and a lateral neck mass are at a higher risk of having nasopharyngeal carcinoma [4]. Woodworkers exposed to high levels of dust have been shown to be at higher risk of developing sinonasal cancers [5]. And most significantly, heavy smokers have a substantially higher risk of aerodigestive tract malignancies, with concurrent alcohol use having a multiplicative effect [6]. Evidence has also preliminarily shown that head and neck cancer patients who have not smoked in their lifetimes (never-smokers) may be more responsive to radiation treatment and have a better prognosis [7]. Whether this alters the treatment plan depends on each case, but its implications for outcome may be helpful for patients to understand.

Family history may similarly suggest the type and aggressiveness of malignancy, and lead to specialized diagnostic testing. It conversely may inform patient families of their risk and need for assessment. For instance, the succinate dehydrogenase (SDH) mutation has been associated with head and neck paragangliomas, and depending on the type could be more likely to have multifocal disease or malignant versus benign disease [8]. In addition, the presence and type of RET proto-oncogene mutation has implications for the aggressiveness of medullary thyroid cancer and the age at which surgery is recommended. A negative RET assay also rules out the possibility of multiple endocrine neoplasia (MEN) IIA or IIB syndromes, a genetic disorder that includes medullary thyroid cancer, hyperparathyroidism, and pheochromocytoma [9]. A list of germline mutations in head and neck cancer is listed in Table 16.1.

16.2.2 Medical Assessment

The general medical health of the patient is important for a number of aspects of cancer care. From a surgeon's perspective, the most important is the ability to tolerate general anesthetic and the long operations that are required to treat and reconstruct head and neck cancers. Radiation oncologists are concerned with history of prior radiation therapy and conditions such as collagen vascular diseases (lupus, scleroderma, Sjogren's) which some view as a contraindication to radiation therapy. Medical oncologists are concerned with preexisting diseases that may be exacerbated by the side effects of chemotherapy and the overall ability to tolerate the draining effects of chemotherapy. Other considerations are that patients with large number of medical problems or comorbidities, have poorer outcomes regardless of the type of treatment. We will discuss each of the different organ systems and its impact on cancer care.

16.2.2.1 Cardiovascular

Cardiovascular complications are the most common cause of perioperative mortality. In assessing cardiovascular fitness, a history of angina, prior heart attacks, symptoms of heart failure, arrhythmias and valvular disease are important, particularly if there are recent changes in symptoms [10]. Determining the functional capacity of the heart is another important part of the history. Patients that are asymptomatic and active have lower risk. A typical question is whether the patient can walk two flights of stairs without getting short of breath. This level of physical activity indicates a good functional capacity has been correlated to a low risk of cardiac events during surgery. The physical exam may reveal some clues of heart disease such as third heart sounds, murmurs or rales in the lungs. Patients suspected of heart disease will need further workup, which may include chest x-ray, electrocardiogram, echocardiography, and stress testing. Patients with signs of heart failure need medical optimization prior to surgery. Patients with large areas of the myocardium at ischemic risk may need cardiac catheterization to determine the degree of coronary artery disease.

Prior to cardiac catheterization, the surgeon and cardiologist need to discuss the treatment plan for any stenotic coronary arteries discovered, because the type of intervention has implications on when surgery can be performed. Stents are felt to keep the coronary vessels open better and drug eluting stents have a lower restenosis rate than bare metal stents. However, the time interval between the cardiac procedure and ability to safely operate on the patient is an important factor in deciding the type intervention. Typically, for angioplasty, surgery needs to be delayed for 14 days following the procedure. In patients that have angioplasty with placement of a bare metal stent, surgery needs to be delayed 4–6 weeks to allow for partial endothelialization of the stent [10]. In addition, antiplatelet drugs (ticlopidine or clopidogrel) and aspirin are administered for 4 weeks. In general, drug eluting stents require a

longer period of antiplatelet therapy (6–12 months) and are not appropriate for use prior to planned or eminent surgery requiring the discontinuation of the antiplatelet therapy [10]. Depending on the urgency and need for surgery, the different treatment options for coronary artery stenosis may be favored.

Beta-blocker medications decrease the risk of cardiovascular events in patients with moderate and high risk. They should be started days to weeks before surgery and titrated to a resting heart rate of 65 beats per minute [10]. Beta blocker usage should be continued after surgery and the optimal duration has not yet been determined [10].

16.2.2.2 Respiratory

Respiratory status is a more important consideration for surgery than for chemotherapy or radiation therapy. A significant proportion of patients with head and neck cancer develop chronic obstructive pulmonary disease and emphysema as a result of chronic long-term tobacco use. Patients with pulmonary disease need a preoperative chest x-ray to assess for pneumonia, particularly aspiration pneumonia, which is common in patients with head and neck cancer. For patients with more severe pulmonary disease, pulmonary function testing and arterial blood gas testing can provide objective data to predict perioperative morbidity.

Pulmonary function is particularly important for patients being considered for partial laryngeal surgeries since it is not well tolerated in patients with severe pulmonary disease. Following partial laryngeal surgery, there is aspiration to some degree in all patients. Patients with pre-existing pulmonary disease have less pulmonary reserve and lesser ability to clear the aspirated contents from their lungs leading to the development of pneumonia. These patients are better served by having either non-surgical treatment or removal of the entire larynx, which separates the breathing from the digestive passages.

16.2.2.3 Renal

Kidney disease is not a contraindication for surgery as long as it is recognized and the electrolyte abnormalities are corrected. Cisplatin is a commonly used chemotherapy agent that causes kidney and auditory damage, and is contraindicated in patients with existing kidney dysfunction.

16.2.2.4 Auditory

Cisplatin can cause damage to the auditory system and is contraindicated in patients with existing hearing loss. Hearing is carefully monitored during treatment with cisplatin and can alter the course of treatment if severe hearing loss is found. Carboplatin is a derivative of cisplatin that has a similar mechanism of action but

does not have the toxic effects on the kidneys and auditory system. This drug is often substituted for cisplatin when kidney or auditory toxicity is of concern.

16.2.2.5 Dental Evaluation

The teeth need to be evaluated and any carious teeth need to be either extracted or repaired before radiation therapy of the mandible. Dental work after radiation, even years later, can cause osteoradionecrosis of the mandible. Osteoradionecrosis after radiation therapy is thought to be due to the "3H's": hypocellularity, hypovascularity and hypoxia [11]. Radiation is thought to have a lethal effect on the cells within the mandible such as osteocytes and osteoblasts, which results in hypocellular bone. The effects of radiation on the microvasculature causes hypovascularity, and ultimately leads to tissues that are hypoxic relative to unirradiated tissues. An additional risk for osteoradionecrosis is that radiation decreases salivary output, which is important for the maintenance of healthy teeth. The xerostomia, or dry mouth, caused by radiation accelerates the formation of dental caries. Daily supplemental fluoride therapy in the form of prescription strength toothpastes, fluoride rinses or fluoride gels are recommended to prevent dental disease that may lead to osteoradionecrosis. Salagen (pilocarpine) or Evoxac (cevimeline) are cholinergic agonists that stimulate glandular tissue to secrete saliva. These medications can stimulate any remaining salivary tissue to produce greater amounts of saliva while at rest.

16.2.3 Physical Exam

The head and neck contain a dense confluence of muscles, lymphatic ducts, blood vessels, and nerves that cancers may easily disrupt. Perhaps more than any other specialty, the head and neck physical exam is therefore a key part of the patient workup to guide diagnosis, imaging choices, or biopsy procedures. A broad surveillance of the scalp and face, especially in those with a long history of sun exposure, can reveal cutaneous malignancies such as squamous cell carcinoma or melanoma. Deep palpation of the oral cavity and oropharynx can give a sense for any submucosal disease not visible to the eye. And cranial nerve abnormalities may elicit a great deal about the location of the tumor, as well as how advanced it has become. For instance, facial nerve palsy may suggest an infiltrative parotid malignancy or a neoplasm in the internal auditory canal, while shoulder droop may suggest involvement of neck metastasis on the spinal accessory nerve.

The lateral neck contains hundreds of lymph nodes that serve as a conduit through which cancer spreads. Enlarged lymph nodes may be inflamed from infection, which is why antibiotics are typically first prescribed to see if they subside. However, palpable nodes that persist in the context of cancer are likely regional metastatic disease, traveling downward through the lymph nodes en route to distant spread. This suggests more advanced disease and is reflected in staging systems (see below).

On the other hand, a patient may present with only a positive lymph node, and without any other discernible primary cancer site. This is termed a carcinoma of unknown primary (CUP).

The flexible fiberoptic laryngoscope has become a standard part of the otolaryngologist's exam. It affords a magnified view of portions of the head and neck that are difficult to see well with a standard exam. After administration of topical anesthetic, a thin 4 mm-wide flexible fiberoptic scope can visualize the nasal cavities, sinus openings, nasopharynx, oropharynx, hypopharynx, and larynx down to the vocal cords. Any abnormalities, paralysis, or suspicious findings can be digitally recorded to explain to the patient, as well as assist in treatment planning. The transnasal esophagoscope additionally examines the esophagus. Both scopes enable direct biopsy of suspicious areas in the clinic while the patient remains awake.

16.2.4 Airway Assessment

ABC is a mnemonic for airway, breathing and circulation, highlighting their importance as initial assessments. This applies to all patients, including those with head and neck cancer. The importance of the oral cavity, oropharynx and nasal cavity in breathing and swallowing make assessment of these functions of particular significance for head and neck cancer patients.

Typically, the problem with head and neck cancer patients is not with breathing or circulation, it is obstruction of the airway. In some cases the obstruction can be treated before breathing becomes problematic, but on occasion, patients need emergent procedures to secure a safe airway. Many people assess the oxygen saturation when dealing with a patient in respiratory distress, but most patients are able to maintain normal oxygen saturations with other compensatory mechanisms. By the time the oxygen saturation is compromised, the patient is typically in severe distress and complete airway obstruction is imminent. One of the earliest signs of airway compromise is a history that the patient is unable to lie flat to sleep. Other early signs of airway compromise include tachypnea, use of accessory muscles of respiration and inspiratory stridor. Stridor can be very subtle and needs to be carefully assessed in patients with potential airway compromise.

The degree of airway compromise determines the treatment. Severe cases require tracheostomy. In selected milder cases, the tumor can be debulked to open the airway long enough for the cancer treatment to shrink the tumor and open the airway [12]. The mildest cases may be observed with the hope that cancer treatment will shrink the tumor. With non-surgical cancer treatment, there may be an initial phase of tumor swelling prior to tumor regression. During the period of swelling, the patients must be followed in case intervention is needed to prevent airway obstruction [13].

In the patient with a compromised airway, multiple decisions need to be made quickly. Should the patient be intubated in the emergency room or in the operating room? Can the patient be put to sleep or should the intubation be done awake with

topical anesthetic? Should a surgeon be on standby for a possible emergency tracheostomy? If a tracheostomy is needed, can the patient be intubated prior to the procedure or does the tracheostomy need to be done with the patient awake and breathing on their own? Can the patient be laid flat for the procedure or do they need the back of the bed at 45° to breathe? The answers to these questions should be determined by the team of physicians caring for the patient and typically include the head and neck surgeon, anesthesiologist and emergency room physician.

16.2.5 Imaging

Unparalleled advances in radiographic imaging have led to improved characterization of head and neck cancers, and the identification of cancers spread otherwise too small to detect in the clinic. Much like prostate cancer, the increased detection of certain types of cancer (such as papillary thyroid microcarcinomas) has led to controversy regarding whether such small disease will manifest as clinically relevant [14]. The type of imaging obtained in head and neck cancer is physician- and institution-dependent; each has certain advantages that may assist in planning for treatment.

Plain x-ray films are cost-effective and impart relatively minimal radiation exposure. Patients routinely undergo a chest x-ray to rule out metastatic spread to the lungs. If applicable, a dental panoramic radiograph (panorex) may be used to assess dentition, odontogenic tumors, or invasion into the maxilla or mandible. Ultrasound imaging is another cost-effective imaging tool, widely used in the assessment of thyroid cancer. Without using radiation, it provides real-time information on thyroid nodules and lymph nodes, including suspicious attributes such as central hypervascularity, microcalcifications, and irregular borders [15]. Such information may determine if a neck dissection needs to be performed in addition to thyroid surgery.

Computed tomography (CT) scans display bony anatomy superior to other imaging modalities, with iodine contrast to enhance tumor characteristics. It requires substantially more radiation exposure than plain films, and iodine contrast is contraindicated in patients with renal disease. Magnetic resonance imaging (MRI) scans are advantageous for their soft tissue detail, further enhanced by the addition of gadolinium contrast, and entail no radiation. However, they are generally more expensive than CT scans and require the patient to lay supine in an enclosed space for approximately 30–60 min, making it difficult or impossible for claustrophobic patients or those in airway distress. Some eligible patients may be prescribed an anxiolytic medication prior to an MRI.

Positron emission tomography-computed tomography (PET-CT) has emerged as an important imaging modality in head and neck cancers [16]. Using an 18F-fluorodeoxyglucose (FDG) tracer preferentially taken up by hypermetabolic cancer tissue, the functional activity of tumor can be mapped to the fine anatomic detail of CT imaging. This has enabled the detection of small lymph nodes not palpable in clinic, or the detection of primary site disease in CUPs not previously identified. The false-positive rate is high, however, since inflammation and infection also

appear as FDG-avid lesions [17]. Certain malignancies such as well-differentiated papillary thyroid cancer also do not take up FDG.

It should be noted that the interpretation of a scan by one radiologist may differ substantially from another, depending on one's expertise and experience. It is vital that when a patient is referred to a different institution for management or a second opinion, that he or she bring a CD of the scans themselves rather than just a radiologist's report. This will allow the second institution's radiologists and physicians to view the imaging to make their own assessment, without needing the patient to undergo costly reimaging.

16.2.6 Tissue Diagnosis

Despite the effectiveness of clinical exam and imaging in identifying possible disease sites, only a tissue biopsy of those suspicious sites reviewed by a pathologist can confirm the diagnosis of cancer. This may be done in the clinic or in the operating room, depending on the location and type of malignancy. If the lesion is easily accessible on the skin or in the oral cavity, and the patient is amenable to local anesthetic, a punch or incisional tissue biopsy may be taken in the office and sent to pathology, where it may take approximately 1 week to reach a diagnosis.

If the patient presents with a neck or thyroid mass, a fine needle aspiration (FNA) biopsy may be performed in the clinic. In this minor procedure, a thin, hollow needle draws a sampling of cells from the mass, which can be analyzed under a microscope while the patient is awake. A diagnosis can be relayed immediately, and the greater risks of an open surgical biopsy are avoided. However, since only a small number of cells are taken, the diagnosis sometimes cannot be determined. The FNA can be repeated, or an ultrasound or CT-guided biopsy can be performed by a radiologist if needed for deeper lesions. If the diagnosis remains indeterminate, an open surgical biopsy in the operating room may ultimately be needed to obtain sufficient tissue for pathology. An open biopsy is often also needed when the FNA diagnosis returns as lymphoma, since tissue architecture not seen on needle biopsy is necessary to determine lymphoma treatment.

If a neck mass is confirmed as cancer but no obvious primary site has been identified, a panendoscopy (direct laryngoscopy, bronchoscopy, esophagoscopy) is classically performed in the operating room under general anesthesia to take a more in-depth look at the head and neck to find the primary lesion. Biopsies may be taken of the most common sites of head and neck cancer (the tonsils, base of tongue, and pyriform sinuses), and some surgeons advocate performing bilateral tonsillectomy to truly rule out disease in these sites [18]. Because tobacco and alcohol are carcinogens that pass through the entire aerodigestive tract, the exam traditionally also assesses for second cancers in the lungs and esophagus. Currently, improvements in PET-CT resolution have led some institutions to forego a panendoscopy for uncomplicated patients and perform directed biopsies based on imaging [19].

Moreover, the risks of anesthesia and low yields from panendoscopy should be considered in each patient. While a negative PET-CT in these common sites is highly suggestive for lack of disease, an exam under anesthesia should still be performed if clinically indicated [20].

16.2.7 AJCC Staging

The American Joint Committee on Cancer (AJCC) Cancer Staging Manual [21] remains the most widely accepted method of classifying the extent of cancer spread. Based on TNM criteria (tumor characteristics, neck lymph node status, and metastasis status) for each cancer type, the stage serves as an important determinant of a patient's prognosis. Each subtype has a different TNM classification. For instance, tumor size is significant in oral cavity cancer, but not in laryngeal cancer, even if both are squamous cell carcinoma. AJCC staging also has implications for recommended treatments, though each patient case is different. Although there are certainly exceptions, early-stage cancers (Stage I–II) often are treated with a single modality (e.g., surgery alone, or radiation alone), while late-stage cancers (Stage III–IV) are treated with multiple modalities (e.g., chemotherapy with radiation). Some late stages (such as Stage IVC) indicate unresectable disease or distant metastasis, where palliative treatment may be appropriate.

16.3 Treatment Considerations

16.3.1 Tumor Board

The complexity of head and neck cancer and the lack of solid evidenced-based medicine have made treatment difficult to standardize. The possibility of cosmetic and functional deformity (e.g., loss of sight, hearing, speech, swallowing) makes the decision for treatment all the more personal and subjective. The tumor board is a weekly multidisciplinary conference where patient cases are considered and a consensus can be formed. It is comprised of surgeons, radiation oncologists, medical oncologists, radiologists, pathologists, and other providers who specialize in head and neck cancer.

Each institution's tumor board is set up differently: some go over all their head and neck cancer cases, while others review only the complex ones; some have the patients appear at the tumor board for physical examination, while others review only their medical record. In all cases, a patient's history and exam are presented, and the radiology and pathology reviewed. Although the best available evidence in the literature is considered, there remains much controversy about the best management, and as such each patient's case is discussed individually. Issues such as

whether a patient in poor health could recover from a long surgery, or whether a patient would be willing to undergo a 6 week daily course of radiation, are taken into consideration. In addition, certain patients are considered for clinical trials for new medications or procedures still under investigation, such as induction chemotherapy, endoscopic skull base surgery, or robotic surgery. Each physician's experience as well as the available evidence help shape the dialogue. Ultimately, a decision regarding treatment is formed that ensure that best practices are maintained. Due to the controversy regarding a number of areas, different tumor boards may diverge on management recommendations, even for the same patient. The best recommendations are those that explain the rationale behind their judgment.

16.3.2 Comorbidities

Ideal treatment guidelines are available and updated yearly from the NCCN for patients with head and neck cancer. Unfortunately, these guidelines are based on studies that have excluded patients with significant medical conditions or have other obstructions to care. Head and neck cancer patients are likely to have a significant history of tobacco and alcohol use, which increases their likelihood of significant medical conditions in addition to their index cancer. Compared to patients with other types of cancer, only lung and colorectal cancer patients had a higher rate of comorbidities [22]. Patients with prostate, breast, and gynecologic cancers had lower rates. These coexistent medical conditions have been termed comorbidities and have been shown to correlate to survival regardless of the type of cancer treatment [23]. In certain cases, the cormorbidities are more important to the care of the patient than the cancer itself [23]. This suggests that very aggressive therapies in patients with advanced cancers may not be warranted because of the low survival rates.

16.3.3 Compliance

Successful cancer treatment is dependent upon compliant patients showing up for their treatments. Most cancer treatment protocols only report on the compliant patients and eliminate the non-compliant ones from their analyses. Compliance has a significant impact on treatment outcomes particularly with radiation therapy. Non-compliant patients with greater than 14 days of treatment interruption had a significantly higher rate of persistent carcinoma in the neck following radiation therapy (79 vs 23%).[24] For non-compliant patients, surgery can be a better option because in most cases, it is performed in one session and does not require repeated treatments.

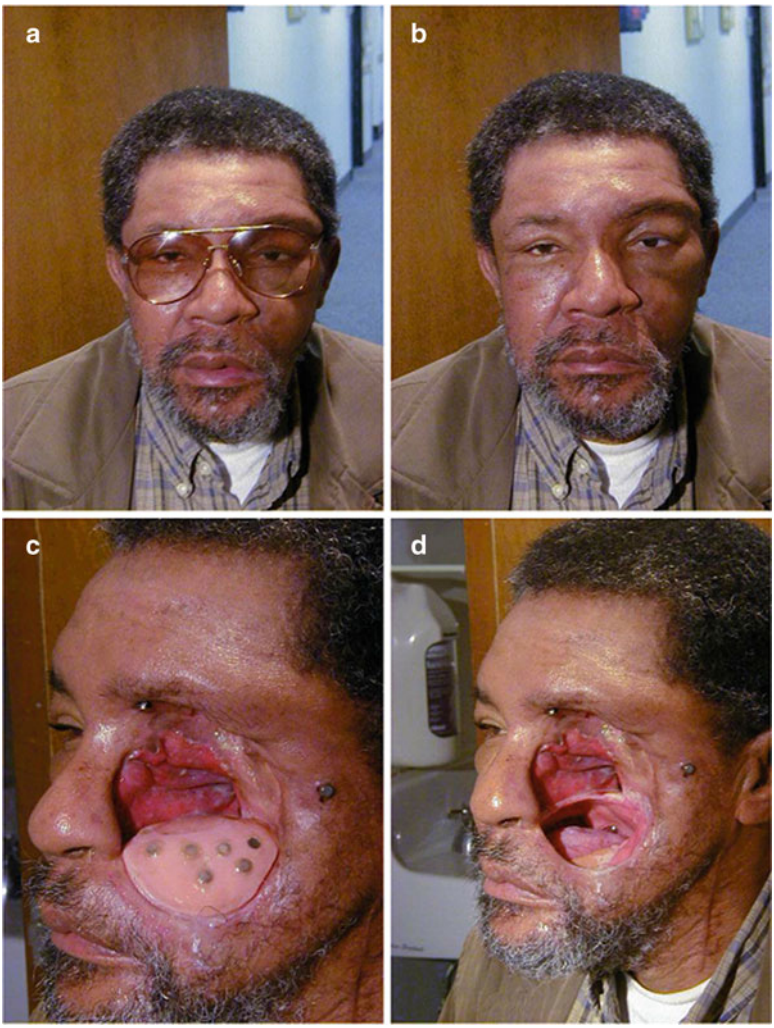

Fig. 16.1 Patient with squamous cell carcinoma of the left maxillary sinus with invasion into the eye, cheek skin and hard palate after surgical resection and radiation therapy. (**a**) Eyeglasses help to hide the seams between the eye/cheek prosthesis and the rest of his face. The prosthesis is held in place by magnets imbedded into the face and the palatal prosthesis. (**b**) The prosthesis matches well with the remaining native tissues even without the eyeglasses for camouflage. (**c**) The orbital and cheek prosthesis removed showing the inside of the orbit and nasal cavities. The prosthesis for the hard palate is still in place. Magnets are embedded in the upper portion of the palatal prosthesis and in the face to secure the eye/cheek prosthesis. (**d**) The palatal prosthesis has been removed showing the hole from the nasal cavity and maxillary sinus into the mouth (Prosthesis made by Dr. David Reisberg and his prosthodontics team at the University of Illinois at Chicago Medical Center)

16.3.4 Prosthodontics

Although reconstructive surgery has improved dramatically over the past 50 years to allow for removal of tumors that previously could not be reconstructed, there are still some instances where the surgical defects cannot be reconstructed with the patient's own tissues and a prosthesis is needed. Maxillofacial prosthedontists specialize in this work that is a blending of medicine and art. Prostheses are commonly used for patients with missing ears, noses, eyes or hard palate (Fig. 16.1). The prostheses need to be carefully sculpted and colored to match patient features. Prostheses can be secured by gluing them to the skin or with magnets implanted in the face or skull.

16.3.5 Nutrition

Head and neck cancer patients are often malnourished when the cancer is diagnosed. Cancer itself will cause cachexia, a loss of weight and appetite. This is particularly pronounced in patients with head and neck cancer because many of these cancers make swallowing difficult. A large proportion of the patients will present with a several month history of difficulty eating solid foods and subsisting on liquids only. Typically, a loss of more than 10% of the body mass is concerning and increases the risk of complications from the treatments. In addition, many of the therapies further impair the ability to swallow. These patients need to be recognized early and their diets supplemented. In many cases this requires placement of a feeding tube either temporarily in the nose or more permanently in the stomach (gastrostomy tube). In general, every attempt is made to provide nutrition to the gastrointestinal tract, but when that is not available, patients can be fed intravenously with total parenteral nutrition. This is expensive and the intravenous access required for this type of feeding increases the risk of infection. More detail on this topic is available in the nutrition chapter.

16.3.6 Speech Pathology

Speech pathologists play a number of important roles in the care of head and neck cancer patients. As their title implies, they help patients with speech. This may range from vocal exercises for patients with submilimeter nodules on their vocal cords to teaching patients who have had their larynxes removed to speak with an electrolarynx (electronic vibrating device to allow speech), with esophageal speech (swallowing air and burping it up for speech) or with a tracheoesophageal prosthesis (prosthesis that allows air from the trachea to be diverted into the esophagus causing vibrations like a burp to be used for speech).

Another very important role of the speech pathologist is the evaluation of treatment of swallowing disorders. In the hospital, this is the primary function of the speech pathologist and is particularly important for the head and neck cancer patients that often have difficulty swallowing. Speech pathologists in conjunction with radiologists perform modified barium swallow testing that by giving patients varying food consistencies coated in barium to determine a patient's ability to swallow. This determines what the patient can safely eat with less risk of aspiration. In addition, speech pathologists teach patients compensatory maneuvers and exercises to help improve the ability to swallow.

16.3.7 Physical Therapy

Physical therapy is of particular importance in patients following surgical resection of their head and neck cancers because those resections often involve dissection of the lymph nodes of the neck. Many of the lymph nodes removed in the neck dissection are in close proximity to the accessory nerve that provides innervation to the trapezius muscle. This nerve is commonly weak after neck dissection and can lead to a limitation in motion of the shoulder, decreased muscle strength or shoulder drop. Physical therapy is important in these patients to maintain the range of motion during recovery of the nerve and muscle function. In addition, exercises can strengthen the other rotator cuff muscles to help minimize symptoms and functional deficits.

16.3.8 Pain Management

Pain management is often the top concern for patients with head and neck cancer. In quality of care studies of patients dying of cancer, pain management was the overwhelming priority [25, 26]. Uncontrolled pain can cause depression, difficulty sleeping and difficulty eating. Hospice care without cancer treatment has been shown to increase survival [27].

The pain from head and neck cancer can be due to direct invasion of the cancer into sensory nerves, invasion of bone, ulceration of the mucosa from the cancer, ulceration related to treatment with chemotherapy or radiation therapy or infection causing ulceration or osteomyelitis. The cancer-related pain is often alleviated as the tumor is treated with chemotherapy, radiation therapy or surgical therapy whether it is for palliation or cure. The morbidity of the therapies needs to be weighed against the benefits of each of the treatments. In addition, antibiotics can relieve pain by treating infection.

Pain medications can be used while other treatments are working or if no other treatments are possible. Typically, non-steroidal anti-inflammatory drugs (NSAID) like aspirin, acetaminophen (Tylenol™) and ibuprofen (Advil and Motrin) are used for mild pain. Ketorolac (Toradol) is a particularly strong NSAID that can be given intravenously. Most patients with cancer pain require the stronger narcotic

pain medications. Many oral pain medications combine acetaminophen and a narcotic such as codeine, oxycodone (Percocet) or hydrocodone (Vicodin). The dosages of these medications are limited by their acetaminophen toxicity to the liver. Morphine and oxycodone can be prescribed in their pure forms without acetaminophen. Both carry the risk of respiratory depression with overdosing and have a high potential for addiction. Fentanyl, another narcotic, is available as a transdermal patch that is placed on the skin once every 3 days to give a baseline level of relief. This has the advantage of decreased dosing frequency and a more even level of pain relief. Studies have shown that patients prefer transdermal fentanyl to long-acting oral morphine because of better pain relief, less constipation and enhanced quality of life [28].

Our preference for patients with chronic severe pain is to titrate them to the lowest level of fentanyl patch required to give relief of the baseline pain and use a combination medication like Vicodin or Percocet for breakthrough pain. In some patients, stronger opiates such as morphine or oxycodone are need for the breakthrough pain.

For chronic pain particularly after completion of cancer treatment, antidepressants such as amitriptyline (Elavil), muscle relaxants such as cyclobenzaprine (Flexeril) and anti-seizure medications such as gabapentin (Neurontin) can be helpful in weaning patients off of narcotic pain medications.

16.3.9 NCCN Treatment Guidelines

In an effort to create more streamlined recommendations, the National Comprehensive Cancer Network (NCCN) created guidelines that are evidence-based and consensus-driven [15, 20]. Written by a panel of experts from multiple cancer centers, the NCCN Guidelines outline a step-by-step decision pathway for each type of head and neck cancer and is regularly updated based on the latest literature. These algorithms are by no means definitive, and individual patient circumstances must be considered when deciding on treatment as previously discussed. However, the NCCN Guidelines serve as a starting point from which many tumor boards base their discussion. Conversely, the experience of the tumor boards help to further update the guidelines themselves by posing practical questions in a real-world setting.

16.4 Patient Counseling

After completion of the diagnosis and workup, an in-depth discussion of treatment options should take place between the physician, the patient, and patient family to synthesize the information and decide on a plan that best suits the needs and wishes of the patient. Side effects and possible complications are important for everyone to be aware of and plan for. By setting honest expectations and involving the patient in decision-making, the knowledgeable patient will be much more prepared to complete

treatment and successfully prepare for potential setbacks. This includes a sense of the follow-up after treatment, likelihood of cure, salvage treatment options, and the merits of palliative care.

16.5 Follow-Up Care

Multidisciplinary care typically continues once primary treatment has completed. Follow-up periods are coordinated amongst the surgeon, medical oncologist, and radiation oncologist with a focus on monitoring recovery and detecting recurrence. Although intervals depend on the type of head and neck cancer and vary among institutions, patients are typically seen every 1–3 months in the first year, every 2–4 months in the second year, every 4–6 months in the third through fifth years, and every 12 months thereafter [20]. Specialists in wound care, prosthodontics, physical therapy, and speech pathology are also involved for post-treatment rehabilitation, for functions such as speech and swallowing.

Support for alcohol and tobacco cessation is emphasized in both the pre-treatment and post-treatment setting. The drawbacks of continuing these habits are unmistakable: the effectiveness of radiation therapy is decreased, average survival time is shorter, and the risks of recurrence, additional new cancers, and treatment complications are greatly increased [29, 30].

In addition to clinic visits and physical exams, imaging and laboratory testing has become an integral part of follow-up. Depending on the site, post-treatment imaging is recommended within 6 months of therapy [20] via different types of imaging, with PET-CT a popular and effective modality [16]. Subsequent imaging during follow-up is institution-dependent, but not routinely recommended for asymptomatic patients or negative baseline scans with the possible exception of an annual chest x-ray to rule out lung metastasis. Based on suspicious findings, biopsies may be performed in clinic or in the OR to evaluate for persistent or recurrent disease.

Laboratory testing has also become routine in follow-up, depending on the type of cancer and treatment. Patients with medullary thyroid cancer are typically followed with serum calcitonin and carcinoembryonic antigen levels [15], while nasopharyngeal carcinoma patients may be followed with serum Epstein-Barr Virus (EBV) levels: these blood assays are highly sensitive for detecting recurrent disease. Patients who have received radiation to the neck also typically have thyroid stimulating hormone (TSH) levels drawn routinely to evaluate for thyroid damage and the need for hormone replacement [20].

16.5.1 Expectations of Cure

Advances in head and neck cancer treatment have considerably improved the ability to manage head and neck cancer. Better free flap techniques, evolving endoscopic

and robotic technology, more selective radiation modalities, and novel targeted therapies have provided better therapeutic options. Nonetheless, head and neck cancer remains a deadly disease. For most head and neck cancers (with squamous cell carcinoma comprising the majority of cases), approximately 30% of patients will develop recurrence after therapy [31], with 90% of treatment failures manifesting in the first 2 years of follow-up [32]. Between 2 and 18% of patients develop distant metastases [33], and overall 40–50% of all head and neck cancer patients ultimately die of their disease [34, 35].

Of note there are major exceptions to these summative figures, which combine aggressive malignancies (such as anaplastic thyroid cancer) with less threatening tumors (such as a small skin cancer). For instance, overall survival of papillary thyroid cancer is above 95% [35], while overall survival for early-stage nasopharyngeal and laryngeal cancers range between 80 and 90% [36, 37]. Any conversation about the expectations of cure should be candid, realistic and tailored to the disease type, the stage, and the patient's individual circumstances.

16.6 Salvage Treatment for Recurrence

Addressing recurrent head and neck cancer is of considerable difficulty due to a lower rate of cure: treatment options are limited by prior therapy, and further contribute to depleting a patient's physical reserve and quality of life. Salvage treatments often lead to a higher and more severe incidence of complications, including cosmetic and functional deformities that are more likely to be substantial and socially disfiguring [38]. Based on the substantial toxicity of retreating a resistant cancer, the limited prospects of cure must be balanced with preserving a patient's quality of life. The decisions for managing recurrence are highly individual to each patient, and are difficult judgments for even experienced physicians to make. A plan for cure may be worthwhile to one patient but not another.

16.6.1 Surgery

Generally, surgery is considered the first-line salvage treatment for recurrences that are resectable [39]. Nonetheless, fibrosis and scarring from previous treatment make surgery difficult and saddled with a potentially high complication rate. A recent meta-analysis of 1,080 salvage surgery cases found that survival correlated best with the recurrent stage, while quality of life correlated best with recurrent stage and site of recurrence [31]. From this work, profiles that detail the efficacy of salvage surgery based on the stage of disease are listed in Fig. 16.2 [31]. Though factors such as co-morbidities, site of recurrence, and performance status are also important, these profiles can provide a rough sense of the quality of life, survival benefit, and rate of complications from salvage surgery.

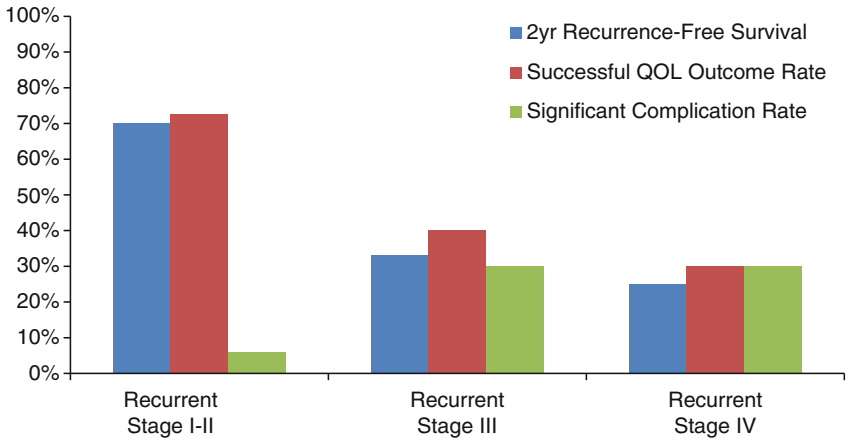

Fig. 16.2 Salvage surgery outcome profiles by stage (Adapted from Goodwin et al. [31]) *QOL* quality of life

16.6.2 Re-irradiation

With the exception of recurrent nasopharyngeal cancer, re-irradiation traditionally has been avoided due to significant toxicity to the patient. Standard initial radiation ranges between 60 and 70 Gy, and some data suggests that the head and neck may safely tolerate a cumulative biologically equivalent dose of 130 Gy, depending on the interval between therapy [40]. Nonetheless, this may not realistically be possible due to complications such as osteoradionecrosis, fistula formation, and esophageal stricture. Radiation is also limited by the cumulative dose to adjacent critical structures such as the eye, carotid artery, and brain; for instance, a cumulative exposure of no more than 50 Gy is recommended for the spinal cord [41]. With the advent of intensity-modulated radiation therapy (IMRT), re-irradiation has found some measure of success in salvage cases by more effectively conforming its delivery and minimizing exposure to noncancerous tissue [42]. In many institutions, a combination of salvage surgery, re-irradiation, and/or chemotherapy has been studied with promising results, but remains investigational.

16.6.3 Chemotherapy and Systemic Agents

A number of different chemotherapeutic agents have been used in the salvage setting, albeit with limited success compared to other modalities. The standard chemotherapeutic agents cisplatin and 5-fluorouracil have been shown to induce partial responses in less than 33% of salvage patients, with a median survival of 4–6 months and an adverse toxicity profile [31, 43]. Less toxic chemotherapies such as taxanes

and targeted therapies such have gained prominence in treatment, and are generally better tolerated among patients with poor performance status. For instance, cetuximab has recently been shown to be effective when used with standard chemotherapy for recurrent or metastatic head and neck cancer [44], and has been approved by the FDA. In addition, less toxic chemotherapy drugs have been given alone in a palliative setting [38, 45].

16.6.4 Palliative Care and Hospice

The morbidity of cancer, as well as the side effects and complications of treating it, can cause substantial functional, physical, and emotional difficulties that likely matter a great deal to the patient, perhaps as much as cure itself. Palliative care is a branch of medicine designed to improve the quality of life of patients and families, and enable them to live with dignity and respect. It is estimated that approximately 20% of head and neck cancer patients, usually advanced cases, would qualify for palliative care at the time of initial diagnosis [46].

Contrary to popular opinion, palliative care is not intended to hasten death, is not necessarily implemented at the end of care or end of life, and does not disqualify patients from life-prolonging therapies. In fact, it can be implemented early in the course of illness along with potentially curative treatment, or even after treatment is completed [47]. A team of physicians, nurses, and specialists focus on alleviating symptoms (commonly pain), as well as provide support and counseling that involve the patient's caregivers. Palliative care differs subtly from hospice care, which concentrates on providing care for patients who have decided to halt further curative treatments and are expected to live on the order of weeks to months. Hospice foregoes care that may be invasive, painful, or have detrimental side effects in order to prioritize the patient's comfort and well-being. For instance, care is usually managed with a visiting nurse at home, where the patient is most comfortable. Both palliative care and hospice manage medications, counseling support, and daily care of symptoms and needs [34].

In head and neck cancer patients, palliative care may play roles in addressing pain, via maintaining an airway, providing emotional support, and managing aspiration and swallowing difficulties that could lead to poor nutrition. Such support teams are therefore crucial in treatment planning, since distressing symptoms could jeopardize completion of radiation treatment, or delay wound healing after surgery [48]. Palliative care often helps guide patients to articulate their wishes and dictate their care through advance directives, durable power of attorney, and DNR/DNI (do not resuscitate/do not intubate) status. This clarifies their desires to the medical team and to their family. Accordingly, a University of Michigan study of 58 families of patients who died of head and neck cancer found that death outside the hospital setting, as well as palliative care team involvement greatly improved the end-of-life experience [49].

In summary, many factors help to determine the type and extent of treatment for patients with head and neck cancer. A multidisciplinary team approach is best suited to provide optimal care.

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Chapter 17
Medical Oncology: Planning Considerations and Practices

Lawrence E. Feldman

Contents

Abstract This is a chapter covers the factors that the head and neck medical oncologist takes into account when first seeing a patient with head and neck cancer and deciding on a course of treatment. Treatment options need to be individualized and one must often weigh the expected outcome and companion risks with each treatment strategy. This effort is best accomplished by a multidisciplinary team that composed of a head and neck surgeon, medical oncologist, and a radiation oncologist. A staging work-up is performed that includes panendoscopy with biopsy, CT scan or MRI of the neck, and PET scan. The decision to perform primary surgery vs. chemoradiotherapy

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depends of factors such as: primary site, stage, ease and accessibility of resection, and acceptable functional and cosmetic results. The decision to perform post-op adjuvant radiation +/− chemotherapy depends on risk of recurrence based on the presence or absence of high risk pathological features such as positive margins or lymph node involvement and extracapsular extension (ECE) of disease. For locally advanced disease (stages III and IV) definitive chemoradiation therapy, not primary surgery is often employed. Additionally, the strategy of induction chemotherapy followed by definitive radiation +/− concurrent chemotherapy may be chosen. For recurrent disease, treatment options include salvage surgery, reirradiation +/− chemotherapy, palliative chemotherapy, or supportive care alone. Finally, targeted therapy with cetuximab is effective or one may consider participation in a clinical trial.

Keywords Medical oncology • Adjuvant treatments • Treatment planning • Induction chemotherapy • Chemoradiation

17.1 Overview of the Approach to the Patient with Head and Neck Squamous Cell Carcinoma

Most patients with squamous cell carcinoma of the head and neck (SCCHN) are approached with curative intent [1]. This view stems from that fact that the plurality of patients (~60%) with SCCHN present with locally advanced disease (stages III, IVa, and IVb) and another 30% present with early stage (stage I and II) disease. Only about 10% present with metastatic (stage IVc) disease and regarded as incurable.

17.1.1 Recognition of Common Presenting Symptoms

Patients that are diagnosed with head and neck cancer often present to the doctor with symptoms that may on first blush seem relatively harmless. Typically these symptoms include one or more of the indicators listed in Table 17.1. [2]

Once a head and neck cancer is suspected the patient typically undergoes a biopsy of the mass and panendoscopy (i.e., laryngoscopy, bronchoscopy, and esophagoscopy). Panendoscopy includes regions of the aerodigestive tract at risk for carcinogenesis, including the oral cavity, pharynx, larynx, esophagus, and bronchus.

17.1.2 Anatomical Sites Within the Head and Neck

At this point the primary site of the tumor is often revealed and deemed to be in one of the five following head and neck regions: oral cavity, oropharynx, larynx, hypopharynx,

Table 17.1 Some presenting symptoms of head and neck cancer

Enlarged lymph node on the outside of the neck
A sore throat/neck
Hoarse voice
A lump or a sore in the mouth, throat, or neck that does not heal or go away
Difficult or painful swallowing
Weight loss
Speaking may become difficult
Difficulty opening the mouth (trismus)
Bleeding from the mouth or throat
Persistent earache
Sinus congestion, especially with nasopharyngeal carcinoma
Numbness or paralysis of the face muscles

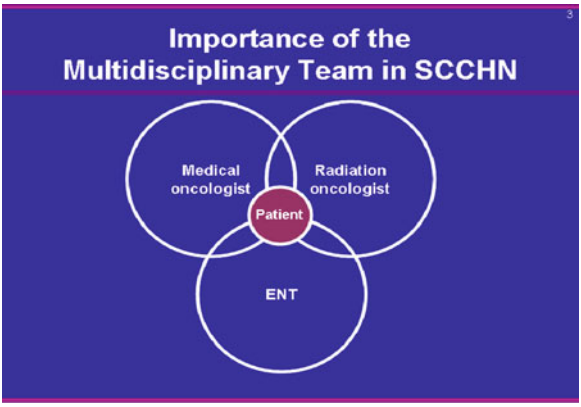

Fig. 17.1 The multidisciplinary team

and nasopharynx. (Other sites such as the lip, salivary glands, and nasal cavity/paranasal sinuses (ethmoid and maxillary) are beyond the scope of this review).

17.1.3 Importance of the Multidisciplinary Team

Once the primary site of the tumor is identified and a histopathological diagnosis of squamous cell carcinoma is made the case is presented at a multidisciplinary head and neck conference and/or clinic with experts in treating head and neck cancer [3]. Ideally this multidisciplinary team should include a head and neck surgeon, radiation oncologist and medical oncologist (see Fig. 17.1). Preferably this team should also include the following specialists: dentist and prosthodontist, audiologist, social worker, nurse, plastic and reconstructive surgeon, speech and swallowing therapist.

A staging work-up is then carried out to establish the extent of the primary tumor and any areas of metastases. Tests that are performed include: CT scan (with and without contrast) of the tumor and neck and/or MRI and whole body PET/CT scan. Tumor staging depends on what adjacent structures are invaded in the case of cancer of the larynx and nasopharynx. Similarly cancers of the oral cavity, oropharynx, and hypopharynx are based on tumor size for T1 and T2 tumors and adjacent structure invasion for T3 and T4 tumors [4].

17.1.4 Role of Upfront Definitive Surgery vs Non-surgical Modalities (i.e., Radiation Therapy and Chemotherapy)

For early stage tumors (stages I and II) single modality therapy [i.e, surgery or radiation therapy (RT)] is recommended. Primary surgery is usually the preferred modality in the case of oral cavity cancers due to ease and accessibility of resection, acceptable cosmetic results, relative tumor radioresistance, and avoidance radiation toxicity. For locally advanced disease (stages III and IV) the decision whether or not to perform upfront surgery is more challenging.

There are 3 main reasons to avoid upfront surgery [5]. The first reason is that the tumor is deemed to be unresectable. This clinical determination is based on features such as: tumor fixation, extension into the nasopharynx, and pathological lymph nodes fixation to surrounding structures. The second reason for avoiding surgery is if the cancer is felt to have a low probability of surgical curability based on such factors as advanced tumor stage (III or IV) or gross involvement of regional lymph nodes in N2 or N3 disease (except T1N2). Finally, a patient who is a candidate may wish to attempt organ preservation with chemoradiotherapy and reserve the option of surgery in case of persistent or relapsed disease.

17.2 Site Specific Approaches

The approach to the treatment of SCCHNC depends on the primary subsite of disease. Therefore this Section will be divided into five separate sub-sections representing the five major disease sites in the head and neck.

17.2.1 Approach to Oral Cavity Cancer (OCC)

The oral cavity is compromised of several sub-sites including: anterior tongue, buccal mucosa, floor of mouth, (FOM), alveolar ridge, hard palate, and retromolar trigone (RMT). The staging of oral cavity (squamous cell) carcinomas (OCC) is based on tumor size and the pathologic details regarding invasion of nearby structures.

The treatment approach to oral cavity squamous cell carcinomas is rather unique as compared to the other major head and neck sites in that the primary modality of

Table 17.2 Reasons given for initial surgical intervention for oral cavity cancer

Relative surgical accessibility compared to other head and neck sites
Ability to obtain pathological staging information
Ability to preserve function (eg., speech, swallowing, and respiration)
Concerns regarding the toxicity (eg., mandibular osteoradionerosis) of intensive chemoradiotherapy (CRT), esp. tumors that are bulky and involve bone
Concerns regarding the relative efficacy of CRT due to possible tumor radioresistance

Table 17.3 Adverse risk features in SCCHN

Extracapsular (lymph node) extension (ECE)[a]
Close (<5 mm) or positive margins[a]
Oral cavity primary
pT3 or pT4
N2 or N3 nodal disease
Nodal disease at cervical lymphatic levels IV or V
Perineural invasion (PNI)
Vascular embolism

[a]Improved survival with post-op chemoradiation compared to post-op radiation alone

treatment, even for locally advanced disease (stages III and IV) is surgery. The reasons why initial surgical intervention for oral cavity cancer is recommended are several fold and listed in Table 17.2.

Excision of the primary oral cavity tumor is then often followed, either at the time of primary resection or at a subsequent surgery, by an ipsilateral lymph node dissection. Additionally, a bilateral lymph node dissection is performed in patients that initially present with bilateral lymphadenopathy (N2c). Following the cancer surgery by the head and neck surgeon it may be necessary to involve a plastic and reconstructive surgeon to insert a tissue graft in the resection bed and secure it with sutures. For example, after a partial glossectomy for a tongue cancer it may be necessary to graft tissue to the tongue to ensure optimal post-operative tongue mobility.

17.2.1.1 Role of Post-Op Adjuvant Treatment

Post-operatively, the pathologist assesses the specimen and determines the pathological stage using the American Joint Commission on Cancer (AJCC) staging classification. Additionally, the specimen is assessed for any adverse prognostic features such as those listed in Table 17.3.

The highest (major) risk features are extracapsular (lymph node) extension (ECE) and close (<5 mm) or positive margins. The presence of other (minor) risk features places a patient at intermediate risk of recurrence. Patients without any adverse risk factors seem to do well without post-op RT. Intermediate risk patients seem to do well with post-op RT alone (i.e., without concurrent chemotherapy). High Risk patients benefit from treatment intensification with concurrent chemoradiotherapy.

In 2004, level 1 evidence was published confirming the role of the addition of concurrent chemotherapy to post-op radiation therapy for patients after surgery that were deemed to be at high risk of recurrence [6–8]. This evidence was provided by two studies, EORTC 22931 and RTOG 9501, that had similar design and included patients with tumors of the oral cavity, oropharynx, larynx, and hypopharynx. Both trials compared post-op chemoradiotherapy to post-op radiation therapy alone for high risk patients. Moreover, a combined analysis of the two trials was performed that revealed a significant survival advantage in the chemoradiotherapy group for patients who had positive margins (<5 mm) and/or extracapsular nodal extension (ECE).

17.2.2 Treatment of Oropharyngeal Cancer

The oropharynx (OP) includes the following structures: base of tongue (BOT), soft palate, palatine tonsils, and the posterior pharyngeal wall. Like staging of OCC, that of cancer of the OP depends on tumor size and what nearby structures if any are invaded [4]. Primary treatment modality for OP cancer that is locally advanced is concurrent chemoradiotherapy with cisplatin being the preferred agent [9, 10]. Alternatively, induction chemotherapy (see Sect. 17.3) followed by concurrent chemoradiotherapy may also be employed for locally advanced disease. Finally, surgical resection of the primary tumor (if feasible) with lymph dissection remains a therapeutic option.

Variables that predict a poor prognosis for OP cancers include: advanced stage, large gross tumor volume, not human papilloma virus (HPV) driven, poor performance status (PF), and the presence of multiple co-morbid conditions [11, 12].

An increasing number (60–80%) of oropharyngeal squamous cell HNC's, particularly those involving the BOT and tonsils, are now thought to be associated with HPV infection [13]. Patients with HPV driven tumors, as compared to those with tobacco-exposure related tumors, are more likely to occur in middle-aged caucasian men, have non-keratinizing histologies, and have small primary tumors with more extensive lymph node involvement. The prognosis of HPV associated OP cancer appears to be more favorable than its tobacco associated counterpart. Due to its favorable prognosis whether less intensive therapy can be employed for these patients remains a clinical research question at this time.

17.2.3 Treatment of Larynx Cancer (LC)

The larynx may be split into three regions: supraglottic, glottic, and subglottic [14]. The majority of LC's occur in the supraglottis and glottis. Primary subglottic tumors occur much less commonly. Staging of LC is not based on tumor size but rather on what adjacent structures are invaded [15]. For example, when fixation of the vocal cords is seen (due to tumor invasion of the arytenoid cartilage) the tumor is staged

as T3. Stage T4a disease is seen with invasion of the thyroid cartilage or the deep extrinsic muscles of the base of the tongue.

Historically, surgery (laryngectomy) and post-op RT was the standard treatment for laryngeal cancer. This approach resulted in a 5 year survival rate of from 0 to 50%. For stage III and IV disease the VA Laryngeal Cancer Study Group Trial (VALCSGT) demonstrated that sequential chemotherapy followed by definitive radiation therapy was an effective alternative to laryngectomy [16]. Moreover, about 60% of patients randomized to the non-surgical approach were able to preserve the larynx. Patients are now routinely offered a non-surgical approach because avoidance of laryngectomy can allow for maintenance of natural voice and swallowing and eliminate the need for a permanent tracheostomy in the neck.

Concurrent chemoradiation became a standard of care for patients with laryngeal cancer based on the RTOG 91-11 trial that was a three arm trial comparing sequential chemotherapy followed by radiation therapy (adopted from the VALCSGT), concurrent cisplatin chemotherapy and radiation therapy, and radiation therapy alone. This study demonstrated that concurrent chemoradiation resulted in the best overall laryngeal preservation rate and increased locoregional control rate in these patients with stage III or IV disease.

17.2.4 Treatment of Hypopharyngeal Cancer

Hypopharyngeal tumors most commonly occur in the pyriform sinus, posterior pharyngeal wall, and the postcricoid region [17]. These tumors often present at an advanced stage at diagnosis and this fact may lead to its relatively poor prognosis compared to other disease sites in the head and neck. Absolute contraindications to surgical resection (i.e., T4b tumors) include: invasion of the prevertebral fascia or carotid artery.

For most T1 and T2 tumors (tumors confined to the hypopharynx and size <4 cm) that do not require a laryngectomy patients may be offered definitive radiation. Alternatively, surgical resection (laryngopharyngectomy and lymph node dissection) may be recommended.

For hypopharyngeal tumors stage T2 and T3 (that would otherwise require a laryngectomy) or T1 tumors that have macroscopic nodal involvement organ preservation (with either induction CT followed by RT or concurrent CRT) is a practical alternative to surgery and shows equivalent OS rates in clinical trials [18]. According to the National Comprehensive Cancer Network (NCCN) there is uniform consensus (category 2A) that induction chemotherapy in this setting is appropriate (see Sect. 17.3) [9].

Patients that have less than a partial response to chemoradiation may then be offered salvage (pharyngolaryngectomy) surgery if feasible. Finally, patients that have more locally advanced (T4a) disease (invasion of thyroid/cricoid cartilage, hyoid bone, thyroid gland, or soft tissues of the neck) surgery with neck dissection is the preferred approach.

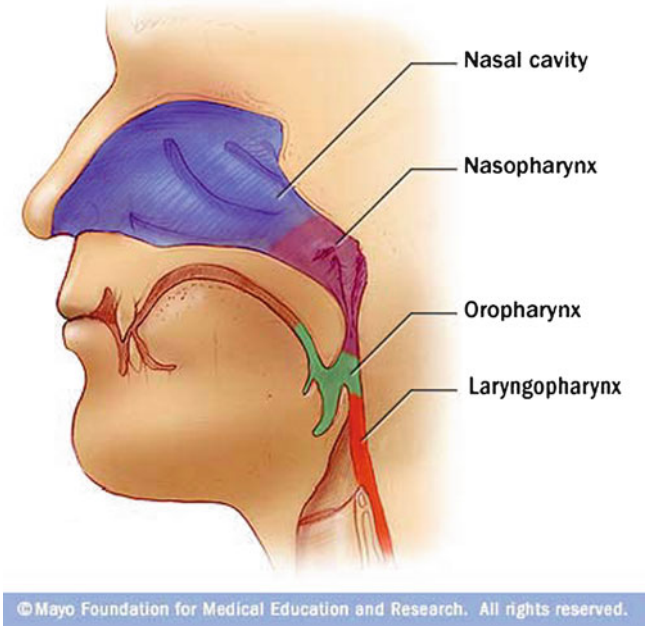

Fig. 17.2 Nasopharyngeal anatomy

17.2.5 Treatment of Nasopharyngeal Cancer

The nasopharynx (NP) incorporates the area behind the nose and above the mouth and throat (see Fig. 17.2). In nasopharyngeal carcinomas (NP) infection with Epstein-Barr virus (EBV) is thought to play an etiological role. Histologically, NP carcinomas have traditionally been classified into three basic cell types: keratinizing squamous cell carcinoma (formerly WHO type 1), differentiated non-keratinizing carcinoma (formerly WHO type 2), and undifferentiated non-keratinizing carcinoma (formerly WHO type 3 or lymphoepithelial carcinoma)[17]. Significant differences among the three histological subtypes have been found in the prognosis in terms of the 5-year overall survival (OS): type I 37%, WHO II was 55%; WHO III was 60%.

The staging of nasopharyngeal tumors is based not upon tumor size but rather upon which structures are locally invaded [19]. Tumors that are T2 reach into the parapharyngeal region, T3 invade the skull base or paranasal sinuses, and T4 tumors extend intracranially and/or involve cranial nerves, hypopharynx, orbit, or infratemporal fossa/masticator space.

The lymph node staging in NP cancer differs from that of all other sites in the head and neck due to differences in frequency, location, and prognostic significance of nodal metastases. For example, stage N1 disease is any unilateral cervical or bilateral retropharyngeal nodes <6 cm above the supraclavicular fossa (SC). N2

nodes are bilateral <6 cm above the SC fossa. N3 nodes are any nodes >6 cm (N3a) or extension to the SC fossa (N3b).

The primary treatment modality for NP carcinoma is radiation therapy as the anatomic location of these tumors makes surgery unfeasible. For stage III and IV disease (M0) the addition of concurrent chemotherapy to radiation therapy has been shown to improve survival by Al-Sarraf [20]. This chemotherapy regimen consists of cisplatin 100 mg/m^2 given every 3 weeks during radiotherapy. Four weeks after radiotherapy patients received cisplatin 80 mg/m^2 + 5-fluorouracil (5-FU) 1,000 mg/m^2/day as a 96 h infusion. Patients received this chemotherapy doublet every 4 weeks for a total of three cycles.

The SWOG/Intergroup study compared RT only to concurrent CT-RT followed by adjuvant CT (Al-Sarraf regimen) in locally advanced NPC [21]. After 5 years of follow-up the progression free survival (PFS) for the RT alone group was 29% compared to 58% for the CT-RT group ($p < .001$). The overall (OS) was 37% for RT compared to 67% for the CT-RT group (p.001). This study established that the combination of CT-RT is superior to RT in pts with locally advanced NPC with respect to PFS and OS.

17.3 Role of Induction Chemotherapy Followed by Radiation

For locally advanced head and neck cancer patients that do not receive primary surgery, primary concurrent chemoradiation remains the standard of care. Another approach that is often employed particularly in patients with T4, N2b, or large volume (LV) disease is induction chemotherapy (IC). With this approach most patients achieve substantial tumor responses. IC has the potential to rapidly alleviate symptoms such as localized pain while awaiting definitive radiation therapy. Also, tumor shrinkage may allow patients and caregivers to become less disheartened by the diagnosis and show increased interest in continuing aggressive management.

In November of 2007, there were two articles published showing an improvement in overall survival (OS) with the addition of docetaxel to cisplatin and 5-FU compared to cisplatin and 5-FU alone (see Table 17.4) [5, 22]. These studies suggest that since TPF is significantly better than PF, and if PF and chemoradiotherapy are equivalent, then TPF may be equal to or better than primary chemoradiotherapy alone.

Paccagnella et al conducted a phase II/III trial prospectively comparing induction chemotherapy (TPF) followed by concurrent chemoradiation (with PF) to the

Table 17.4 Induction chemotherapy trials in locally advanced HNC

	Vermorken trial (n = 358)			Posner trial (n = 501)		
	TPF	PF	p value	TPF	PF	p value
PFS (mo)	11.0	8.2	0.007	36	13	0.004
OS (mo)	18.8	14.5	0.02	71	30	0.006

Table 17.5 A randomized phase II trial: induction TPF vs no induction

Paccagnella Trial (n = 101)	Induction TPF	No Induction	p value
CR rate (%)	50	21	0.004
OS (mo)	39.6	33	0.187
1-year survival	86	78	0.268

identical chemoradiotherapy (with PF) alone (i.e, no induction) [23, 24]. The favorable results of this trial of induction TPF chemotherapy and concurrent chemoradiotherapy (Table 17.5) in the treatment of locally advanced disease lend support to the induction chemotherapy strategy.

17.4 Treatment of Recurrent and Metastatic Disease

Recurrent disease occurs at an equal rate in either a locoregional or distant location. For recurrence in a locoregional location the patient often presents with same symptoms and/or signs as that of the initial presentation. These symptoms and/or signs may include: enlarged cervical lymph node, sore throat, lump or a sore in the throat that does not heal or go away, difficult or painful swallowing, weight loss, difficulty speaking or hoarse voice. Distant recurrence most commonly occurs in the lungs, bones, brain, lymph nodes (outside of the neck), or liver.

For recurrent locoregional disease surgery is the first consideration and may be curative. However the surgical option is often excluded due to the technical unfeasibility and/or poor patient performance status. Reirradiation may be an option for some patients with locally recurrent HNC [25]. Since the toxicities of HNC reirradiation may be severe and/or life-threatening this treatment is best done at centers with substantial experience with this approach. Patients that may be candidates for reirradiation include those with unresectable recurrent disease and in the post-op adjuvant setting after salvage surgery. Reirradiation is given with curative intent in patients with a good performance status and performed as monotherapy or with concurrent systemic therapy.

Chemotherapy for recurrent or metastatic (R/M) HNC for palliation purposes consisted most commonly of single agent methotrexate (MTX) until the late 1980s and early 1990s. Tumor response rates to MTX were reported to be in the 30% (8–50%) range.

In the mid 1980s cisplatin regimens were developed such as the so-called Wayne State regimen that consisted of cisplatin 100 mg/m^2 on day 1 and 5FU 1,000 mg/m^2 on days 1–5 (CF). The initial report of this regimen yielded an overall response rate (RR) of 70% and a complete response rate (CR) of 27% [26]. Subsequent trials reported average RR's with this regimen of about 50% and CR rate of about 16%.

Based on the promising results of this regimen, the Southwest Oncology Group (SWOG) conducted a three arm trial with patients with recurrent or metastatic head

and neck cancer comparing CF vs carboplatin + 5FU (CbF) vs MTX [27]. The overall response (OR) rate was best with CF (32%) followed by CbF (21%) and then MTX (10%). There was no statistical difference in median survival time (MST) at 6.6, 5.0, and 5.6 months for CF, CbF, and MTX, respectively. By this time CF became arguably the most widely used regimen for R/M HNC.

In 2006 cetuximab a biological agent (monoclonal antibody) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of HNC [28]. This agent is the first anti-cancer agent to be FDA approved for HNC since MTX about 30 years earlier. There are now a total of three indications for its use in squamous cell HNC (SCCHN) that are listed below along with studies that provided foundation for these approvals.

1. In combination with radiation therapy (RT) for the treatment of locally or regionally advanced SCCHN [29].
2. As a single agent for the treatment of patients with recurrent or metastatic SCCHN for whom prior platinum-based therapy has failed [30].
3. In combination with platinum-based therapy plus 5-florouracil (5-FU) for the first-line treatment of patients with recurrent locoregional disease and/or metastatic SCCHN [31].

17.5 Summary

The anatomy, staging, and treatment of SCCHN (according to the specific sub-site of the disease) within the head and neck area is complex. The goals of treatment are to personalize care, alleviate symptoms, minimize treatment related toxicity, and extend survival. These goals are best accomplished with a multidisciplinary team approach that includes a head and neck surgeon, radiation oncologist and medical oncologist. Historically surgery +/− radiation therapy when feasible has been in general the standard of care. However, when a functional organ can be preserved organ preservation strategies with sequential or concurrent chemotherapy and radiation may be a viable alternative and does not appear to reduce long term survival.

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Chapter 18
Role of Surgery in Treatment of Head and Neck Cancer

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Contents

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Abstract This chapter discusses the role of the surgeon in the diagnosis, evaluation, and treatment decision making for head and neck cancer patients. The key decision point in the treatment planning is often whether to proceed with nonsurgical therapy (i.e., chemotherapy and radiotherapy, often in combination), or surgery. When two treatment options have equivalent oncologic outcomes, the decision comes down to several factors. These include tumor characteristics, patient factors, and physician/treatment center preferences. With all these considerations in mind, recommendations for treatment come after discussions at multidisciplinary tumor conferences.

Head and neck cancer may develop in the neck, oral cavity, oropharynx, nasopharynx, sinonasal cavity, larynx, hypopharynx, and salivary glands. Evaluation of patients with cancer in each of these sites is discussed. The treatment of cervical lymph node groups depends on the site and stage of the primary site of head and neck cancer; the rationale for treating the lymph nodes is explained. The benefits and disadvantages of surgical and non-surgical therapies are discussed for each of the head and neck cancer sites. When surgery is chosen, treatment may leave a patient with a defect that can dramatically alter his or her appearance or ability to swallow or communicate. Surgeons play a critical role in minimizing these effects with reconstructive efforts.

Keywords Surgical oncology • Neck • Oral cavity • Oropharynx • Nasopharynx • Sinonasal cavity • Larynx • Hypopharynx • Salivary glands

18.1 Introduction

The surgeon plays an important role in the diagnosis, treatment, rehabilitation, and long-term surveillance of patients with head and neck cancers. Treatment strategies have evolved significantly since the specialty of Head and Neck Surgery emerged in the mid-twentieth century [1]. At that time, surgical treatment was viewed as the standard of care for head and neck cancers. Throughout the rest of the twentieth century, the emergence of effective nonsurgical interventions, especially radiotherapy and chemotherapy, has allowed these modalities to gain popularity [2, 3]. In fact, for some anatomic subsites of head and neck cancer, nonsurgical modalities are now more commonly used than surgery [4]. Interestingly, these shifts have occurred without any randomized controlled trials demonstrating better outcomes with surgical or nonsurgical treatments. Not surprisingly, a great deal of controversy exists in the field of Head and Neck Cancer [5, 6].

18.2 The Role of the Surgeon in the Care of Head and Neck Cancer Patients

18.2.1 Initial Assessment

For the most part, patients with head and neck cancers are referred from their primary care providers or dentists to physicians practicing Otolaryngology-Head and Neck Surgery, or other specialties such as Oral Surgery. The initial office visit begins with a thorough history of current symptoms, medical problems, and use of tobacco, alcohol or other risk factors. A detailed head and neck physical examination is then performed. If indicated, brief endoscopy can be performed in the clinic to examine mucosal surfaces of the nasal cavity, nasopharynx, oropharynx, hypopharynx, and larynx (Fig. 18.1).

Close examination of the lesion in question is performed. Characteristics of the cancer are documented carefully, including size, anatomic structures involved, and effects of the tumor on function of involved structures. Biopsy of the cancer can often be accomplished in the office if it is accessible. If a tumor or enlarged lymph node is palpable in the neck or salivary glands, a biopsy can be performed via fine needle aspiration (FNA), which is highly sensitive and specific for many head and neck cancers [7].

Assessment for most patients includes radiologic imaging. The most common imaging modalities are ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), although other types of imaging may be necessary depending on the location and pathology of the tumor in question [8, 9]. Imaging gives the clinician important information regarding the size and location of the primary tumor, extent of its invasion, presence of regional metastases (typically to lymph nodes of the neck), and the presence of distant metastases (for example, to the lung, liver, or bones).

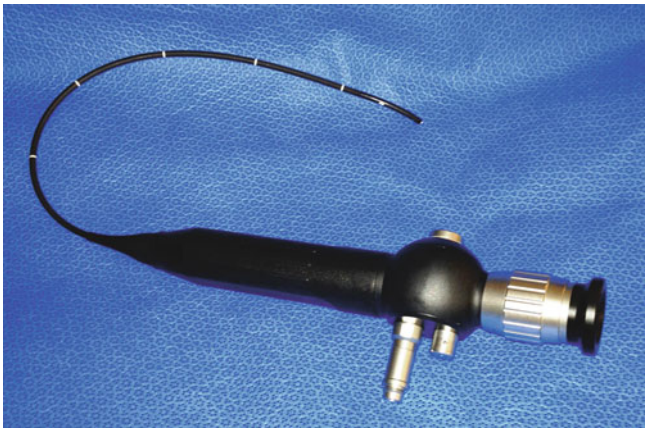

Fig. 18.1 A flexible fiberoptic laryngoscope is used by otolaryngologists to examine the upper aerodigestive tract. The flexible narrow end is inserted through a patient's nose, and is passed behind the soft palate to view the tongue base, pharyngeal walls, larynx, and hypopharynx

Staging endoscopy is often performed prior to initiation of treatment. This is accomplished in the operating room under anesthesia, and involves a close inspection of the tumor and all mucosal surfaces of the upper aerodigestive tract, esophagus, and tracheobronchial tree. If biopsies of the tumor had not been possible in the office, they can be performed during this examination. Since the majority of patients with head and neck cancer are abusers of tobacco and/or alcohol [10], there is a significant percentage with concurrent "second primary" tumors in addition to the known primary tumor, which can be detected with this thorough examination [11].

18.2.2 Staging of Head and Neck Cancer

Once the results of the biopsies are known, appropriate imaging studies have been performed, and thorough evaluation of the cancer has been performed, the Head and Neck Surgeon is then able to classify the cancer into a stage. This is typically done using the American Joint Committee on Cancer (AJCC) staging system [12]. Cancers are given a "TNM" stage, where "T" indicates the extent of the primary tumor (T1, T2, T3, or T4), "N" indicates the extent of regional lymph node spread (N0, N1, N2, N3), and "M" indicates the presence of distant metastases (M0 or M1). The TNM categories are combined for each patient, for example T2N1M0 or T4N3M1. There are 32 possible combinations of these stages (4 T categories, 4 N categories, and 2 M categories), which are then grouped into overall clinical staging (Stage I, II, III or IV). See Table 18.1 for details of this clinical staging protocol.

The purposes of clinical staging are to provide a standard description of tumors in communication between clinicians and to institutional and national cancer registries, to aid physicians in treatment planning, and to provide an indication of prognosis. It is also important to have a standardized classification

Table 18.1 Stage grouping of head and neck cancers (except salivary gland and thyroid cancers)

Stage I	T1N0M0
Stage II	T2N0M0
Stage III	T3N0M0
	T1 or T2 or T3N1M0
Stage IV	T4 Nany M0
	T any N2 or N3 M0
	T any N any M1

From [12]

to allow evaluation and comparison of the effectiveness of different treatment modalities for similar tumors [13].

18.2.3 Treatment Decision Making

When evaluation of the cancer has been completed and the tumor has been staged, treatment decisions are then made. In general, treatment for stage I or II tumors (often referred to as "early stage") can be effectively accomplished with a single modality, i.e. either surgery or radiotherapy. With a few exceptions, treatment for "advanced stage" tumors (Stage III or IV) is typically multidisciplinary, utilizing a combination of surgery, radiotherapy, and chemotherapy.

Decisions about which course of treatment to pursue are often difficult. In most cases, there are at least two treatment strategies with equivalent efficacy but very different risks and side effect profiles. The Head and Neck Surgeon counsels patients about the available treatment strategies [14].

If surgery is considered the standard of care (for example, in salivary gland [15] or oral cavity [16] cancers), recommendations for surgery are given with a clear communication of the risks and sequelae of surgery, and a discussion of the effectiveness and risks of alternative nonsurgical therapies. Thus a patient can proceed with surgery fully informed of the rationale for this decision.

On the other hand, there are many cases when surgical and nonsurgical therapies have equivalent effectiveness (for example, in some oropharyngeal and laryngeal cancers) [17]. In these cases, the surgeon provides a description of the surgery, along with its risks and benefits. This should be accompanied by a discussion of the nonsurgical options. Patients are offered a consultation with radiation oncologists or medical oncologists, during which further discussion can be held. At this point, if there are no convincing arguments in favor of one course or the other, patients are then required to make a decision.

In most cases, there are a number of factors that lead a treatment team to recommend either surgical or nonsurgical therapy. Characteristics of the cancer are important. These include the histopathology, the location of the tumor and anatomic structures

involved, the extent of invasion, and the presence and extent of regional nodal metastases. The experience, training, and preferences of the treating physicians play an important role. The experience of the hospital and clinical support staff and the technology available at the treatment facility are important considerations. Patient factors are crucial in these decisions as well. For example, surgery may entail too much risk due to the presence of comorbidities. Patients with head and neck cancer often have pulmonary or cardiovascular disease, malnutrition, and functional debilitation, all of which may affect their ability to tolerate aggressive therapy. The absence of family or social support may make the ability to commit to travel back and forth for several weeks of radiation treatments impossible for a patient. Finally, the patient may have strong opinions about his or her ability to tolerate the sequelae and risks of surgical or nonsurgical treatments.

On occasion, tumors may be inoperable, due either to extent of invasion or to patient comorbidities. Patients may be unwilling or unable to accept the sequelae of some surgeries. In these cases, radiotherapy or chemoradiotherapy can be discussed as potential curative treatment strategies, and appropriate referrals can be made. In some cases, such as recurrent inoperable tumors, or in patients with severe comorbidities, the surgeon and patient may agree that palliative therapy is the best course [18, 19]. The surgeon can assist these patient with symptoms related to disease progression, for example by performing tracheotomy to relieve shortness of breath caused by airway obstruction by an enlarging tumor.

It can often be helpful to present the newly-diagnosed head and neck cancer patient to a multidisciplinary Head and Neck Tumor Conference (or "Tumor Board"), which meet regularly at most cancer treatment centers [20]. At the author's institution, the Tumor Board consists of surgeons, radiation oncologists, medical oncologists, radiologists, and pathologists, with representatives from dentistry, speech and language pathology, and nutrition. Discussions are held weekly, allowing thorough discussion of these patients, and introducing them to the various providers from these disciplines that will be involved in their care. Research coordinators are also present, and help indicate which clinical trials these patients may qualify for and assist in their enrollment into such studies.

18.2.4 Treatment

In many head and neck cancers, surgery is often considered the standard of care. The strategy for surgery is to remove the primary tumor completely, along with removal of any involved lymph nodes or lymph node groups that are at risk for harboring metastatic cancer [21]. Complete extirpation of these tumors involves not just removal of the cancer, but also removal of a cuff, or margin, of normal tissue surrounding the disease. This margin may be 1–2 cm of healthy mucosa, musculature, facial skin or soft tissues, and/or bone, depending on the location and size of the tumor.

Pathologic information obtained from surgery can be vital in determining the prognosis of the disease and need for adjuvant treatment such as radiotherapy or chemoradiotherapy [22]. Important high-risk features that may be seen on pathology

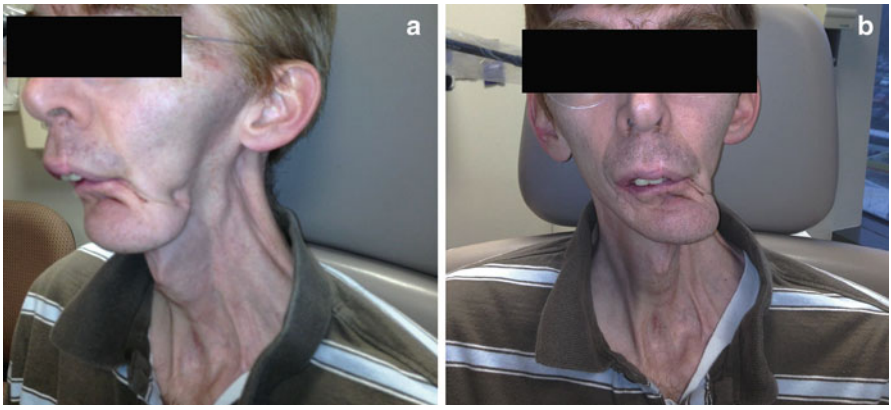

Fig. 18.2 This patient underwent radical resection of an aggressive oromandibular tumor many years ago, prior to the advent of microvascular tissue transfer, and was not reconstructed. The patient has been cured of his cancer but suffers from deficits in speech, swallowing, and cosmesis

include positive or close margins surrounding the disease; invasion of nerves, blood vessels, or lymphatic channels; involvement of multiple or bulky lymph nodes in the neck; and extension of the cancer outside the capsule of an involved lymph node [23].

Reconstruction plays an important role in surgery for head and neck cancer. Depending on the surgical defect created, patients may suffer severe consequences to their appearance, their communication, and their ability to manipulate food and swallow (Fig. 18.2). Utilizing a variety of techniques, attempts are made to replace "like for like." For example, if a tongue defect is created, thin pliable forearm tissue is often utilized. Reconstruction of a defect involving the full thickness of the mandible and a portion of the cheek skin may be best served by transferring bone and skin from the fibula and lower leg. This type of reconstruction is termed "free tissue transfer," and is quite complex, requiring special equipment and training [24]. Reconstruction is most often performed during the same anesthetic as the resection. Full discussion of reconstructive techniques is given in Chap. 23.

18.2.5 Post-treatment Surveillance

Following treatment of patients for head and neck cancer, with either surgical or nonsurgical therapy, the surgeon often participates in post-treatment surveillance of these patients [25]. This involves periodic monitoring with office examination, imaging studies, and endoscopy with biopsies as needed. If cancers do indeed recur, they can hopefully be detected at an early treatable stage. In cases where prior radiotherapy has been given, it is unusual that a second course of radiation can be offered. Therefore, in that scenario, surgery is usually the only curative treatment option, referred to as "salvage surgery." Another important reason to follow these patients long-term is the

early detection of second primary tumors, which occur in 10–15% of head and neck cancer patients with risk factors such as tobacco abuse [26, 27].

18.3 Cancer of the Neck

18.3.1 Introduction

Malignant tumors of the neck include a group of primary cancers of structures within the neck (e.g., lymphomas, sarcomas) as well as metastases of cancer to cervical lymph nodes. Any discussion of cancer of the head and neck must include the importance of the cervical lymphatic system in the spread of cancer from primary sites in the upper aerodigestive tract and salivary glands. The rich lymphatic drainage of the head and neck may contribute to the frequency of regional metastases [28]. In fact, in squamous cell cancer of the upper aerodigestive tract, up to 50% of patients with newly diagnosed tumors have cervical node metastases [29]. The presence of cervical metastases is a strong prognostic indicator, with positive nodes portending a 50% decrease in survival rates compared to similarly staged primary tumors without positive lymph nodes [30].

18.3.2 Anatomy

The AJCC has adopted the grouping of lymph nodes in the neck into anatomic zones (see Table 18.2). This allows a standardized description for the purposes of clinical description, reporting to cancer registries, and evaluation of treatment efficacy. Each zone of the neck has defined anatomic boundaries (Fig. 18.3). In addition, early studies of comprehensive neck dissection specimens revealed that primary tumors in different locations had predictable drainage patterns to particular lymph node groups [31, 32]. This becomes important in tailoring therapy (surgery and/or radiotherapy) to nodal groups at high risk of metastases from each primary tumor site.

Another group, the retropharyngeal nodes, is not included in these groups, but is well known to receive metastases from the oropharynx and nasopharynx.

18.3.3 Primary Tumors of the Neck

18.3.3.1 Lymphoma

Lymphoma, a malignancy of lymphocytes, arise in lymphoid tissue throughout the body, including lymph nodes, the spleen, tonsils, and bone marrow. A patient with lymphoma often presents with an enlarged lymph node, not infrequently in the neck. Other head and neck structures may be involved, including the palatine or lingual tonsils, the orbit, or the thyroid gland [33].

Table 18.2 AJCC cervical lymph node groups, anatomic boundaries, and location of tumors that frequently metastasize to each level [12]

Level	Location	Anatomic borders	Common primary tumor sites to metastasize to this level
I	Submandibular	Mandible, anterior and posterior digastric bellies	Oral cavity, lower lip, nasal cavity, maxilla
	Submental	Anterior bellies of digastric muscles and hyoid bone	
II	Superior jugular chain	Skull base, the carotid bifurcation, and the anterior and posterior borders of the sternocleido-mastoid muscle	Oral cavity, oropharynx, nasal cavity, nasopharynx, larynx, hypopharynx, and parotid gland
III	Mid-jugular chain	Carotid bifurcation, the omohyoid muscle, and the anterior and posterior borders of the sternocleidomastoid muscle	Oral cavity, oropharynx, nasopharynx, larynx, and hypopharynx
IV	Lower jugular chain	Omohyoid muscle, clavicle, and the anterior and posterior borders of the sternocleido-mastoid muscle	Larynx, hypopharynx, cervical esophagus
V	Posterior triangle of the neck	Sternocleidomastoid muscle posterior border, trapezius muscle, and the clavicle	Nasopharynx and oropharynx
VI	Central compartment	Hyoid bone to the sternal notch, and between the two carotid arteries	Tumors of the thyroid gland, larynx, hypopharynx, and cervical esophagus

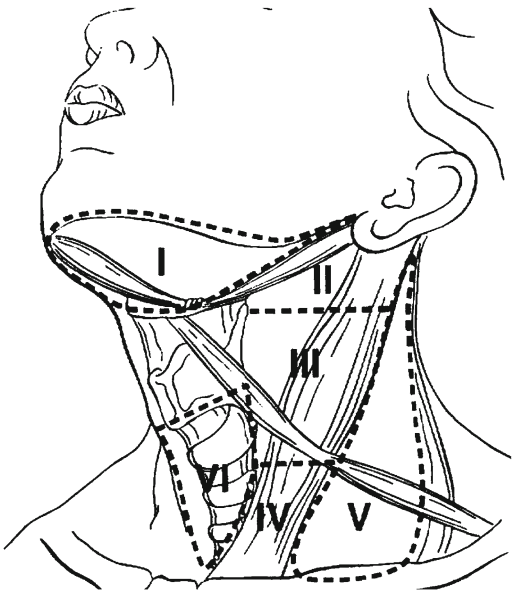

Fig. 18.3 Cervical lymph node groups (From AJCC cancer staging manual, 7th edition [12])

There are multiple subtypes of lymphoma, generally divided into two subgroups: Hodgkin's lymphoma and non-Hodgkin's lymphoma. Classification is accomplished by histopathologic features and molecular and genetic profiles. Lymphomas derive from the various subtypes of lymphocytes, including B-cells, T-cells, and natural killer (NK) cells [34]. After a detailed evaluation, lymphomas are staged based on the number and location of involved body sites, and the presence of constitutional symptoms, such as fevers, sweats, and weight loss.

The treatment for lymphoma is nearly always nonsurgical, for the most part utilizing combination chemotherapy and for some patients, radiotherapy. Head and neck surgeons often perform biopsies of the enlarged lymph nodes to make the diagnosis of lymphoma [35].

18.3.3.2 Thyroid Cancer

Thyroid nodules are common in the general population, present in up to 6% of women and 1.5% of men. Ten to 15% of these nodules are malignant, while the rest represent follicular adenomas, colloid adenomas, or cysts [36]. Malignancies are classified pathologically as papillary carcinoma, follicular carcinoma, medullary carcinoma, and anaplastic carcinoma. Factors that confer a higher risk of malignancy for a given thyroid nodule include young or elderly patients, positive family history of thyroid cancer, previous history of irradiation to the neck or other radiation exposure, rapid enlargement, presence of enlarged cervical lymph nodes, and hoarseness with hypomobility of the vocal cord [37, 38].

Treatment for thyroid cancer usually begins with thyroidectomy (either total thyroidectomy, or for smaller tumors, lobectomy). Removal of suspicious lymph nodes from level VI of the neck is commonly performed, and on occasion, lateral neck dissection (levels II–V) is required [39]. In high risk cases, postoperative radioactive iodine ablation is offered (see Fig. 18.4). For well-differentiated thyroid cancers (papillary and follicular subtypes), prognosis is excellent [40]. For medullary thyroid can cer, prognosis is more guarded, and for anaplastic cancer, survival rates are dismal.

Entire textbooks about the evaluation and treatment of thyroid cancer have been written [41], and a comprehensive discussion is beyond the scope of this text.

18.3.3.3 Soft Tissue Tumors

A diverse group of tumors may develop in the soft tissues of the neck. These include benign processes such as lipomas, neurofibromas, schwannomas, or paragangliomas. There are rare malignant processes for which surgery may play a role, such as sarcomas. Sarcomas arise from tissues such as fat (liposarcoma), smooth muscle (leiomyosarcoma), skeletal muscle (rhabdomyosarcoma), fibrous tissue (fibrosarcoma), among others. Treatment involves multiple modalities, most often surgery and postoperative radiotherapy or chemoradiotherapy, depending on the type of sarcoma, location of disease, ability to remove the tumor surgically, among other factors [42].

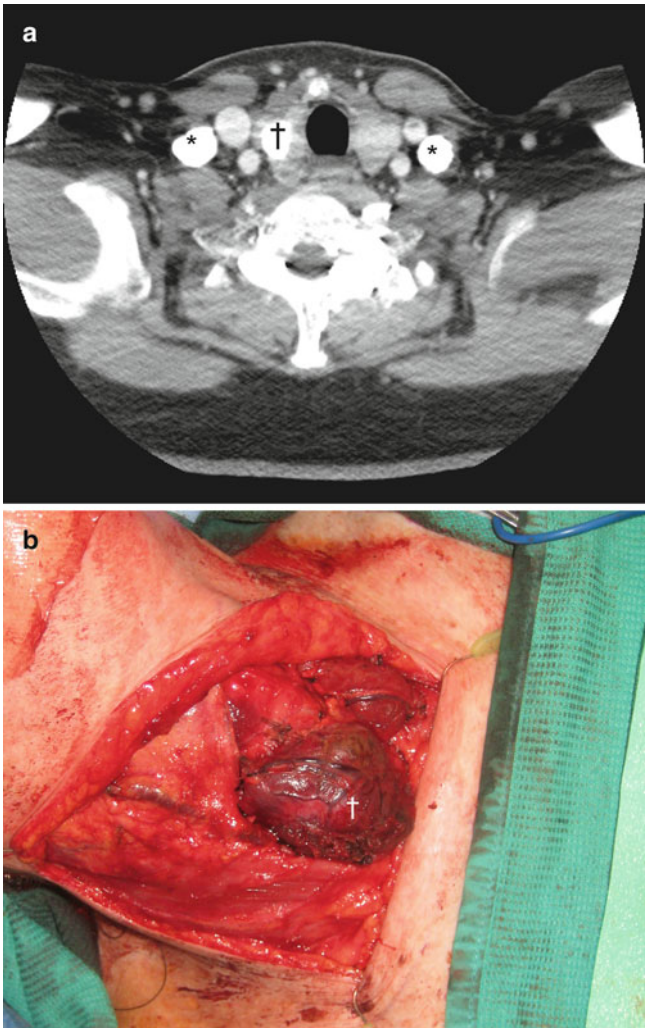

Fig. 18.4 (**a**) Patient with papillary thyroid cancer with calcified nodule in right thyroid lobe (†) and in multiple bilateral lymph nodes (*) (**b**) Therapy began with total thyroidectomy with central compartment and bilateral neck dissection. Right thyroid lobe denoted by †

18.3.4 Cervical Lymph Node Metastases

Most types of head and neck cancer are well-known to metastasize to the cervical lymph nodes. These nodes must be addressed in the initial evaluation, management, and long-term surveillance of head and neck cancers. Spread to the lymph nodes of the neck (termed "regional metastases") may occur for primary tumors of any size and location. When physical examination and pre-treatment imaging do not reveal any enlarged lymph nodes, it remains possible that subclinical disease may be present in the lymph nodes (termed "occult" disease).

18.3.4.1 Clinical Evaluation

For patients with known head and neck primary tumors, any palpable mass in the neck should be investigated. Lymph node involvement may occur on the ipsilateral side of the neck as the primary tumor (e.g., a right mandibular gingiva cancer with a right neck node), on the contralateral side of the neck (e.g., a right tongue base cancer with a left neck node), or on both sides of the neck (e.g., a supraglottic laryngeal cancer with bilateral neck nodes).

Although there are clearly exceptions, some primary tumor factors are associated with an increased risk of spread to the cervical lymph nodes [43]. Some head and neck tumor locations are more prone than others to regional metastases, e.g., the nasopharynx, oropharynx, and hypopharynx, while other locations rarely metastasize, e.g., the glottic larynx. Larger primary tumors have a higher rate of regional metastases than smaller tumors. The same applies for tumors with a greater depth of invasion, especially in the oral cavity [44]. Other pathologic features, such as invasion of nerves (termed "perineural invasion") or lymph and blood vessels (termed "lymphovascular invasion") portend a higher risk for lymph node spread.

Patients may or may not have symptoms related to the involved lymph node(s). Most frequently, metastatic cervical lymph nodes are painless and slowly progressive. Some patients, however, may experience pain, rapid growth, fixation to surrounding structures (e.g., the mandible or sternocleidomastoid muscle), or weakness of nearby cranial nerves (e.g., the marginal mandibular branch of the facial nerve or spinal accessory nerve).

Imaging studies provide important information about the cervical lymph nodes, and are recommended in all head and neck cancer patients prior to treatment [45]. For patients without any evidence of lymph node involvement on clinical examination (N0 stage), imaging may detect mildly enlarged or abnormally appearing lymph nodes. For patients with palpable nodes (N+), imaging studies are utilized to determine the size, location, and number of suspicious nodes; to assess the relationship of the nodes to the surrounding structures and the probability of being able to surgically remove the disease; to detect obvious extension of disease outside the capsule of the lymph node; and for patients undergoing nonsurgical therapy, to serve as a baseline for comparison to post-treatment films. The most common imaging modality is CT scan, although MRI, PET scan, and ultrasound are also useful and are frequently employed.

18.3.4.2 Treatment of Patients with an N0 Neck

If, after clinical and radiologic evaluations are completed, a patient with head and neck cancer has no obviously involved lymph nodes, the treating clinicians must decide how to address the N0 neck. In a significant number of patients with N0 necks, occult lymph node involvement may have occurred. Therefore, the decision comes down to treating the primary tumor and including the lymph node groups that are at risk, or treating the primary tumor only and observing the lymph nodes clinically, initiating treatment if disease should appear in the future [46].

In general, when a decision has been made to treat the lymph nodes, most facilities treat the neck with the same modality as the primary tumor (i.e., surgery or radiation). In N0 necks, this is termed "elective treatment." Prior studies have demonstrated the presence of lymph node involvement following surgical removal of neck nodes ("neck dissection") for various locations and stages of primary tumor. Based on these studies, we are now able to estimate the risk of occult lymph node involvement based on the location and stage of the primary tumor. As a general rule of thumb, when the risk of occult disease is 15–20% or higher, most facilities will recommend elective treatment of the neck [47].

If the primary site is treated with radiation, the lymph node groups at risk for occult metastases are included in the treatment fields. When surgical resection of the primary site is performed, elective neck dissection can be performed at the same time. In recent decades, a shift has occurred from the performance of a comprehensive neck dissection (which includes all ipsilateral lymph nodes in levels I through V) to a selective neck dissection. Selective neck dissection refers to the removal of all lymph nodes from the groups at risk for an individual primary tumor. For example, a patient with an oral cavity cancer with an N0 neck may undergo resection of the primary tumor and selective neck dissection of ipsilateral levels I–III [48], whereas resection of a supraglottic cancer would be accompanied by selective neck dissection of bilateral levels II–IV [49].

A clear advantage of treating an N0 neck with surgery as opposed to irradiation is the information provided by pathologic evaluation of the specimen. A clinically N0 neck may turn out to actually be pathologically N+, which has implications on prognosis and recommendations for further therapy.

Studies are currently underway evaluating the effectiveness of sentinel node biopsy for certain head and neck cancers, especially in the oral cavity. If a sentinel node is identified, it can be excised with less morbidity than a selective neck dissection. Pathologic study of the sentinel node dictates the need for more comprehensive treatment of the neck. As techniques are refined, this may supplant or supplement the use of selective neck dissection in the future.

18.3.4.3 Treatment of Patients with an N+ Neck

The presence of metastases in cervical lymph nodes is the most significant prognostic factor in patients with squamous cell cancer of the head and neck. For smaller (T1 or T2) tumors, patients are upstaged from a Stage I or II cancer to a Stage III or IV cancer (for N1 or N2-3 disease, respectively). This is accompanied by a worsening of overall survival by about 50% [50]. It is thought that the molecular mechanisms that allow spread to cervical lymph nodes may be similar to those that allow distant spread, which confers a dismal prognosis.

With that in mind, most patients with N+ neck disease are approached aggressively, with comprehensive treatment of the neck using multiple modalities. In general, when surgery is chosen, surgical therapy of the N+ neck is followed by adjuvant radiotherapy or chemoradiotherapy. Concurrent chemotherapy and radiotherapy is

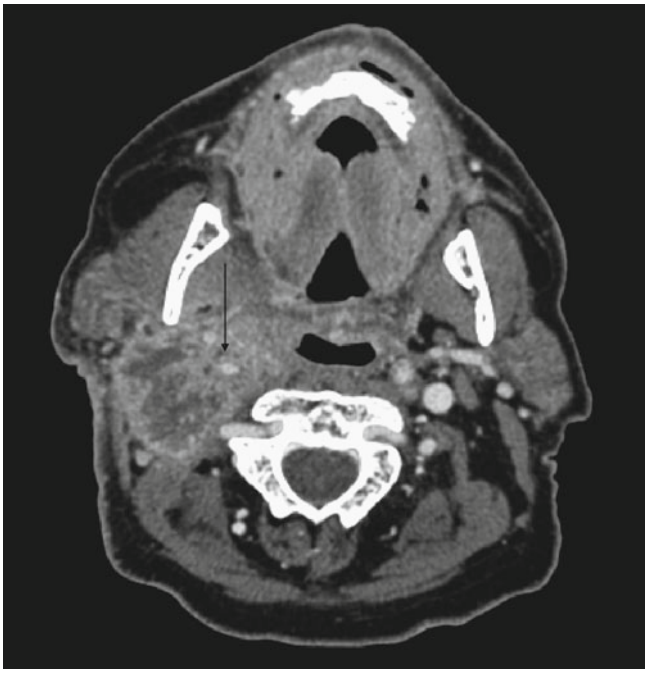

Fig. 18.5 Patient with metastatic tongue base cancer to a right neck lymph node. The internal carotid artery (*arrow*) is completely encased by the metastatic disease. This patient was not considered a surgical candidate and was referred for chemo-radiotherapy. His prognosis for cure is poor

also an effective treatment for the N+ neck, with a number of patients requiring salvage surgery for persistent or recurrent neck disease [51].

Surgery for the N+ neck can be either comprehensive neck dissection or selective neck dissection, depending on the extent of the disease [52]. Comprehensive neck dissections are categorized as "radical neck dissection," which involves resection of all lymph nodes from levels I–V, the sternocleidomastoid muscle, internal jugular vein and spinal accessory nerve, or a "modified radical neck dissection," which removes levels I–V but preserves one or all of the sternocleidomastoid, jugular vein and spinal accessory nerve. Somewhat controversially, selective neck dissections are possible for a select group of N+ patients, usually those with small, single, mobile nodes in level I or II [53].

Following surgery, adjuvant therapy with radiotherapy or chemoradiotherapy is offered, with recommendations depending on the pathologic findings. Extracapsular spread (ECS) of tumor outside the confines of the lymph node, presence of multiple positive lymph nodes, and large bulky lymph nodes are pathologic signs that indicate a high risk of recurrence [54]. In those cases, adjuvant treatment with radiotherapy or chemoradiotherapy is recommended.

A patient may have such extensive neck involvement that the disease is consid ered unresectable by his or her surgeon (see Fig. 18.5). Some signs, if present, confer an extremely poor prognosis and high rate of severe complications when surgery

is performed. These include involvement of the overlying neck skin, the underlying vertebral bodies, the brachial plexus, the skull base, and the carotid artery [55, 56]. The surgeon and patient must decide if the severe morbidity associated with surgery in those situations is worth the very small chance for cure, or whether nonsurgical treatments or palliative therapy may be more advisable.

18.3.5 Metastasis from an Unknown Primary Tumor

On occasion, the appearance and growth of a neck mass in an otherwise asymptomatic patient is the first presenting symptom of a head and neck cancer. This is usually diagnosed as metastatic cancer via a FNA biopsy, either by the surgeon or prior to referral. In these scenarios, the surgeon performs a thorough clinical evaluation of the upper aerodigestive tract. In most cases, a primary tumor is evident [57]. However in a small number of patients, the primary tumor eludes detection. Such a patient has an "unknown primary tumor," also referred to as an "occult primary tumor."

18.3.5.1 Evaluation

The surgeon plays an important role in these patients. The first steps involve a careful and comprehensive search for the primary tumor. This typically involves imaging. CT scans are helpful in delineating the extent of the neck disease, and may show a mucosal abnormality indicating the primary tumor. Recent studies have shown PET scans to be quite helpful in locating occult primary tumors [58]. Following imaging, a careful examination under anesthesia using microscopy or magnifying endoscopy of all mucosal surfaces may allow identification of a small primary tumor. Biopsies can be performed of any suspicious locations identified on imaging or examination (Fig. 18.6). If the evaluation to this point is unsuccessful in locating the primary tumor, directed biopsies can be performed of mucosal sites most likely to harbor occult tumors; the vast majority of occult tumors are identified or emerge eventually in the tonsils or tongue base, with lesser numbers in the nasopharynx, supraglottis, and hypopharynx [59]. Some authors recommend performing tonsillectomy, as primary tumors may be present in the depths of the tonsillar crypts and not apparent on the visible surface of the tonsil [60, 61]. Utilizing comprehensive imaging, exam under anesthesia, and tonsillectomy, approximately 40–50% of occult primary tumors can be identified.

18.3.5.2 Treatment

When no primary tumor is identified after the thorough workup outlined above, the treatment of patients with occult primary tumors is controversial. Some centers advocate performing a comprehensive neck dissection as the first step [62]. This would be

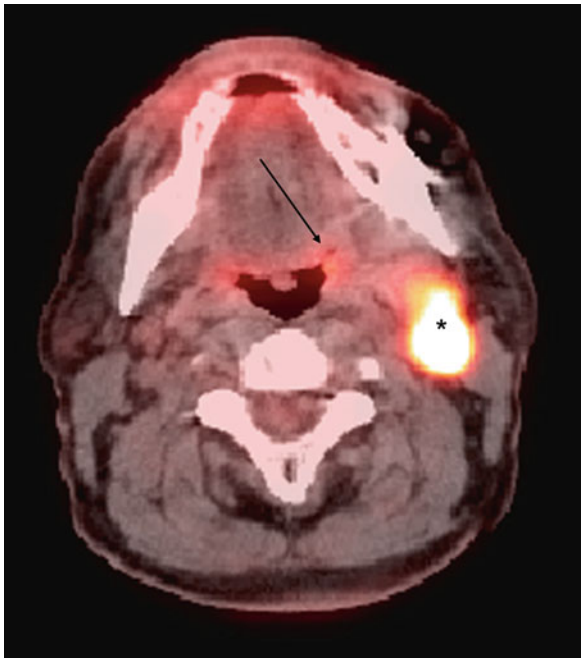

Fig. 18.6 Patient with metastatic squamous cell cancer in a left neck lymph node from an unknown primary site. PET scan reveals hypermetabolic activity in the left neck node (*) as well as the left tonsil (*arrow*). Although physical appearance of the left tonsil was normal, subsequent biopsies revealed squamous cell carcinoma

followed by radiotherapy or chemoradiotherapy, as dictated by the pathologic results. Other centers recommend treatment with chemoradiotherapy initially, with use of salvage neck dissection for persistent or recurrent disease in the neck [63].

At the author's institution, both approaches are used. Radiotherapy is typically given not only to the neck, but to the mucosal surfaces of the pharynx and larynx as well, in hopes of eliminating the likelihood of the mucosal primary tumor emerging. This wide-field radiation is morbid. One can infer that identification of the primary tumor allows radiation treatments to be targeted to the small area involved, sparing the rest of the mucosa; this explains the necessity for such a comprehensive search for the primary tumor prior to treatment. There are studies demonstrating acceptable rates of failure when the neck alone is treated, sparing the upper aerodigestive tract from the morbidity of wide-field irradiation [64].

18.4 Cancer of the Oral Cavity

18.4.1 Introduction

Approximately 30,000 cases of oral cavity cancer are diagnosed annually in the U.S., comprising about 20–30% of head and neck cancers [65]. Clearly, the rate of oral cavity cancer is higher in patients with the risk factors of smoking, alcohol

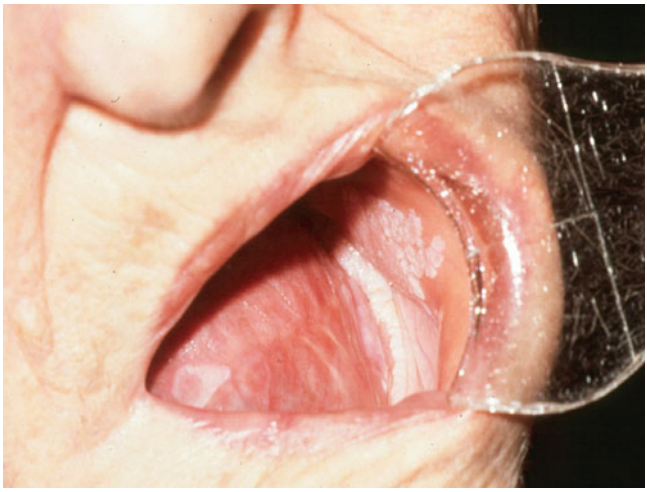

Fig. 18.7 Leukoplakia of the mandibular gingiva and buccal mucosa in a patient with long history of oral tobacco use

abuse, and oral tobacco use [66]. Oral cavity cancer may occur on the lips, buccal mucosa, upper and lower gingiva (gums), hard palate, floor of mouth, oral tongue, and retromolar trigone (between the upper and lower third molar teeth).

Squamous cell cancer comprises the vast majority of oral cavity cancers. Other rare tumors may occur throughout the mouth and include cancers of the minor salivary glands (most commonly, adenoid cystic carcinoma and mucoepidermoid cancer), mucosal melanomas, and Kaposi sarcoma (common in patients with acquired immunodeficiency syndrome [AIDS]). It has been proposed that squamous cell carcinoma develops in a stepwise fashion, with initial dysplastic lesions appearing as leukoplakia or erythroleukoplakia (Fig. 18.7), eventually developing the molecular changes resulting in severe dysplasia, carcinoma-in-situ, and finally, invasive carcinoma [67].

Surgery plays a crucial role in the diagnosis, staging, and treatment of oral cavity pre-cancerous and cancerous lesions.

18.4.2 Evaluation

Lesions in the oral cavity are most frequently detected by the patients or their primary care physicians or dentists, at which point they are come to the attention of a surgeon for further diagnosis and care. Most patients with oral cavity cancer have a non-healing sore or ulceration that is frequently painful (Fig. 18.8). There may be effects on the patients' abilities to chew, swallow, or otherwise manipulate food in the mouth. Tumors of the tongue may result in dysarthria (slurring of speech). Gingival tumors may cause erosion of bone and loosening of teeth. Numbness of the tongue, lip, teeth,

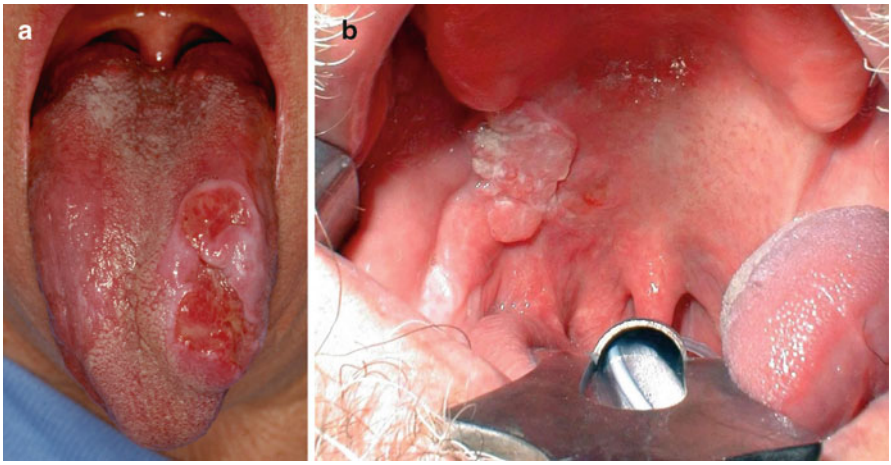

Fig. 18.8 (**a**) Painful ulcerative lesion of the left oral tongue. Subsequent biopsy revealed squamous cell carcinoma (**b**) Squamous cell cancer of the right retromolar trigone

or roof of mouth may indicate cranial nerve invasion. Inability to open the mouth (trismus) indicates a deeply invasive tumor into the pterygoid musculature. Advanced stage tumors may lead to malnutrition, severe pain, and even airway obstruction.

Important characteristics on examination include the size and location and involved structures. The depth of the tumor can be appreciated with palpation. Cranial nerve examination can assess for obvious perineural invasion. Palpation of the neck for lymphadenopathy is critical. If accessible, a tissue biopsy can be performed in the clinic using local anesthesia. Imaging studies are important to evaluate the extent of primary tumor invasion and to detect occult metastatic lymph nodes.

18.4.3 Nonsurgical Treatment

Early stage (I or II) tumors are effectively treated with either surgery or radiation. Some patients may be better candidates for radiotherapy due to unacceptable anesthesia risks or if they adamantly refuse surgery. Irradiation of the oral cavity, while effective in curing early stage tumors, has significant disadvantages [68]. Surgery can fully treat early stage tumors in a matter of hours, while radiotherapy is given over many weeks. Irradiation of the oral cavity may lead to side effects such as taste loss and xerostomia, which may be more debilitating than the deficit caused by surgery. Osteoradionecrosis of the mandible, which can be devastating, is a known side effect of radiotherapy of the oral cavity [69]. Finally, treating with radiotherapy eliminates this modality as a potential treatment for any future second primary head and neck tumors that may develop. With all this in mind, in general, most centers treat early oral cavity cancers with surgery [70]. Advanced stage tumors (III or IV) are best treated with multimodality therapy. In the vast majority of cases, this is initiated with surgery, followed by adjuvant radiation or chemoradiation therapy.

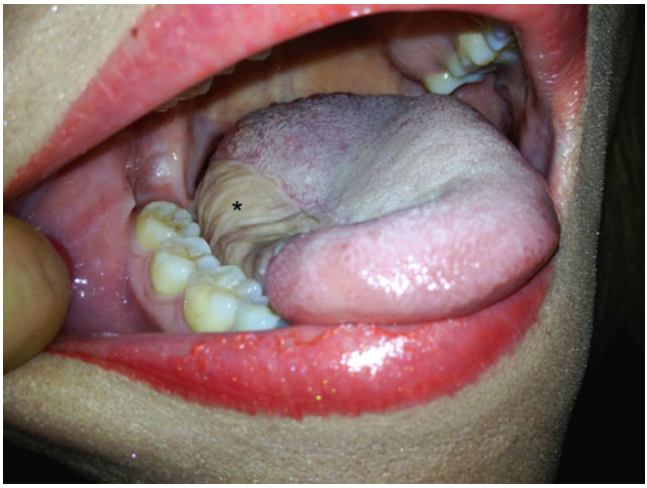

Fig. 18.9 Patient with small tongue cancer, resected and reconstructed with a skin graft (*) 1 year prior. Functional status is excellent without deficit in tongue mobility, speech, or swallowing

18.4.4 Surgical Treatment

Surgeries for cancer of a few representative sites in the oral cavity are discussed below. These are the most common areas of involvement by squamous cell carcinoma in the oral cavity.

18.4.4.1 Tongue Cancer

The oral tongue is the most common location of oral cavity cancers. Small tumors (T1 or T2) of the tongue are usually easily visualized through the mouth. Surgery typically involves excising the tumor with a margin of normal tongue mucosa and musculature. Margins of the specimen are evaluated to ensure the cancer has been completely extirpated. Small mucosal defects are closed primarily or allowed to heal by secondary intention. Larger defects may be better served with resurfacing, e.g. with a skin graft, to prevent tethering of the tongue (Fig. 18.9). In all but the most superficially invasive tumors, elective neck dissection is performed for N0 necks, and appropriate comprehensive neck dissection is performed for N+ disease, usually during the same anesthetic. In general, patients can expect excellent functional outcomes, with slurred speech and deficits in swallowing depending on the amount of tongue resected and the severity of tethering present after surgery.

Larger tumors of the tongue (T3 or T4) require more aggressive surgery. Neck dissections are performed in nearly all cases. These tumors frequently involve the deep musculature of the tongue and floor of mouth. In these scenarios, half or more of the tongue may need resected in order to obtain negative margins (Fig. 18.10). Occasionally the tumor cannot be fully removed transorally, and the surgeon must

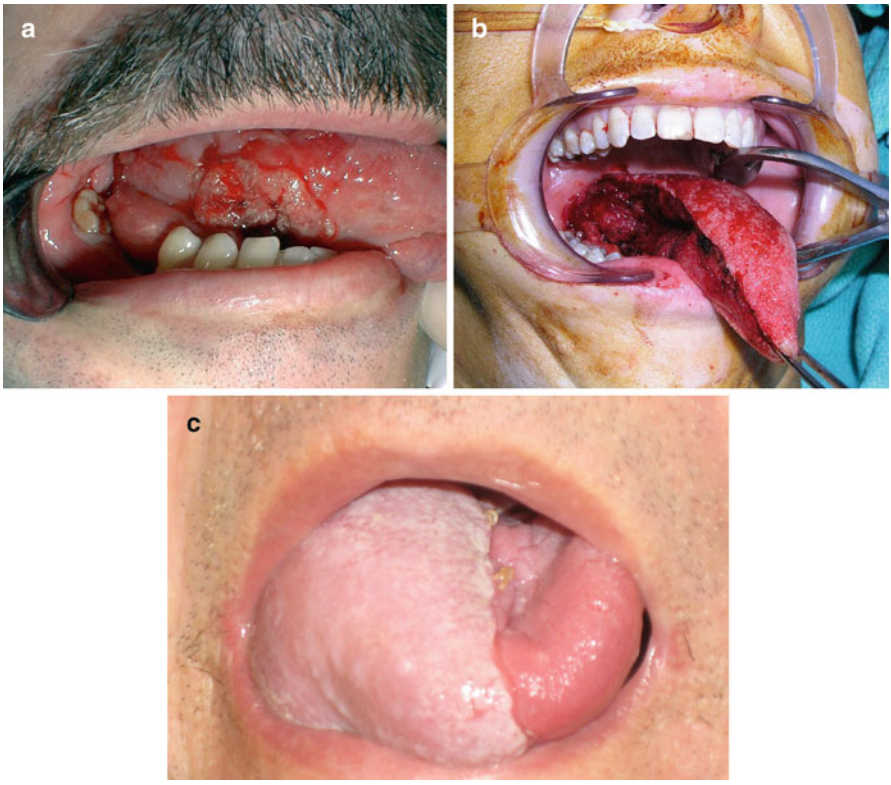

Fig. 18.10 (**a**) Patient with large ulcerative squamous cell carcinoma of the right oral tongue, invasive of the underlying tongue musculature. (**b**) Surgical defect following removal of right oral tongue cancer (termed "hemi-glossectomy") in a different patient. This patient also underwent neck dissection during this same surgery. (**c**) A radial forearm free flap was used to transfer thin, pliable skin of the wrist to reconstruct the right hemi-tongue. One month later, the reconstruction allows for clearly understandable speech, intake of soft diet, and excellent mobility of the remaining left hemi-tongue

divide the deep tongue musculature through the neck to be able to remove the tumor. Reconstruction of large tongue defects requires transfer of tissue from elsewhere in the body (free tissue transfer), often from the forearm or thigh [71]. Functional status depends on the amount of residual native tongue that is able to be preserved and the skill of the reconstructive surgeon [72].

18.4.4.2 Buccal Cancer

The buccal (cheek) mucosa is commonly involved in patients who use oral tobacco. Smaller tumors can be removed transorally with negative margins and minimal functional deficits after skin grafting. More difficult are the larger (T3, T4) tumors.

These often extend to surrounding structures, such as the lips, mandibular or maxillary gingiva, or the overlying cheek skin. Resections are frequently full-thickness, involving the facial skin, with through-and-through defects. Defects of any resection but the most superficial tumors usually require free tissue transfer for reconstruction [73].

18.4.4.3 Floor of Mouth Cancer

The floor of mouth consists of mucosa between the tongue and mandibular gingiva. Smaller tumors free of the gingiva may be removed transorally. Tethering of the tongue to the gingiva at the site of surgery can be expected, and therefore resurfacing with skin grafts is often employed. Small tumors that abut the mandibular gingiva or bone require more extensive surgery. In these cases, negative margins are impossible to obtain without removing a partial thickness of bone to serve as the deep margin under the tumor; this is referred to as a marginal mandibulectomy [74]. When a portion of the ventral tongue is removed, tethering of the tongue can be expected unless skin grafting or free tissue transfer (usually forearm) is employed.

Larger tumors often invade deeply into the musculature of the tongue or floor of mouth or into the bone of the mandible. Bone invasion requires full-thickness resection of mandible, termed segmental mandibulectomy. Without reconstruction, these defects are cosmetically and functionally devastating. Free tissue transfer of bone (for example, from the fibula or scapula) is utilized with excellent results to restore appearance and function in these patients [75].

18.4.4.4 Gingival Cancer

Cancer of the gingiva may occur in either the mandible or maxilla. Smaller tumors may not exhibit bone invasion. In these cases, excision of a cuff of bone to serve as a deep margin is usually required, but a portion of the thickness of the mandible may be able to be preserved, a procedure termed "marginal mandibulectomy" (see Fig. 18.11). Full thickness mandibular resection is required in cases of bone invasion, termed "segmental mandibulectomy". These are discussed above in Sect. 18.4.4.3.

For maxillary gingival involvement, removal of even a thin layer of bone often results in communication into the sinonasal cavity. Removal of larger tumors creates a sizeable communication. Without rehabilitation of these defects, there can be severe effects on patients' speech and their ability to manipulate food. Rehabilitation with a specially fashioned dental appliance is an effective way to obturate the communication [76]. Reconstruction with local muscle transfer (especially the temporalis muscle) [77] or with free tissue transfer [78] results in closure of the communication and restoration of speech and eating without the need for a dental appliance.

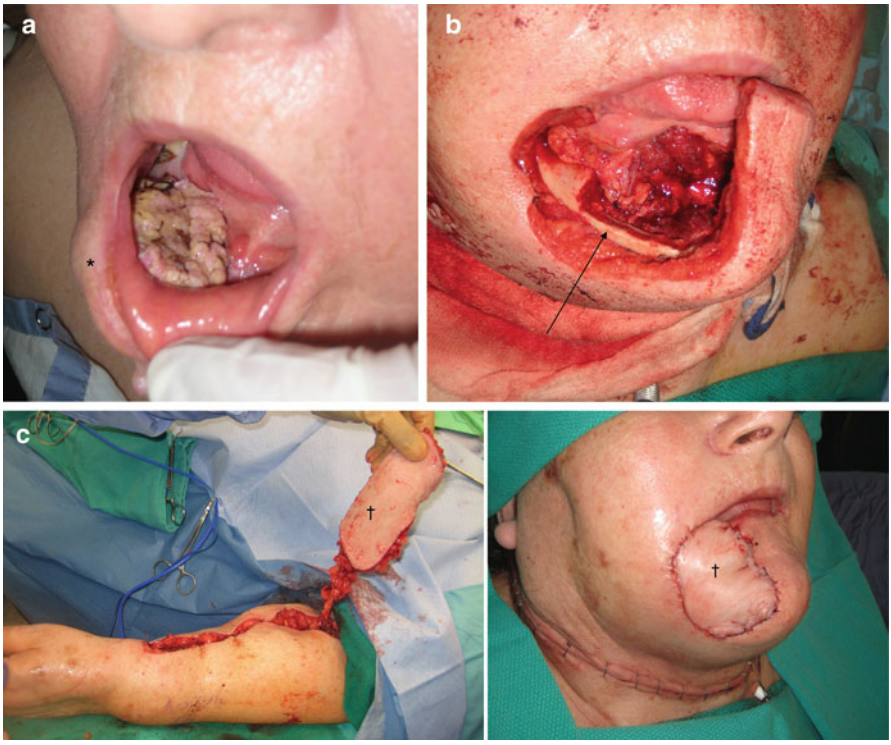

Fig. 18.11 (**a**) Patient with exophytic painful tumor of mandibular gingiva, with extension into the soft tissues of the lower lip skin (*). (**b**) Resection involved the lower lip, the mandibular gingiva, and partial thickness of mandibular bone (*arrow*). Neck dissection was performed simultaneously. (**c**) Harvest of radial forearm free flap (†) from the left wrist, ready to be transferred to the surgical defect for reconstruction. (**d**) Postoperative appearance of reconstruction. Portions of the free flap skin paddle were used for reconstruction of the intraoral defect as well as the lower lip (†)

18.5 Cancer of the Oropharynx

18.5.1 Introduction

The oropharynx consists of the tonsils, tongue base, soft palate, and pharyngeal walls. Risk factors for other sites of head and neck cancer are similar to the oropharynx, especially smoking and alcohol abuse. As rates of tobacco abuse have declined in the past 15–20 years, the incidence of squamous cell cancer of all head and neck sites has fallen, with the exception of the oropharynx [65]. Interestingly, it appears that an epidemic of tonsillar and tongue base cancer is underway [79]. Epidemiologic data shows that over the last decade or so, cancer of the oropharynx is occurring in a younger population than cancer in other head and neck sites, and is now occurring in more nonsmokers than smokers.

This epidemic is attributed to the Human Papillomavirus (HPV) [80]. While the incidence of HPV-related oropharyngeal cancer is rapidly increasing, tumors caused by HPV appear to respond very well to therapy and are much more curable than tumors related to smoking. This appears to hold true for all treatment modalities, surgical [81] and non-surgical [82].

18.5.2 Evaluation

Symptoms of oropharyngeal cancer may be subtle and lead to delayed diagnosis. The primary tumor may cause pain, malodorous breath, a foreign body sensation, sore throat, or otalgia (pain in the ear referred from the oropharynx). Advanced tumors may invade the pterygoid musculature of the mandible, causing trismus. It is not uncommon for the primary tumor to be asymptomatic, with the initial presenting symptom being an enlarging neck mass from cervical lymph node metastasis. Even the smallest oropharyngeal tumors may have cervical metastases.

Physical exam findings depend on the location of the primary tumor. The soft palate and uvula should be amenable to direct inspection. The superficial mucosa of the tonsillar fossa can be examined, but the deeper portions of the tonsil are not visible and require palpation to assess. The tongue base can be assessed via palpation and mirror examination, and a very detailed exam is possible with office endoscopy.

Biopsy of visible tumors of the soft palate and tonsil can often be performed in the office under local anesthesia. Tumors in the tongue base or pharyngeal walls usually require biopsy in the operating room under anesthesia. Enlarged neck nodes can be biopsied via fine needle aspiration.

Imaging studies are critical to assess the pre-treatment extent of the disease, to determine the structures involved by the primary tumor, and identify occult cervical nodal disease. CT or MRI are the most common imaging modalities used for oropharyngeal malignancy, and PET scans are being utilized more frequently (Fig. 18.12).

18.5.3 Non-surgical Treatment

Radiation therapy alone is frequently used as treatment for early-stage oropharyngeal tumors. For more advanced tumors, concurrent chemotherapy and radiotherapy are frequently utilized [83]. Most centers are using an advanced radiotherapy technique referred to as Intensity Modulated Radiation Therapy (IMRT), which involves conformal external beams to treat a defined area of disease to the prescribed dose. This allows the radiotherapist to limit the dose of radiation to surrounding healthy tissues, reducing the side effects [84]. Excellent oncologic outcomes have been demonstrated for non-surgical therapy, even for advanced-stage cancers. HPV-related cancers appear to respond very well to treatment, with cure rates approaching 90% [85].

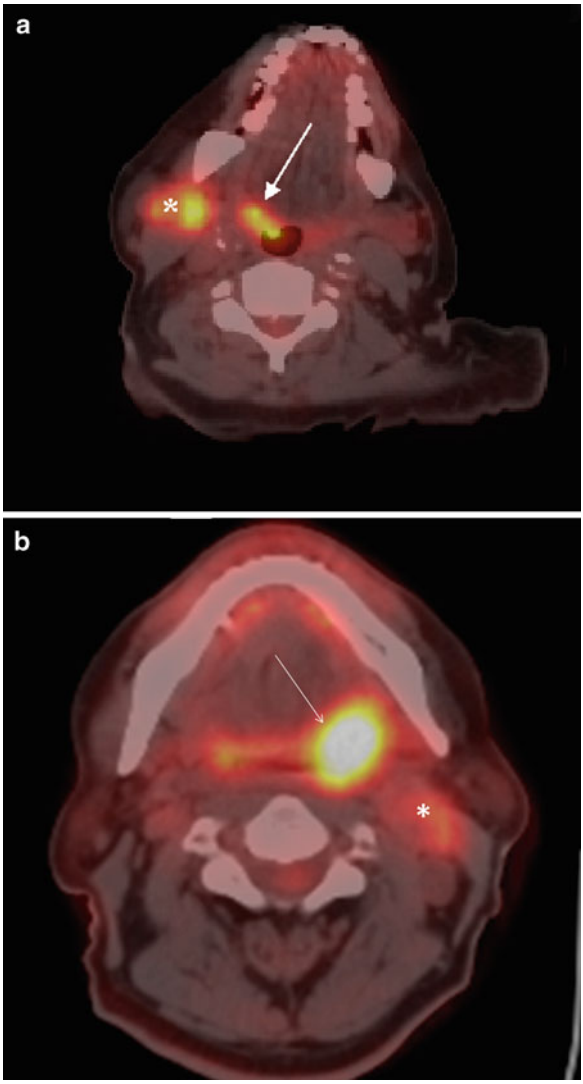

Fig. 18.12 (**a**) PET scan of a patient with a small right tongue base cancer (*arrow*) with metastasis to the right neck lymph nodes (*). (**b**) PET scan of a patient with a large left tonsil cancer (*arrow*) with metastasis to a left neck lymph node (*)

Side effects of radiation treatment appear to be dose-dependent, and are worse when concurrent chemotherapy is utilized. Xerostomia (dry mouth), dysphagia, taste changes, osteoradionecrosis, pharyngeal and esophageal strictures, and soft tissue fibrosis are all frequent sequelae of chemo-radiotherapy. Studies have shown 10–38% of patients are unable to eat and require use of a feeding tube following chemoradiotherapy for oropharyngeal cancers [86–88].

18.5.4 Surgical Treatment

Surgery has long been utilized for the treatment of oropharyngeal cancers [89]. Stage I–II cancers are a minority of oropharyngeal cancers. These may be treated by surgery alone. Surgery for more advanced stage tumors is most often followed by adjuvant radiotherapy or chemoradiotherapy, depending on the pathology results from surgery. Adjuvant treatment is sometimes able to be de-intensified following surgery [90]. Thus, in patients with advanced-stage tumors who undergo minimally invasive surgery followed by de-intensified adjuvant radiotherapy, functional outcomes may be improved compared to those that undergo treatment with toxic chemoradiotherapy protocols [91].

The rate of cervical lymph node involvement for even small oropharyngeal tumors is quite high. Therefore, it is recommended that surgical therapy for oropharyngeal cancers include a neck dissection [83]. All oropharyngeal sites but the most lateral tonsillar tumors are at risk for bilateral metastases [92].

18.5.4.1 Transoral Approaches

In some patients, smaller cancers may be excised via transoral approaches, without the need for any facial or neck incisions to expose and access the primary tumor. Neck dissection can be performed during the same surgery or may be staged as a separate procedure a week or two later [93].

Small tumors limited to the soft palate are easily excised, with side effects dependent on the amount of palate excised. Large soft palate resections result in velopharyngeal incompetence, with hypernasal speech (due to escape of air into the nasopharynx) or nasal regurgitation of food or liquids when swallowing.

Tumors limited to the tonsillar fossa, without extension through the pharyngeal constrictor muscles, are candidates for transoral excision. This involves a resection of the anterior and posterior tonsillar pillars, a portion of the soft palate and tongue base, and the pharyngeal constrictor muscle as a deep margin. This can be accomplished with simple headlight [94], or may require advanced surgical techniques including transoral laser microsurgery (TLM) [95] or transoral robotic surgery (TORS) [91]. These defects are typically left to heal by secondary intention, and functional results of these surgeries appear to be excellent, with low rates of speech abnormalities or swallowing dysfunction (Fig. 18.13).

Transoral excision of tongue base tumors is more difficult. These are typically accomplished via TLM or TORS techniques [96]. Defects are again left to heal by secondary intention. Speech and swallowing outcomes appear to be excellent, as long as resection is limited to smaller tumors that do not cross midline of the tongue base or invade deeply into the tongue base musculature.

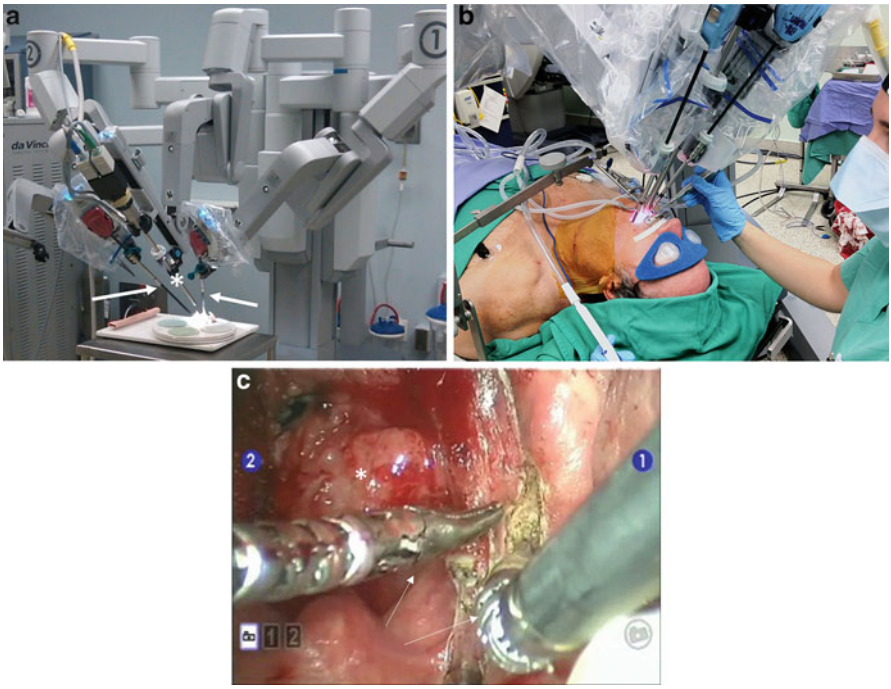

Fig. 18.13 (**a**) DaVinci Surgical System (Intuitive Surgical Inc, Sunnyvale, California). Two surgical arms (*arrows*) and one camera arm (*) are inserted into the patient's mouth. The surgeon manipulates these arms from a separate console, utilizing the magnified three-dimensional view provided by the camera. (**b**) Patient undergoing resection of tonsil cancer utilizing TORS. Two surgical arms and one camera arm are inserted into the mouth without need for facial incisions. Surgeon's assistant sits at the patient's head to provide suctioning and other helpful tasks. (**c**) View of the surgeon through the intra-oral camera. Two robotic surgical arms (*arrows*) controlled by surgeon during resection of a right tonsil cancer (*)

18.5.4.2 Transmandibular Approaches

The ability to visualize and access the entirety of an oropharyngeal tumor through the mouth depends on the size of the tumor and the particular oral anatomy of the patient. For larger oropharyngeal tumors, or for patients with retrusive mandibles, narrow mandibular arches, trismus, or inability to extend the neck, transoral resection may be impossible [97]. A number of techniques have been refined to address these patients.

A "mandibulotomy" approach involves an incision in the anterior mandible, allowing each side of the mandible to be distracted laterally [98]. The tongue and floor of mouth are detached from the inner surface of the mandible, distracting them medially. This allows exposure to the entire oropharynx, including the tonsillar fossa, pharyngeal walls, and tongue base. Tumors can be resected with excellent visualization and ability for the instruments to access the entire oropharynx. The oropharyngeal defect requires reconstruction in these cases, typically with a free tissue transfer or pectoralis major flap. Following inset of the reconstructive flap,

the tongue and floor of mouth are re-attached to the mandible, and the two segments of mandible are brought into alignment and rigidly fixed with a plate and screws.

Segmental mandibulectomy involves a full-thickness resection of the mandible. This is utilized in patients with tumors that abut or extend into the mandible or to the pterygoid muscles. Once the incisions in the mandible have been performed, this segment of the mandible can be distracted laterally, and full visualization and access to the tumor are then possible. This operation, known colloquially as the "Commando operation," has been utilized for over 100 years [99]. Reconstruction is required following resection. This can be accomplished with soft tissue only, soft tissue with a reconstructive bar, or with a bony free flap and reconstructive bar.

18.5.4.3 Transcervical Approaches

Smaller tumors of the oropharynx may be resected by first entering the pharynx through the neck. One such technique is referred to as the "lateral pharyngotomy" approach. Following neck dissection, the pharyngeal constrictors are divided, and then the mucosa is divided at some distance from the tumor. Another technique is the "transhyoid" approach. In this case, the muscles superior to the hyoid are divided, exposing the mucosa of the vallecula. This is then divided, allowing entrance into the pharynx. In either approach, these pharyngotomies are then enlarged, encircling the tumor and maintaining a healthy margin of mucosa [100].

Since transcervical approaches are typically for smaller tumors, the defects are often small enough to be closed primarily with sutures. Larger resections may require soft tissue flaps to allow complete closure.

Transmandibular and transcervical techniques are oncologically sound for removal of oropharyngeal cancers. However, functional outcomes appear to be worse than for transoral approaches and non-surgical treatments. Clearly, there are detrimental effects on voice, articulation, and swallowing [101]. These effects are worse with larger amounts of tissue resection. With this in mind, for primary treatment of oropharyngeal cancers at many institutions, these techniques are less commonly used now than in the past, replaced instead with transoral surgeries or chemoradiation protocols [83]. At the author's institution, these open techniques are used in patients who are poor candidates for chemoradiotherapy, for large aggressive-appearing tumors, and for salvage treatment of residual or recurrent tumors following chemoradiation.

18.6 Cancer of the Larynx

18.6.1 Introduction

Laryngeal cancer is diagnosed in approximately 12,000 patients yearly in the U.S. [102]. Most cases can be attributed to smoking and alcohol abuse, although environmental and occupational exposures such as wood dust, asbestos, and certain fumes have been shown to confer some risk. Some studies have demonstrated some increased risk in patients with gastroesophageal reflux disease [103].

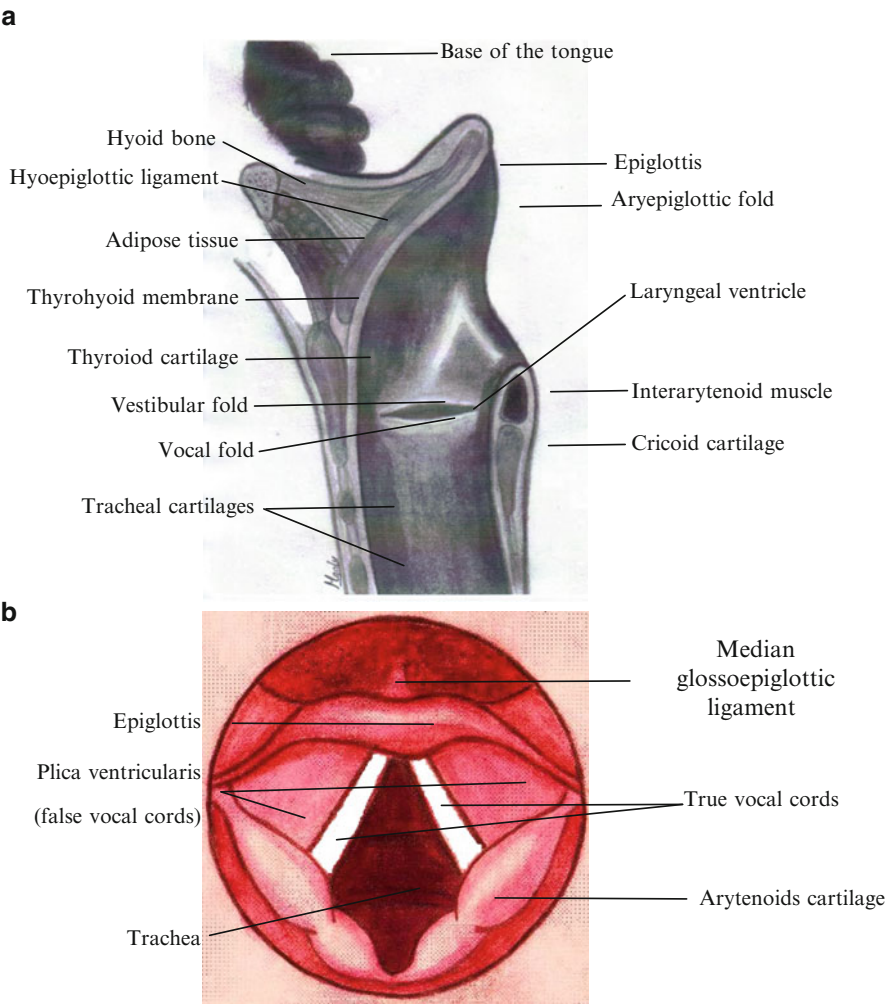

Fig. 18.14 (**a**) Schematic drawing of the larynx, lateral view. (**b**) Schematic drawing of the endoscopic view of the larynx

For any discussion of laryngeal cancer, it is important to have an understanding of laryngeal anatomy. The framework of the larynx includes the hyoid bone, the thyroid cartilage, and the cricoid cartilage. The larynx can be divided anatomically into the supraglottis, glottis, and subglottis. Cancers of the different subsites of the larynx have distinct clinical presentations, oncologic behaviors, and prognoses. The supraglottis includes the epiglottis, the aryepiglottic folds, the arytenoids, and the false vocal folds. The glottis includes the vocal cords, and extends inferiorly for 1 cm. Below this, the subglottis extends to the lower aspect of the cricoid cartilage (Fig. 18.14).

18.6.2 Evaluation

For supraglottic tumors, patients will often describe pain, sore throat, otalgia, dysphagia, foreign body sensation, and, if the cancer extends to the vocal folds, hoarseness. Patients with supraglottic tumors frequently have cervical lymph node metastases. Glottic cancer nearly always causes hoarseness as the initial symptom, with some patients experiencing a chronic cough or need for throat-clearing. It is rare for true vocal cord cancers without extension outside the glottis to metastasize to cervical nodes [104]. Subglottic tumors are very rare and have similar symptoms, but are known to spread to cervical lymph nodes. Larger tumors in any of these sites may result in airway obstruction, with patients describing shortness of breath with exertion, or in severe cases, at rest.

The most important feature of the physical examination of patients with laryngeal cancer is an assessment of their respiration. Stridor (noisy breathing) indicates airway obstruction to some degree. With progressive obstruction of the airway, breathing may become labored, and patients may use accessory muscles to assist in inhalation. Patients with near-complete airway obstruction will become fatigued and experience hypoxia, a true emergency [105]. If indicated, patients may require emergent placement of a tracheostomy tube to prevent or relieve complete obstruction.

Changes in the voice are common, especially for patients with glottic cancer. Assessment of the larynx can be attempted with laryngeal mirror exam. The neck is palpated for cervical lymphadenopathy and to ensure there is no palpable extension of the tumor external to the larynx. Office endoscopy is critical in laryngeal cancer patients to assess not only the exact structures involved by the tumor, but also to evaluate the mobility of the true vocal cords, which is important in staging of laryngeal cancers.

Imaging studies give important information regarding the extent of the tumor, which helps to stage the cancer and plan treatment. For example, invasion of the pre-epiglottic space, paraglottic space, or thyroid cartilage are features that can be seen on imaging but not physical examination. Cervical lymph nodes are evaluated as well (Fig. 18.15).

For patients with suspicious laryngeal lesions, tissue diagnosis is accomplished by biopsy in the operating room. During this laryngoscopy, precise tumor mapping can be performed. If endoscopic treatment is considered, the surgeon can ensure acceptable exposure of the entire tumor during this laryngoscopy.

18.6.3 Nonsurgical Treatment

Early stage (T1–T2) tumors of the larynx are effectively treated with radiotherapy alone [106]. There are excellent local control rates for both glottic and supraglottic tumors. Treatment of early stage glottic tumors can be limited to the larynx, but most radiotherapists advocate treatment of the cervical lymph nodes in supraglottic tumors [107]. Advantages of radiotherapy for these tumors include the ability to avoid surgery and obtain satisfactory voice outcomes (often returning to normal or

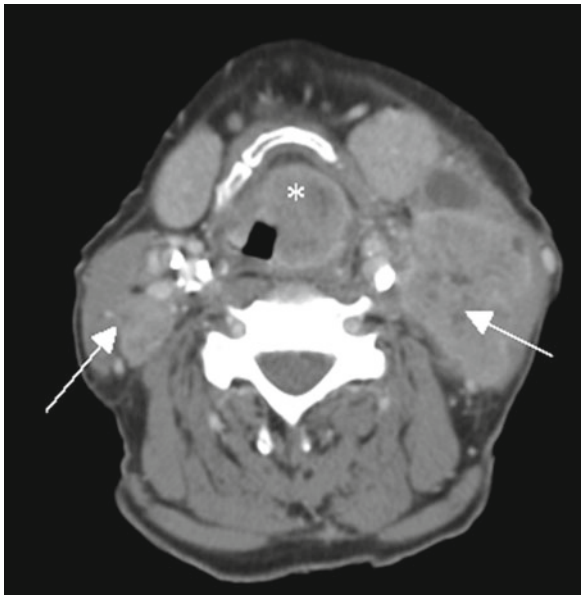

Fig. 18.15 CT scan of patient with supraglottic cancer (*) involving epiglottis, aryepiglottic folds, and pre-epiglottic space. Bilateral lymphadenopathy is present (*arrows*)

near-normal). Sequelae of radiotherapy include dysphagia, sore throat, and often some degree of hoarseness. Rare side effects include the development of chondroradionecrosis of the laryngeal cartilages [108]. Use of radiotherapy precludes its future use in any subsequent recurrences or second primary tumors. Should a small tumor recur following radiotherapy, salvage surgery with a conservation laryngeal procedure may or may not be possible. Total laryngectomy is often required in that situation; any patient undergoing nonsurgical therapy for early stage tumors must be prepared for that possibility [109].

Advanced stage tumors are often candidates for treatment with non-surgical therapy. Landmark studies performed in the 1990s demonstrated the effectiveness of chemoradiotherapy in not only curing laryngeal cancer, but also in allowing the larynx to be preserved [110, 111]. Since then, the popularity of chemoradiotherapy protocols has spread, while the use of surgery has declined. An evaluation of nationwide survival outcomes has demonstrated a slight decrease in survival from laryngeal cancer since these studies were published [112]. There were strictly defined criteria in the studies for patient inclusion, and it is unclear whether inappropriate patients are being included in these "organ preservation" protocols as their popularity has spread. Treatment of tumors that extend into the laryngeal cartilages (T4 stage) is controversial; at the author's institution, radiotherapists decline to treat most of these patients and recommend total laryngectomy. This is due not only to the decreased efficacy of nonsurgical therapy for T4 tumors, but also because of the poor function of a larynx that has been fully treated but had been destroyed by the cancer prior to treatment.

Side effects of chemoradiotherapy for advanced stage tumors are more severe than for early stage tumors. There is a much higher rate of dysphagia and long-term

feeding tube use in advanced stage tumors [113]. Aspiration and pneumonia are not uncommon after chemoradiotherapy [87], and this risk must be discussed with any patient undergoing nonsurgical therapy for advanced stage laryngeal cancer. Vocal outcomes are often poor. Tracheostomy tubes may be necessary for life. In this sense, organ preservation protocols may allow for the preservation of a non-functional larynx, with obvious detriments to the quality of life in survivors. As an alternative to chemoradiotherapy, the surgical treatment of advanced stage tumors is total laryngectomy, which appears to have equivalent cure rates to non-surgical treatment. Therefore, the predictable sequelae of laryngectomy must be weighed against the less predictable long-term sequelae of chemoradiation protocols when making treatment decisions.

18.6.4 Surgical Treatment – Early Stage Laryngeal Cancer

Cure rates for single modality treatment of early stage laryngeal cancers using surgery or radiotherapy appear to be equivalent [114]. Treatment decisions depend on the tumor location and stage, abilities and training of the treating physicians, patient comorbidities, and patient and physician preferences.

18.6.4.1 Endoscopic Surgery

Endoscopic surgery is accomplished through a laryngoscope, without the need for external incisions. Typically, this surgery is accomplished with a carbon dioxide (CO2) laser attached to a microscope [115]. The laser performs precise cuts through the mucosa and laryngeal tissues with a cutting mode, and allows for hemostasis through a coagulation mode. While traditional "open" cancer surgeries remove tumors *en bloc*, endoscopic CO_2 laser resections are often performed in a piecemeal fashion, cutting and removing portions of the tumor at a time, allowing the microscopic view to delineate the margin between healthy and diseased tissues. Studies are underway regarding the use of the surgical robot to perform TORS for certain supraglottic tumors, rather than the laser and microscope [116].

Wounds are left to heal by secondary intention, and sensate mucosa re-lines the defect within weeks. Tracheotomy can be avoided in almost all cases. Depending on the size and location of the surgical defect, patients may experience some aspiration while healing. Swallow therapy is initiated early to enhance protective mechanisms so patients may learn to swallow effectively without aspiration.

Early stage tumors of the larynx are good candidates for endoscopic management. Larger, more advanced stage tumors are better served with open procedures, except in the hands of the most experienced laser surgeons [117]. Patients with poor mouth opening, poor ability to expose the entire larynx, inability to extend the neck fully, or other anatomic limitations may not be able to be treated with endoscopic surgery. Certain locations of small tumors (e.g., the anterior commissure,

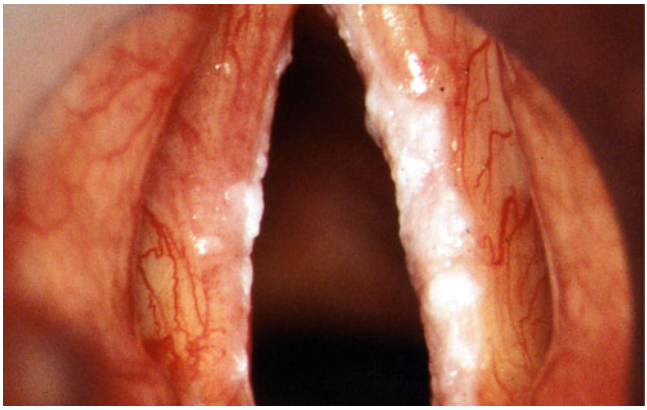

Fig. 18.16 Endoscopic view of early stage right true vocal cord squamous cell carcinoma. This was treated with CO2 laser resection. Leukoplakia on the left true vocal cord was benign and resolved spontaneously

the inferior aspect of the epiglottis) are difficult to expose and therefore may not be able to be excised with endoscopic laser techniques.

Tumors of the glottis are often discovered at an early stage, as patients develop hoarseness with even very small tumors, leading to early diagnosis (Fig. 18.16). Endoscopic resection of tumors of the true vocal cord can be performed with narrow margins, preserving uninvolved portions. Following resection of very superficial tumors, patients' voices may return to normal [118]. For patients requiring more extensive resection of the vocal cord, permanent hoarseness can be expected. Swallowing function is usually unaffected.

Small tumors of the supraglottis may be amenable for endoscopic management, depending on their location and ability to expose the entire tumor endoscopically. In these cases, the final voice outcome is usually completely normal. Swallowing function returns to normal in most patients but requires intensive swallow therapy, depending on the size and location of the defect [119]. Bilateral neck dissection is recommended for supraglottic tumors, and can be done during the same anesthetic as the endoscopic primary tumor resection or, more commonly, as a staged procedure a week or two later.

18.6.4.2 Open Surgery

For patients with small laryngeal tumors who desire surgery but are not candidates for endoscopic management, open laryngeal conservation surgeries are available. These are obviously more invasive than endoscopic techniques, requiring external incisions, placement of a tracheotomy tube, and prolonged return of swallowing function. When indicated, neck dissection can be performed during the same procedure, utilizing the same incision as these open surgeries.

Vertical partial laryngectomy, also termed vertical hemilaryngectomy, can be performed for T1 and T2 tumors of the glottis, and some select T3 tumors [120]. This involves entering the larynx externally through incisions in the thyroid cartilage. The portion of the thyroid cartilage underlying the tumor is then removed with the tumor and a margin of healthy laryngeal soft tissues surrounding the tumor. Using local muscle flaps, the missing portion of the larynx can be reconstructed.

Supracricoid partial laryngectomy is another conservation surgery that may be appropriate for glottic or some smaller supraglottic tumors. In this surgery, the entire thyroid cartilage is removed with both true vocal folds, both false vocal folds, and part or all of the epiglottis. The arytenoids and cricoid cartilage are preserved, and are sutured superiorly to the hyoid bone to complete the reconstruction [121].

Another option for supraglottic cancer is the horizontal partial laryngectomy, also termed open supraglottic laryngectomy [122]. In this surgery, a horizontal incision is made through the thyroid cartilage. The ventricle between the true and false vocal cords is incised, and the superior portion of the thyroid cartilage is removed along with the hyoid bone, epiglottis, aryepiglottic folds, and false vocal folds. Reconstruction is performed by suturing the lower portion of the thyroid cartilage superiorly up to the tongue base.

Patients undergoing laryngeal conservation surgery must have adequate pulmonary reserve and a strong cough, as aspiration is a near-certainty during the healing phase [123]. If surgical therapy is decided upon and the patient is not a candidate for any of the open or endoscopic procedures, a total laryngectomy may be the appropriate surgical option, even for small tumors.

18.6.5 Surgical Treatment – Advanced Stage Laryngeal Cancer

18.6.5.1 Total Laryngectomy

There are rare T3 or T4 tumors of the larynx that may be amenable to laryngeal conservation surgery. Otherwise, the surgical treatment of choice is a total laryngectomy. Patients who have failed radiotherapy for advanced stage tumors require total laryngectomy, termed "salvage laryngectomy." Occasionally, total laryngectomy may be required for diagnoses other than squamous cell cancer, such as severe chronic aspiration or advanced invasive thyroid carcinoma [124].

Following neck dissection as indicated, the larynx and trachea are skeletonized from the surrounding musculature and soft tissues. The larynx is divided off the superior portion of the trachea, and the trachea is sewn to a circular incision in the lower neck skin, creating a "stoma." The surgeon then removes the hyoid bone, thyroid cartilage, and cricoid cartilage, along with the internal structures of the larynx, separating these from the pharynx and cervical esophagus (Fig. 18.17). The resulting defect in the pharynx is then sutured, creating a "neopharynx."

Complications from this procedure are not uncommon, especially in irradiated patients undergoing salvage laryngectomy [125]. Failure of the neopharynx to heal

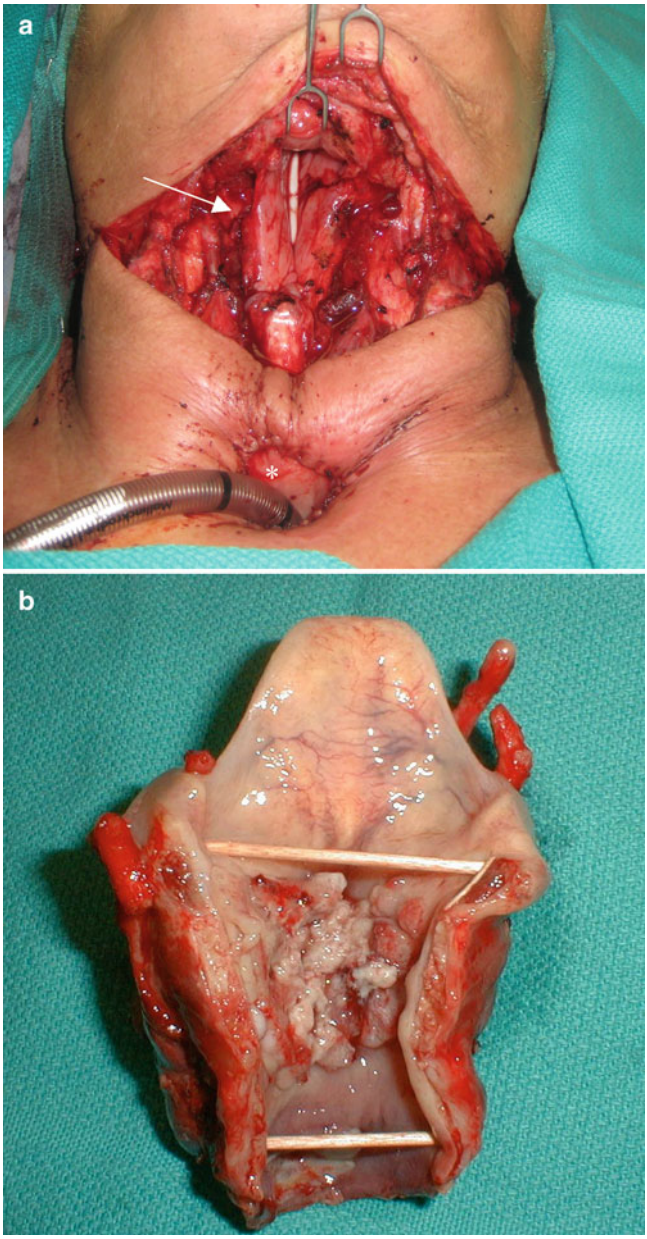

Fig. 18.17 (**a**) Surgical defect following total laryngectomy and bilateral neck dissection. The trachea is sewn to the lower neck skin to create a "stoma" (*), and the tissues of the pharynx (*arrow*) are sewn together. (**b**) Total laryngectomy specimen, posterior view. Large tumor can be seen involving bilateral false and true vocal cords

appropriately may lead to fistula, in which oral secretions exit the pharynx into the neck, and exit through the skin incision. This usually heals without consequence if recognized and treated appropriately. A laryngectomy effectively separates the respiratory tract from the alimentary tract. After healing, patients resume a normal diet without fear of aspiration. The obvious major sequela of total laryngectomy is the loss of vocal communication.

Vocal rehabilitation after total laryngectomy has evolved over the decades, and three options are currently available for patients [126]. The first, an electrolarynx, is a battery-powered handheld device that vibrates the tissues of the neck or mouth to create a mechanical sound. Although easy to learn, the mechanical quality of the sound produced may be unsatisfactory to some patients. Esophageal speech is another option. In this method, the patient learns to swallow boluses of air, which can then be "belched" to create vibrations through the pharynx. These vibrations are formed into understandable words. Finally, tracheoesophageal speech can be used. This involves a surgical procedure to create a small tract between the trachea and esophagus. A small one-way valve is then placed into the tract, which, when the stoma is occluded during exhalation, diverts the exhaled air into the pharynx. This air creates vibrations that are formed into words [127]. These latter two options create a deep, gravelly, but more natural sounding voice than the electrolarynx. Not every patient is a candidate for these techniques, either because of physical limitations or ability to learn the maneuvers.

18.7 Cancer of the Hypopharynx

18.7.1 Introduction

Squamous cell cancer of the hypopharynx is thankfully rarer than most other head and neck cancer sites [128]. Hypopharyngeal cancer has a notoriously poor prognosis, with frequent regional and distant metastases. These tumors behave aggressively, and are often diagnosed at a late stage [129]. Most patients with hypopharyngeal cancer have a history of tobacco use, often with heavy alcohol use as well.

The hypopharynx includes the mucosa surrounding the larynx, extending from the level of the oropharynx down to the cervical esophagus. The three anatomic subsites of the hypopharynx are the bilateral piriform sinuses (located between the aryepiglottic folds and the thyroid cartilage), the posterior pharyngeal wall, and the postcricoid mucosa (at the entrance of the cervical esophagus).

18.7.2 Evaluation

Symptoms of hypopharyngeal cancer are vague and often insidious in nature. Early symptoms may include dysphagia, foreign-body sensation, sore throat, and otalgia

(referred ear pain). At early stages, physical examination is usually normal, leading to a delay in diagnosis. As tumors progress, patients may develop a palpable cervical lymph node, hoarseness, weight loss, and in very sizable tumors, airway obstruction.

Physical exam should include assessment of the overall functional and nutritional status of the patient. A complete head and neck physical examination may be normal, as evaluation of the hypopharynx can be difficult. Office endoscopy is usually required to detect these tumors, revealing a granular or ulcerative lesion, or in some cases only pooled saliva and secretions. Assessment of the mobility of the vocal cords is imperative for staging of the cancer.

Evaluation via laryngoscopy in the operating room allows for complete mapping of the tumor. Biopsies can be performed for tissue diagnosis. Imaging studies (typically CT, PET, and/or MRI) are examined to determine complete extent of the tumor. Hypopharynx tumors are notorious for submucosal extension beyond what can be appreciated during endoscopy [130]. The presence of obvious regional or distant metastases can be assessed.

18.7.3 Nonsurgical Treatment

In most treatment centers, surgery (laryngopharyngectomy) is the most commonly recommended treatment for hypopharyngeal cancers. For early-stage hypopharyngeal tumors, radiation or chemoradiation protocols appear to be a reasonable alternative to surgery, with good local control and laryngeal preservation rates [131]. More advanced tumors are better served with surgery followed by adjuvant radiotherapy or chemoradiotherapy, though some patients are unable or unwilling to undergo surgery. Cure rates and functional status for these patients are poor with non-surgical therapy. Rates of hypopharyngeal stenosis with resultant dysphagia and aspiration are high [132]. While the voice is preserved, the high rate of aspiration and stenosis render a significant number of patients unable to eat [133]. With that in mind, at the author's institution, chemoradiotherapy is only recommended to patients with advanced hypopharyngeal cancer who are unfit for an aggressive surgery or find the sequelae of laryngopharyngectomy unacceptable.

18.7.4 Surgical Treatment

Early stage tumors of the hypopharynx are rarely encountered, as diagnosis is not usually made until the tumor is at an advanced stage. Thus laryngeal conservation surgeries for hypopharyngeal cancer are much more rarely used than for laryngeal cancer. Surgical options for smaller hypopharyngeal tumors are similar to those for supraglottic cancer. Endoscopic CO2 laser resection has been reported (Fig. 18.18), but studies are limited to surgeons with a great deal of experience with endoscopic

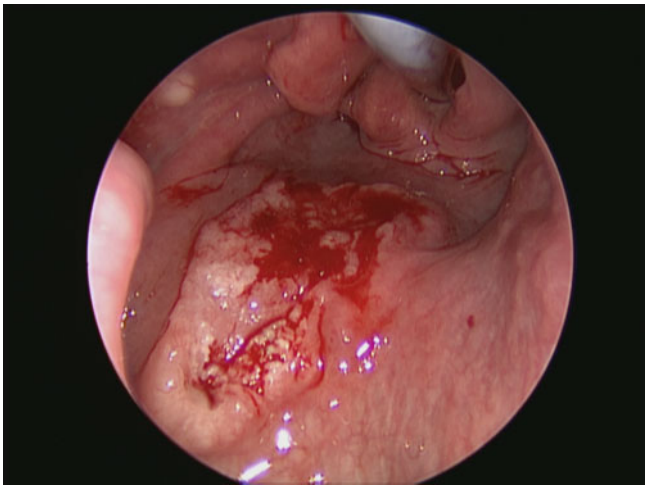

Fig. 18.18 Endoscopic view of a T2 squamous cell cancer of the left posterior pharyngeal wall. This was treated with endoscopic CO2 laser microsurgery and bilateral neck dissection. The patient is disease-free 3 years after surgery

techniques, and this technique is rarely used in the U.S. [134]. A variety of partial laryngectomy procedures with extension laterally to include resection of the piriform sinus (partial laryngopharyngectomy) have been reported, with good local control rates [135]. Prolonged dysphagia and significant aspiration can be expected, requiring patients to have excellent pulmonary reserve.

The most commonly performed surgery for patients with poor pulmonary reserve or with advanced stage tumors is a total laryngectomy with partial pharyngectomy. Even if the mucosa of the larynx may be uninvolved by tumor, most piriform sinus tumors encroach on the aryepiglottic folds or paraglottic space, requiring resection of the entire larynx. The extent of pharyngeal resection depends on the location and size of the tumor. Given the propensity for submucosal spread, most surgeons resect generous margins of pharyngeal mucosa surrounding the tumor (Fig. 18.19). Direct closure of the neopharynx is possible, but may result in a very narrow lumen, making swallowing impossible except for liquids. With that in mind, the pharyngeal defect is often closed with a reconstructive flap, either a pectoralis major flap or a free tissue transfer.

Special mention should be made regarding tumors that involve the postcricoid region or that circumferentially involve the entire hypopharynx. These tumors require a total laryngopharyngectomy, i.e., removal of the entire larynx and pharynx, extending from the level of the tongue base and tonsils down to the cervical esophagus. The swallowing conduit must be restored with free tissue transfer. Options include a rectangle-shaped skin flap (e.g. from the forearm or thigh) folded into a tube, or a segment of jejunum [136].

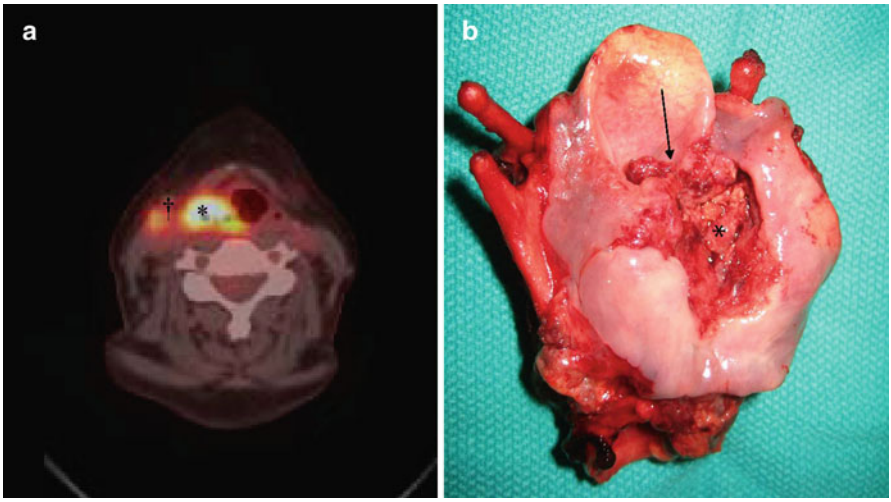

Fig. 18.19 (**a**) PET scan of a patient with large right hypopharyngeal cancer (*) with involvement of right neck lymph node (†). (**b**) Surgical specimen following total laryngopharyngectomy. Hypopharyngeal tumor (*) extends over aryepiglottic fold (*arrow*) to involve supraglottis. The patient underwent bilateral neck dissection and reconstruction of the pharynx with a radial forearm free flap

18.8 Cancer of the Nasopharynx

18.8.1 Introduction

Nasopharyngeal cancer is a rare tumor in the U.S., but is more common in certain populations, for example, in immigrants from China and their descendants [137]. The Epstein – Barr virus (EBV) is strongly associated with nasopharyngeal carcinoma, and appears to be involved in the pathogenesis of most of these tumors [138]. Tobacco and alcohol abuse do not appear to be strong risk factors.

The World Health Organization (WHO) classifies nasopharyngeal carcinoma into three subtypes, based on histopathology: keratinizing squamous cell carcinoma, differentiated nonkeratinizing carcinoma, and undifferentiated carcinoma. The latter two subtypes have a better prognosis than the first [139].

18.8.2 Evaluation

A patient with nasopharyngeal cancer may present with a variety of symptoms. The most common presentation is a neck mass, most frequently in level II or V [139]. Bilateral metastases are not uncommon. Nasal symptoms may be present, including

epistaxis or bloody nasal secretions, and for larger tumors, nasal obstruction. If a nasopharyngeal tumor obstructs the Eustachian tube, patients may develop a middle ear effusion and conductive hearing loss, which is occasionally the presenting symptom. Advanced stage tumors may invade the skull base and local structures, resulting in headaches or cranial nerve deficits.

Physical examination of a patient with nasopharyngeal carcinoma should include careful palpation of the cervical lymph nodes. Other physical findings may include a hyponasal voice, cranial nerve deficits, and a middle ear effusion. Examination of the nasopharynx requires endoscopy, which can be performed in the office with topical anesthesia. Suspicious masses can be biopsied in the office.

Imaging is a necessity to evaluate the extent of primary tumor invasion and cervical lymphadenopathy. CT and MRI are most frequently utilized.

18.8.3 Nonsurgical Treatment

The deep central location of the nasopharynx and the intimate relationship with vital structures, such as the carotid arteries, cavernous sinus, and cranial nerves, make surgery for nasopharyngeal cancer extremely difficult. The mainstay of treatment of nasopharyngeal cancer is therefore either radiotherapy or combined chemoradiotherapy protocols [140]. Thankfully, most nasopharyngeal carcinomas are sensitive to radiation and respond very well. For the most part, IMRT techniques are used to limit doses to nearby structures such as the pituitary gland, brainstem, spinal cord, and parotid gland [141].

For disease that recurs in the nasopharynx following radiotherapy or chemoradiotherapy, a second course of radiotherapy is usually possible [142]. A second course is not surprisingly associated with a higher rate of toxic side effects.

18.8.4 Surgical Treatment

For the most part, surgery for nasopharyngeal cancer is limited to cases of recurrence after prior irradiation. Residual or recurrent disease in the cervical lymph nodes can be treated in a straightforward manner with a neck dissection. Addressing disease in the nasopharynx requires complex surgical approaches to allow visualization and manipulation of these tumors.

Anterior surgical approaches may include dislocation of the palate ("transpalatal" approach) or the entire maxilla ("maxillary swing" approach) [143]. Alternatively, skilled surgeons may proceed from laterally through the mastoid and infratemporal fossa to access the nasopharynx [144]. Minimally invasive approaches utilizing the surgical robot have been reported, which appears to be feasible in selected tumors [145].

18.9 Cancer of the Nasal Cavity and Paranasal Sinuses

18.9.1 Introduction

Cancers of the nasal cavity and paranasal sinuses are rare, comprising about 3% of head and neck cancers [146]. Unlike most other sites of head and neck cancer, where squamous cell cancer comprises the vast majority of histopathology, cancers in this location have a diverse range of pathologies. Squamous cell carcinoma is the most common malignancy in the sinonasal cavity, and other epithelial tumors such as adenocarcinoma and adenoid cystic carcinoma are seen here as well. Sinonasal undifferentiated carcinoma and olfactory neuroblastoma (also known as ethesioneuroblastoma) are tumors unique to the sinonasal cavity. Other very rare tumors occasionally seen in the nose and sinuses include lymphomas, mucosal melanomas, sarcomas, and metastases from other sites. These tumors have differing prognoses and clinical behaviors [147].

Risk factors for nasal and sinus cancers include tobacco abuse and occupational exposures to wood dust, nickel, formaldehyde, and other industrial chemicals [148].

18.9.2 Evaluation

Symptoms of the primary tumor depend on its location, size, and extent of invasion. Early tumors may be asymptomatic or have vague nonspecific symptoms mistaken for rhinitis or sinusitis. Patients with nasal tumors may have epistaxis, nasal obstruction, or anosmia (inability to smell). Tumors in the paranasal sinuses may cause pain in the affected sinus, numbness of the facial skin or other cranial nerve manifestations, or orbital symptoms. Patients may have diplopia (double vision), blurred vision, or proptosis of the globe.

Physical examination should include careful palpation of the cervical lymph nodes. Cranial nerve examination must be thorough. Any patient with a tumor involving the orbit should undergo detailed ophthalmologic examination. Nasal endoscopy in the office can yield important information regarding the location and extent of the tumor. Biopsies of sinonasal masses are not recommended in the office setting unless prior imaging has been performed to help prevent uncontrollable epistaxis with vascular tumors or cerebrospinal fluid (CSF) leak with lesions such as encephalocele [149].

For most sinonasal malignancies, both CT and MRI are recommended (Fig. 18.20). The complementary information they provide is critical to determining the extent of the tumor and in treatment planning 548[150].

18.9.3 Nonsurgical Treatment

For the most part, surgery is the mainstay of treatment for sinonasal tumors. Radiotherapy or chemoradiotherapy are typically used in the adjuvant or neo-adjuvant

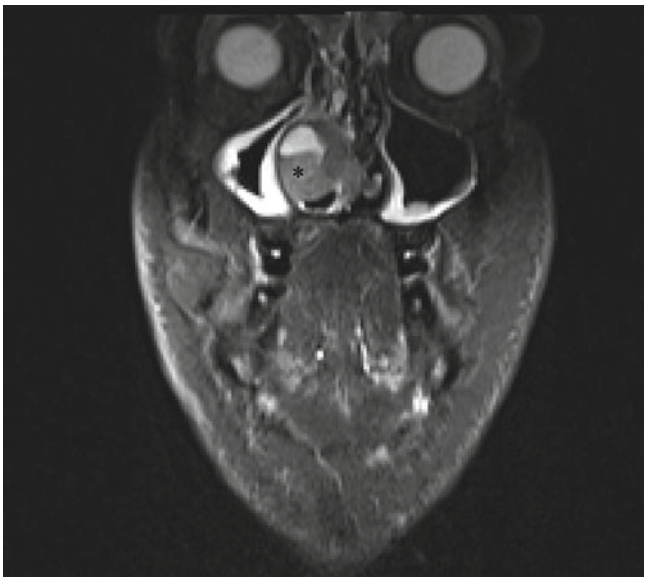

Fig. 18.20 MRI of a patient with an adenocarcinoma of the right sinonasal cavity (*)

setting [151, 152]. Patients unable or unwilling to undergo surgery may be offered nonsurgical therapy, but should understand that this is not the standard of care.

18.9.4 Surgical Treatment

The surgical approach required to extirpate a sinonasal cancer depends on the size, location, and extent of invasion of the tumor. A variety of approaches exist.

For anterior nasal tumors involving the nasal skin, a partial or total rhinectomy may be required. Reconstruction of the nose may be accomplished with local skin flaps, cartilage grafts, or in the case of total rhinectomy, a latex nasal prosthesis. A lateral rhinotomy involves an incision along the nasofacial junction, allowing the nose to be reflected medially and the cheek skin laterally, thus exposing the nasal cavity and lateral nasal wall. This skin incision may be extended through the upper lip and under the lower eyelid, which allows the entire cheek skin to be reflected laterally and exposes the entire hard palate, maxilla, and orbital walls [153].

A craniofacial approach is utilized for tumors at the roof of the nasal cavity or in the frontal sinuses. Performed in conjunction with a neurosurgeon, a craniotomy is performed in the anterior skull, allowing the frontal lobe of the brain to be retracted superiorly and exposing the roof of the nasal cavity from above. The head and neck surgeon can then access the tumor from the nasal cavity and the two surgeons

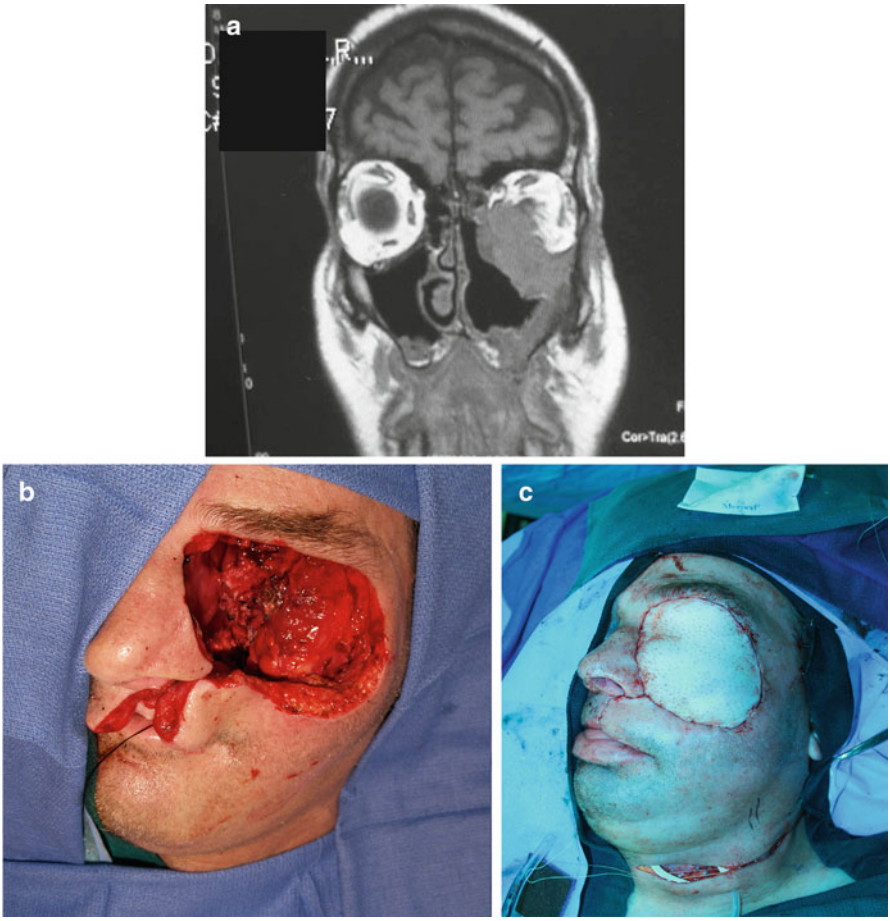

Fig. 18.21 (**a**) MRI of a patient with squamous cell carcinoma of the left maxilla, invading into the left orbit. (**b**) Surgical resection required a total maxillectomy with orbital exenteration and removal of left cheek skin. (**c**) Reconstruction using anterolateral thigh free flap. Skin from the thigh was used to reconstruct the hard palate defect and external skin defect

make necessary bone cuts to extirpate the disease with adequate margins. Tissue is interposed between the brain and the nasal cavity to help prevent CSF leak and meningitis [154].

Reconstruction of these defects depends on the extent of the resection. For example, if the floor of the maxilla is excised, a bony or soft tissue flap may separate the oral cavity from the nose, or a specially designed upper denture plate may be used. If the floor of the orbit is resected, a bone flap or bone graft or polyethylene implants are necessary to prevent descent of the orbital contents with disfigurement and diplopia. If the entire contents of the orbit are resected, the orbital cavity may be filled with soft tissue (Fig. 18.21), or skin grafted with a prosthesis used to fill

the cavity and give a more natural appearance [155]. Other defects may not need reconstruction, for example after simple resections of the nasal septum or lateral nasal wall.

An approach currently undergoing extensive study is the endoscopic resection of select nasal and paranasal sinus tumors [156]. This is accomplished using operating telescopes and endoscopic instruments. Facial incisions are avoided when this technique is utilized. Indications for tumors that may be appropriate for such approaches are being defined as the experience with this approach grows.

When neck lymph node metastases are noted pre-operatively, neck dissection should be performed [157]. The risk of occult nodal metastases varies with the histopathology, but in general, elective neck dissection for the N0 neck is not typically recommended.

18.10 Cancer of the Salivary Glands

18.10.1 Introduction

Salivary gland cancers are rare, accounting for about 5% of head and neck cancers [158]. They comprise a heterogeneous group of tumors, with varying clinical behavior and prognosis. Salivary glands are categorized as major salivary glands (the parotid, submandibular, and sublingual glands), and minor salivary glands (microscopic glands distributed throughout the upper aerodigestive tract).

There are over 20 described malignancies of the salivary glands. The most common are mucoepidermoid carcinoma, adenoid cystic carcinoma, adenocarcinoma, carcinoma-ex-pleomorphic adenoma, acinic cell carcinoma, and squamous cell carcinoma. This group makes up 97% of salivary gland cancers, with the remaining 3% representing very rare pathologies [159].

18.10.2 Evaluation

Most salivary gland cancers are detected by the patient as a palpable mass, although some are detected as incidental findings on imaging performed for unrelated reasons. Benign salivary neoplasms are common, and some symptoms may raise the suspicion for malignancy, including pain, rapid growth, fixation to the overlying skin or surrounding tissues, and cranial nerve deficits. A history of facial or scalp skin cancer in a patient with a parotid mass should raise the suspicion for a metastasis from the skin cancer to an intra-parotid lymph node. Minor salivary gland tumors in the mouth may present as a smooth submucosal nodule or as an ulcerative lesion. Facial skin or palatal numbness may be indicative of perineural invasion.

During a complete head and neck physical examination, particular focus should be given to the cranial nerves. For parotid malignancy, facial nerve function should be carefully documented. Characteristics of the tumors, including fixation to skin or surrounding tissues, tenderness, and the presence of smooth vs. vague borders, may give some indication as to the aggressiveness of these tumors. Careful examination of the cervical lymph nodes is crucial.

Imaging studies are as important in salivary gland cancers as in other head and neck malignancies. MRI offers superior delineation of the soft tissues of the head and neck, and may be able to demonstrate perineural spread. CT is especially useful if bony invasion is suspected.

Biopsy via FNA in the office is usually the preferred method of tissue diagnosis. If this is unsuccessful, open incisional biopsy may be necessary. Occasionally, following a surgery for presumed benign neoplasm, a malignancy is discovered on pathologic evaluation.

18.10.3 Nonsurgical Treatment

Surgery, often followed by adjuvant radiotherapy, is the standard of care for salivary gland cancers [15]. Radiotherapy may be utilized as primary treatment for patients who are unable to undergo extensive surgery or for unresectable tumors.

Certain pathologic features from surgery have been established as high-risk features, and adjuvant radiotherapy is recommended when these are seen. These features include cancers with high-grade histology, T3 or T4 tumors, presence of nodal metastases, perineural invasion, positive margins, and extraglandular extension [160]. Studies demonstrating effectiveness of chemotherapy in these tumors have not been published, presumably due to the rare occurrence of these cancers.

18.10.4 Surgical Treatment

The primary treatment modality for salivary gland tumors is surgical resection. Parotidectomy is the standard surgery for parotid gland malignancies (Fig. 18.22). This may be limited to a superficial parotidectomy (removal of the portion of the gland lateral to the facial nerve) or may necessitate total parotidectomy (removal of superficial and deep lobes). Special attention is paid to the facial nerve, and efforts are made to preserve this nerve if possible. Branches of the facial nerve with obvious invasion by the tumor are sacrificed. Obtaining a clear margin may necessitate tracing the facial nerve proximally through the mastoid bone into the skull base. If stumps of a sacrificed nerve are shown to be free of cancer, a nerve graft can be sewn [161]. Extensive malignancies may require sacrifice of overlying facial skin or underlying mandible or zygoma, with reconstruction as needed (Fig. 18.23)

For submandibular gland tumors, complete resection of the submandibular gland is performed. Nerves in the proximity of this gland included the marginal mandibular

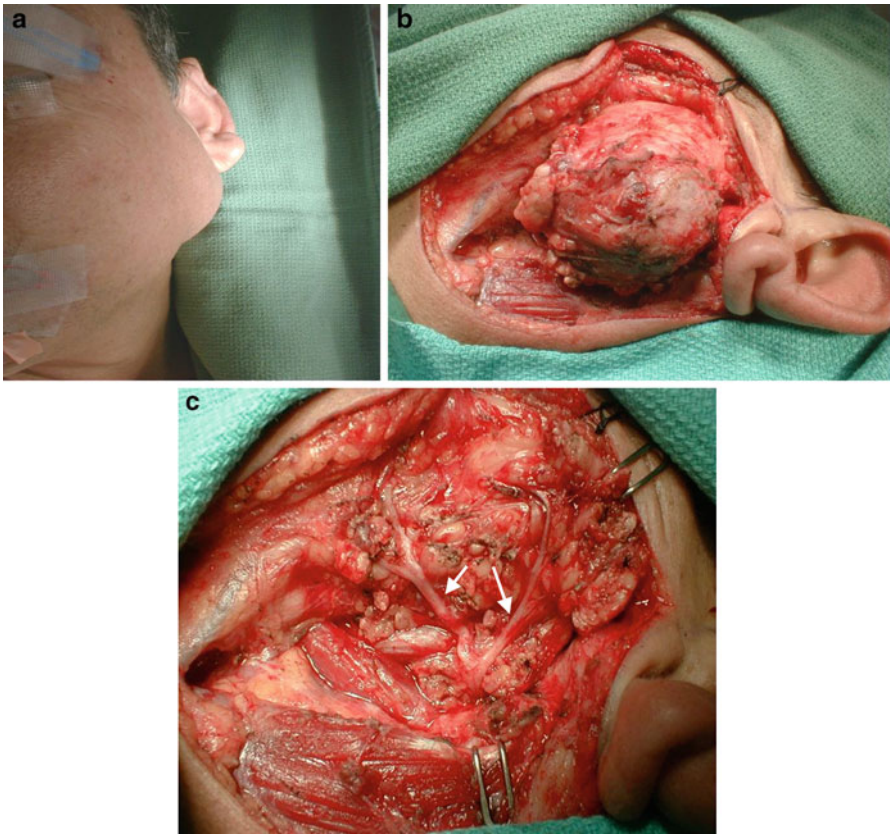

Fig. 18.22 (**a**) Preoperative appearance of left parotid tumor. (**b**) Exposure of left parotid tumor. (**c**) Surgical defect following superficial parotidectomy. Note branches of the facial nerve (*arrows*), which were dissected free from the overlying tumor and able to be preserved

branch of the facial nerve, the lingual nerve, and the hypoglossal nerve; these are sacrificed and grafted as needed. Sublingual gland tumors likewise necessitate removal of the entire gland, usually performed through the mouth. The lingual nerve lies adjacent to this gland and is at risk during this procedure.

For minor salivary gland tumors, surgery depends on the location and extension of the disease. Smaller tumors may be excised with minimal difficulty. Larger tumors typically require a radical resection. This may involve removal of the mandible, maxilla, tongue, lip, or other structures, depending on the tumor in question.

Neck dissection is performed for any clinically positive nodes. Smaller, low-grade tumors do not require elective neck dissections. Higher grade or larger tumors, or those involvement of cranial nerves or overlying skin, have been shown to have high rates of occult lymph node involvement. For these tumors, then, elective neck dissection is warranted [162].

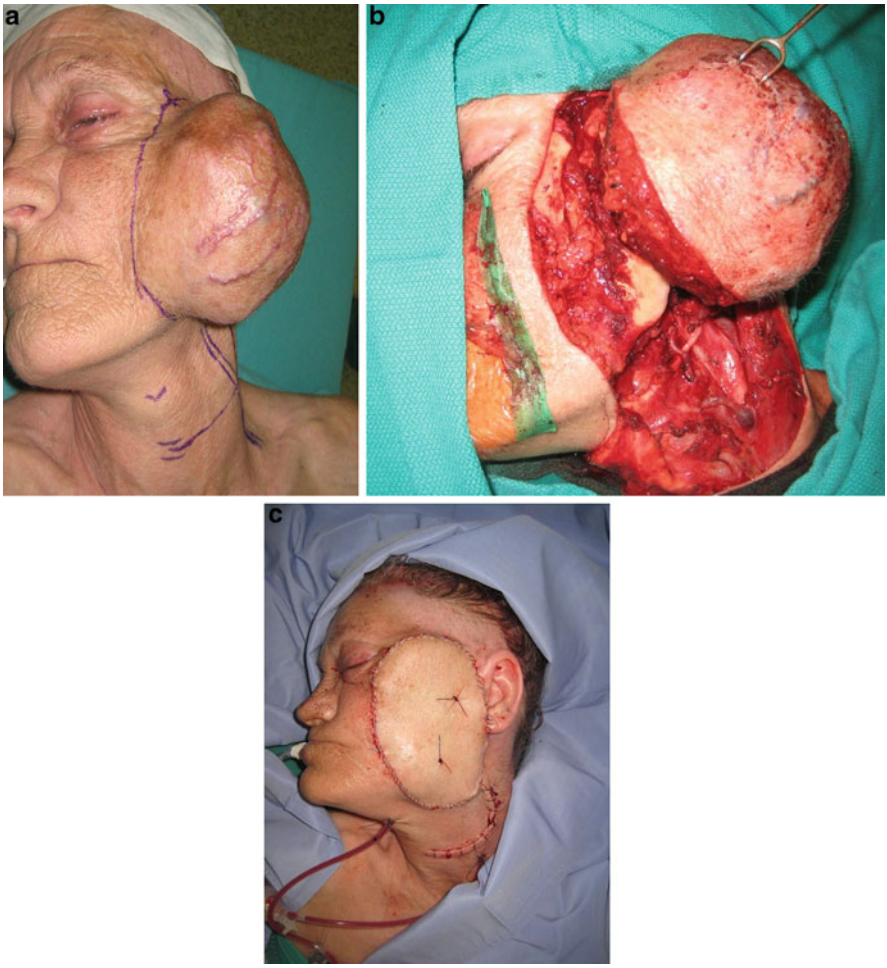

Fig. 18.23 (**a**) Preoperative appearance of large neglected carcinoma-ex-pleomorphic adenoma of the left parotid gland. The patient had facial nerve paralysis prior to surgery. (**b**) Surgical resection required modified radical neck dissection, removal of zygoma, and sacrifice of facial nerve and cheek skin. (**c**) Postoperative appearance following reconstruction of facial skin and soft tissue with anterolateral thigh free flap

18.11 Conclusion

Head and neck cancer treatment has undergone considerable changes over the last few decades. Significant advances in nonsurgical therapies have resulted in major paradigm shifts for the treatment of these cancers. The recognition of HPV as a causative factor in oropharyngeal cancer and the study of the ongoing epidemic of these cancers have been remarkable. Development of free tissue transfer has allowed

preservation of appearance and function following aggressive resection of very advanced tumors. New techniques, such as endoscopic skull base surgery and TORS, are being investigated actively and hold considerable promise.

Future areas of research include further applications of minimally invasive techniques, delineation of appropriate candidates for less toxic chemoradiation protocols, use of newer imaging techniques for diagnosis and surveillance, and usefulness of sentinel lymph node biopsies. Cancer survivorship refers to the quality of life following curative therapy for head and neck cancer. A great number of studies are underway comparing quality of life outcomes in patients treated with different modalities. While the different modalities may have equivalent oncologic outcomes, treatment decisions may rest on the ability to provide survivors with the best outcomes related to speech, swallowing, appearance, and overall quality of life.

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Chapter 19
Diagnostic Imaging Considerations

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Contents

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Abstract This chapter summarizes a review of previous and current knowledge of diagnostic imaging modalities of head and neck cancer. A quick analysis of each modality will be presented. Recent modalities like positron emission tomography – computed tomography PET-CT, Magnetic resonance imaging (MRI) will be discussed with more details through case presentations. The role of imaging in treatment planning and post-treatment outcomes will also be highlighted.

Keywords Head and neck cancer • Imaging modalities • Lymph node metastasis • Treatment plan • Prognosis

Abbreviations

PET-CT	Positron emission tomography – computed tomography
MRI	Magnetic resonance imaging
USG	Ultrasonography
PACS	Picture archiving and communication system

FNAC	Fine needle aspiration cytology
LN	Lymph node
DW	Diffusion weighted
MIP	Maximum intensity projection
HNSCCA	Head and neck squamous cell carcinoma

19.1 Introduction

Diagnostic imaging is of great significance in the management of head and neck cancer patients. Treatment planning and prognosis depend heavily on imaging findings in addition to clinical and histopathological findings. A multi-disciplinary team of oncologists, radiologists, and surgeons work together, to plan the best treatment choices that are available for the patient. Accurate localization of a suspected malignant tumor and early detection of metastatic lymph nodes has a great impact in predicting the prognosis as well as in the choice and extent of therapy. Therefore, radiology not only plays a primary role in detecting the tumor, but also it helps monitoring the response to therapy during and after treatment [1]. Imaging may also provide important clues to the diagnosis when representative biopsies are difficult to obtain in deeply located lesions or when located in close relation to vital structures. These findings can profoundly influence the staging and management of patients with head and neck cancer. Finally, imaging may be used to detect recurrent or persistent disease before it becomes clinically evident, possibly with a better chance for successful retreatment. The single most important factor in the optimal use of all this information is the joint co-operation between the radiologist and the physician/ surgeon team in charge of patient care [2].

19.2 Imaging Modalities

The sixth edition of the American Joint Committee, on Cancer staging manual specifically states that “any diagnostic information which contributes to the overall accuracy of the pretreatment assessment should be considered in clinical staging and treatment planning” [3]. Many radiographic modalities are available for evaluation of head and neck cancer. The most commonly used modalities include computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography- computed tomography (PET-CT). The information from cross-sectional imaging is an important component for initial staging and post-treatment evaluation of the patient with head and neck squamous cell carcinoma [4].

In the following text we will give a closer look on the available imaging modalities. Some of these modalities are no longer used in evaluation of head and neck cancer, but knowledge about them is important because it explains the development in technology in diagnostic imaging field.

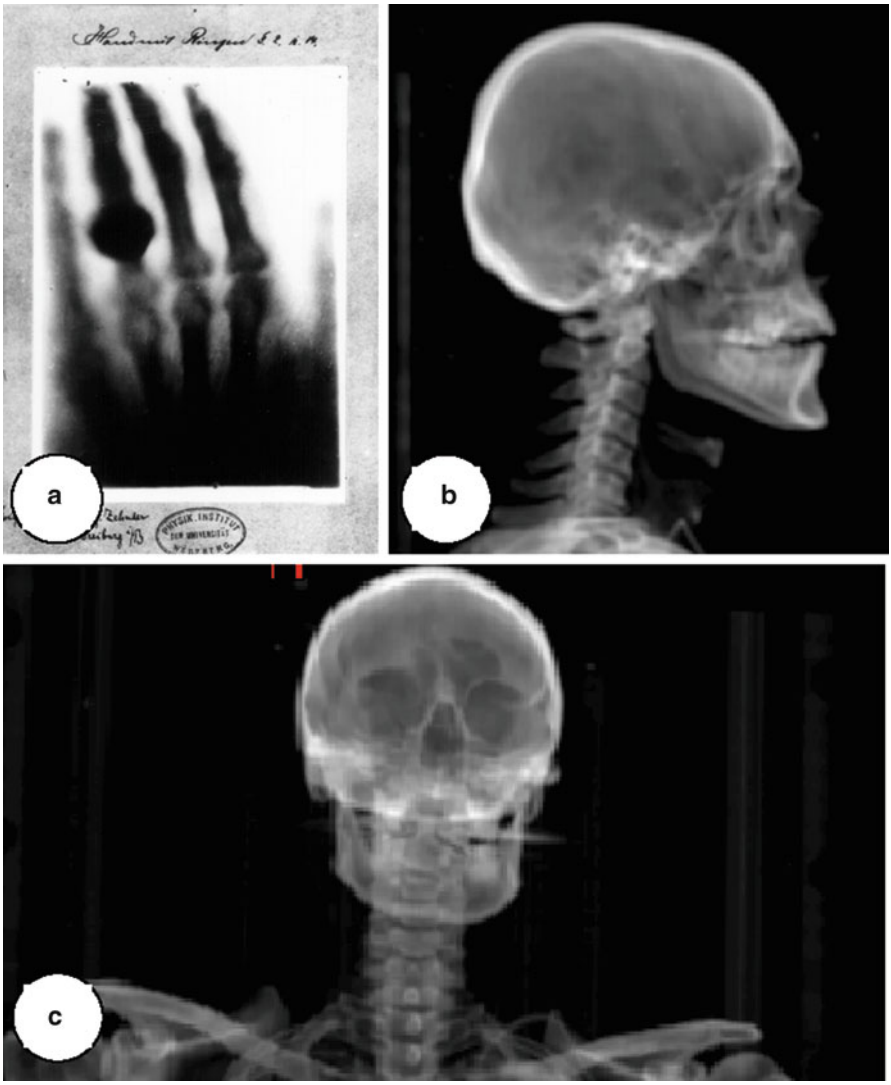

Fig. 19.1 Conventional x-ray images. (**a**) First medical x-ray of Roentgen's wife hand in 1895. (**b**), (**c**) lateral and anterior x-ray views of head and neck

19.2.1 Plain Radiography

There is a long history of the use of the conventional radiography back to 1895 when Conrad Roentgen made the first X-ray film image of his wife's hand (Fig. 19.1a). X-rays are a form of radiant energy that is similar in many ways to visible light. The difference between it and visible light is that they have a very short wavelength and are able to penetrate many substances that are opaque to

light. The X-ray beam is produced by attacking a tungsten target with an electron beam within an x-ray tube [5, 6].

Conventional film radiography uses a screen-film system within a film cassette as the x-ray detector. When X-rays pass through the human body, they get attenuated while passing through body tissues of different densities where absorption and scattering of the beam happens and produce an image pattern on film. The film is then removed from the cassette and developed by chemicals. The final product is an x-ray image of the patient's anatomy on a film [7].

19.2.2 Computed Radiography (CR)

Computed radiography (CR) is a filmless system that eliminates the problem of chemical processing and provides digital radiographic images which is easier to use and store. The same X-ray tube, and exposure control systems used in conventional radiography are still utilized for CR. The only difference is just the use of a phosphor imaging plate for the film screen cassette. The phosphor-coated imaging plate interacts with x-rays transmitted through the patient to capture an image. The digital image is transferred to a computerized picture archiving and communication system (PACS). The PACS stores and sends out digital images via computer networks to give medical care providers in many locations simultaneous direct access to the diagnostic images.

19.2.3 Digital Radiography (DR)

Digital radiography (DR) is a film-free and cassette-free system for capturing X-ray images in digital format. DR substitutes a fixed electronic detector or charge-coupled device for the film screen cassette or phosphor imaging plate. Direct readout detectors produce an immediate DR image. Direct digital image capture is particularly useful for angiography, because it provides rapid digital image subtraction, and for fluoroscopy, because it captures video images with low, continuous levels of radiation [8].

19.2.4 Interpretation of Radiography

The body has different densities, therefore radiography was able to demonstrate these differences into five basic radiographic densities: air, fat, soft tissue, bone, metal, and radiographic contrast media (which are suspensions Iodine and Barium compounds highly attenuate the x-ray beam and are used to outline anatomic structures). The X-ray beam can pass with very little attenuation through air, allowing nearly the full force of the beam to blacken the image. Bone, metal, and radiographic

contrast agents attenuate a large quantity of the x-ray beam, allowing very little radiation through to blacken the image. Thus, bone, metallic objects appear white on radiographs. Fat and soft tissues stand in the middle attenuating intermediate amounts of the x-ray beam, resulting in proportional degrees of image blackening (shades of gray). Thick structures attenuate more radiation than thin structures of the same composition. Anatomic structures are seen on radiographs when they are outlined in whole or in part by tissues of different x-ray attenuation (Fig. 19.1b, c) [9].

In diagnosis of suspicious lesions, plain radiography is considered as a classic or conventional method, which is no longer used particularly in diagnosis of head and neck cancer after the emergence of the modern modalities that provide more accurate anatomical details with high resolution capabilities. As the value of x-ray techniques was very limited to stage head and neck cancer, they are now replaced by cross-sectional imaging modalities. However, plain radiography is still widely used in radiotherapy. Also, a "barium swallow" is still in use after pharyngeal surgery to investigate the presence of fistulae and in evaluating other functional disorders after radiotherapy [2].

19.3 Cross Sectional Imaging

Ultrasonography (USG), Computed tomography (CT) and magnetic resonance imaging (MRI) are techniques that can provide cross-sectional images. These techniques cross-examine a three-dimensional volume or slice of patient tissue to produce a two-dimensional image. The digital images obtained by USG, CT, and MRI examinations are ideal for storage and access on PACS (a computerized picture archiving and communication system).

19.3.1 Ultrasonography

Ultrasound imaging is one of the most important and widely used diagnostic tools in modern medicine. Recently, it has been introduced to the head and neck region to investigate and assess soft tissue swellings. The potential of ultrasound as an imaging modality was discovered in the late 1940s and early 1950s when John Wild and John Reid developed an ultrasonic imaging instrument and were able to reveal the capability of ultrasound for imaging and characterizing cancerous tissues at frequencies as high as 15 MHz. Ultrasonography of the head and neck is mostly used to evaluate soft tissue lesions specially the thyroid gland, salivary glands, and cervical lymph nodes [10].

Ultrasonography in combination with fine needle aspiration cytology (FNAC) is the most accurate method for neck nodal staging in most head and neck cancers [11]. However, execution of this procedure is relatively time consuming, and the obtained results are operator dependent [12].

19.3.1.1 Basic Ultrasound Principles

Sound is a mechanical wave resulting from a vibrating source, such as tuning fork or a string musical instrument. When this source vibrates, adjacent particles in air are displaced. These particles in turn push against other adjacent particles. The constant pushing is known as particle vibration. Ultrasound refers to sound waves beyond the human audible range. Diagnostic applications of ultrasound in the medical field use frequencies of 1–12 MHz. In medical Ultrasound the vibrating source is a ceramic element that vibrates in response to an electrical signal. The vibrating motions of the ceramic element in the transducer cause the particles of the surrounding tissues to vibrate. As the source vibrates, it periodically presses against and pulls away from the adjacent medium with resultant particle compression and expansion (rarefaction) in the medium. This movement of energy through the anatomical structures is called a wave. Patients are examined with a transducer that converts electrical energy into mechanical energy. When the sound beam is directed into the body at various angles; reflection, absorption and scatter change the returning signal to be weaker than the initial impulse [13].

19.3.1.2 Doppler Ultrasound

The first applications of the Doppler principle were in astronomic studies. This principle is still playing a major tool for cosmologic research. Then, other applications started gradually to emerge. Paul Langevin from France developed the first sonar equipment for detecting submarines. He also used piezoelectric crystals for transmitting and receiving ultrasound waves. This technology was used to sense submarines, initially during World War I and more extensively during World War II. Then, development of diagnostic Doppler ultrasound technology emerged. First, it was used in obstetrics and gynecology. Doppler sonography has allowed exploration and understanding of human fetus hemodynamic, which was inaccessible before. The Doppler refers to a change in frequency of a sound wave when either the source or the listener is moving relative to one another. When the source moves toward the listener, the perceived frequency is higher than the emitted frequency. This creates a higher pitched sound. If the sound moves away from the listener, the perceived frequency is lower than the transmitted frequency, and the sound will have a lower pitch. In the medical application of the Doppler principle, the frequency of the reflected sound wave is the same as the frequency transmitted; only if the reflector is stationary. Color Doppler can be used to characterize the maxillofacial soft tissue vascular anomalies (Fig. 19.2) [13, 14, 15].

19.3.1.3 Advantages of Ultrasonography

Ultrasonography has an exclusive and valuable role in imaging the neck region. It can provide excellent and reproducible anatomic images that are safe, comfortable to the patient and inexpensive. The role of ultrasonography has evolved to

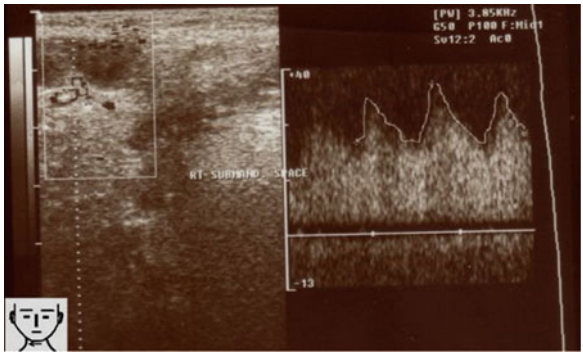

Fig. 19.2 Color Doppler sonogram (displayed in grayscale), with duplex Doppler analysis, depicts a wave form indicative of arterial blood flow signal in the examined area

provide important data in many clinical indications: to determine pathology, volumetric, vascular status, tumor size, and guided fine needle biopsy [16].

Ultrasonography also has some distinctive characteristics that are advantageous in comparison to other competing modalities such as computed tomography (CT) and Magnetic Resonance Imaging (MRI). It is portable, so it can be easily transported to the bedside of a patient. It is a form of a nonionizing radiation and is thought to be safe until now. It can produce images in real time. It has a resolution in the millimeter range, which may be improved if the frequency is increased. It can depict blood flow information by applying the Doppler principle.

19.3.1.4 Limitations of Ultrasonography

Although Ultrasonography has many unique characteristics, it still has some limitations.

- Ultrasonic examination is only through a limited window.
- Organs containing gases and bony structures are hard to be imaged adequately.
- Special training for the radiologist is needed to perform and interpret it.
- Inability to obtain good images from certain types of patients like obese patients.

In summary, air and dense anatomic structures such as bone obstruct evaluation of structures lying deep to them. Skeletal structures are barely accessible if at all with US, at least in the adult [17].

19.3.1.5 Ultrasonography and Cancer Screening

Cancer screening is an examination in subjects who are asymptomatic and generally healthy. It is a group of diagnostic procedures that are frequently done on asymptomatic subjects for early identification of a possible malignancy. Discovering the disease in its early stages can modify the natural history of the cancer and consequently improve the treatment outcomes. Cancer surveillance is usually done for asymptomatic individuals but at high risk to develop malignancy. Both screening and surveillance are considered preventive methods in oncology which can help decreasing the morbidity and mortality rates. Their goal is the prevention/delay, within reasonable

costs and through early diagnosis and treatment. Malignancy development takes place in two phases the preclinical phase, which begins at the time of the biologic development of the disease itself which is followed by a clinical phase that begins with the onset of symptoms. So, Ultrasonography is better than other ionizing techniques such as CT because it is noninvasive and inexpensive [18].

19.3.1.6 Ultrasonography of Cervical Lymph Nodes

The number of lymph nodes in a normal neck is nearly 300 lymph nodes. The pharyngeal nodes tend to be very small in size, usually less than 0.5 cm in their short axis and flattened or oval in the transverse view of the neck. Enlarged lymph nodes are usually due to either inflammation or hyperplasia [19]. High-resolution Ultrasonography shows a white line of fat and intranodal blood vessels running through the center of the lymph node known as a hilar line. The hilar line is present in most benign lymph nodes greater than 0.5 cm and is also more prominent in older patients. A hilar line is hardly seen in malignant lymph nodes. Because lymph node hyperplasia is frequently common in the neck, only those lymph nodes >0.5 cm in the short axis are usually biopsied. Those with a short axis 0.5 cm in the pharyngeal region reaching 0.8 cm in their short axes should have their location marked and be reexamined in 6 months. Metastatic lymph node appearance is generally more rounded in the transverse view with a short/long axis ratio >0.5 cm. Postreatment ultrasound surveillance for cancer is done in the transverse view, since all lymph nodes may appear elongated in the longitudinal view (Fig. 19.3). Another finding of malignancy in addition to a rounded shape and the absence of a hilar line is the position of internal jagular vein which migrates anterior next to the carotid artery in the postoperative neck. Metastatic nodes are commonly located in proximity to the jugular vein or within the carotid sheath; any deviation of the jugular vein away from the carotid artery strongly suggests malignancy. In addition to causing deviation of the internal jugular vein, malignant lymph nodes tend to compress the vein and cause a partial obstruction to blood flow. Benign lymph nodes rarely do this until they become quite large [20].

19.3.1.7 Ultrasonography and Cancer Staging

Treatment planning is principally influenced by the pretreatment staging of the disease. Advanced stages most likely affect the prognosis of the disease which worsens by 50% with advanced stages. In most cases, the treatment of choice in the initial stages is surgical excision of the primary tumor which may be more conservative or more radical depending on the anatomic relation of the tumor to its surrounding structures. The anatomic- pathologic evaluation should involve a reasonable margin of healthy tissue around the excised lesion.

There are several phases of diagnosis that should be followed. This includes (1) the first or initial diagnosis (identification of the lesion and its topographical position), (2) characterization or differential diagnosis of the lesion, in the terms of

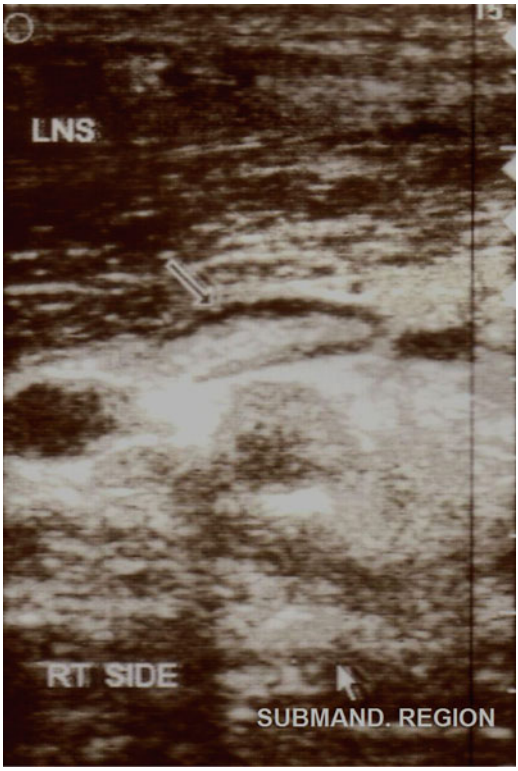

Fig. 19.3 Sonogram shows normal elongated oval shape lymph nodes (LNS) (*arrow*) in the submandibular region

non-tumor vs. tumor, benign vs. malignant and primary vs. metastatic, (3) staging (assessment of the spread of the disease, for diagnosis, treatment and prognosis), (4) treatment plan including surgery, radiotherapy, chemotherapy, combinations between different choices, (5) assessment of response of the tumor during and after therapy (both in the short term for cure and complication judgment and in the long term for follow up and assessment of recurrent lesions). Accurate staging is critical in the patient who will undergo surgical interaction. In early stages, surgical removal of the primary tumor is the treatment of choice. This choice can be more radical or more conservative according to the relation of the tumor to surrounding vital structures and lymph node involvement (metastases). In cases, with locally advanced tumors (locoregional infiltration), palliative surgery and/or cytoreductive surgery may be performed. Tumor debulking, i.e. the removal of more-or-less large parts of the tumor mass, can affect positively the response of systemic or radiation therapy (adjuvant). Sometime starting with chemotherapy and /or radiotherapy (neoadjuvant) before surgery can improve the surgical outcomes and reduce postsurgical complications. In this way curative surgery may be able to obtain a result similar to that of radical surgery but without adjuvant treatment, or it may be possible to eliminate (potential) micrometastases after surgical resection, or to re-evaluate a lesion not initially considered for radical surgery (debulking). In fact, the goal of neoadjuvant treatment is to obtain a downstaging of the tumour [18].

Another modality of Ultrasonography is the endoscopic ultrasound (EUS). It can be used for evaluation of pharyngeal lymph nodes which cannot be examined by external ultrasonographic examination. EUS was used in staging of esophageal cancer. It provided a detailed view of the esophageal wall, helping in determining tumor depth of infiltration, and characterizing lymph nodes as malignant or benign. It was the most accurate modality for regional staging of esophageal cancer and is more accurate than computed tomography and positron emission tomography scan for the characterization of nodal status [21].

19.3.2 Computed Tomography

In 1970, the CT technology was developed. This technology was initially used in brain imaging, and then it was rapidly extended to the whole body. When comparing the conventional radiograph with CT, the difference is that; radiograph capture a whole picture, while CT take several captures in the form of slices where each slice shows the anatomical contents of this section. CT images are produced by a combination of x-rays, computers, and detectors. In the CT unit, the x-ray tube rotates around the patient, and images are produced by exposure to a very thin beam of X-ray. A computer-controlled bed transfers the patient in short increments through the opening in the scanner housing. Each image or slice requires only a few seconds. The thickness of these axial images or slices ranges from 1 to 10 mm depending on the indications of each study. An average CT study takes approximately 10–20 min. As in a radiograph, the amount of the x-ray beam that passes through each slice or section of the patient will be attenuated according to the density of each tissue. However, in CT, the x-ray beam hits the detector instead of film, and the detectors subsequently convert it to an electron stream. This electron stream is digitized (i.e. converted to numbers known as CT units or Hounsfield units); then a computer software converts these numbers to corresponding shades of black, white, and gray which is printed on a film. Dense structures like bone allow only a small amount of x-rays to strike the detectors. The result is a white density on the film. On the other hand, air will absorb little of the x-ray beam, allowing a large number of x-rays to strike the detectors. The result is a black density on the image. Soft tissue structures appear gray on the image (Fig. 19.4a, b).

This CT digital information can be displayed on a video monitor, stored on magnetic tape, transmitted across computer networks, or printed on radiographic film via a format camera.

19.3.2.1 High-Resolution Computed Tomography

High-resolution computed tomography (HRCT) refers to CT studies that result in thin slices that are approximately 1.0–2.0 mm thick.

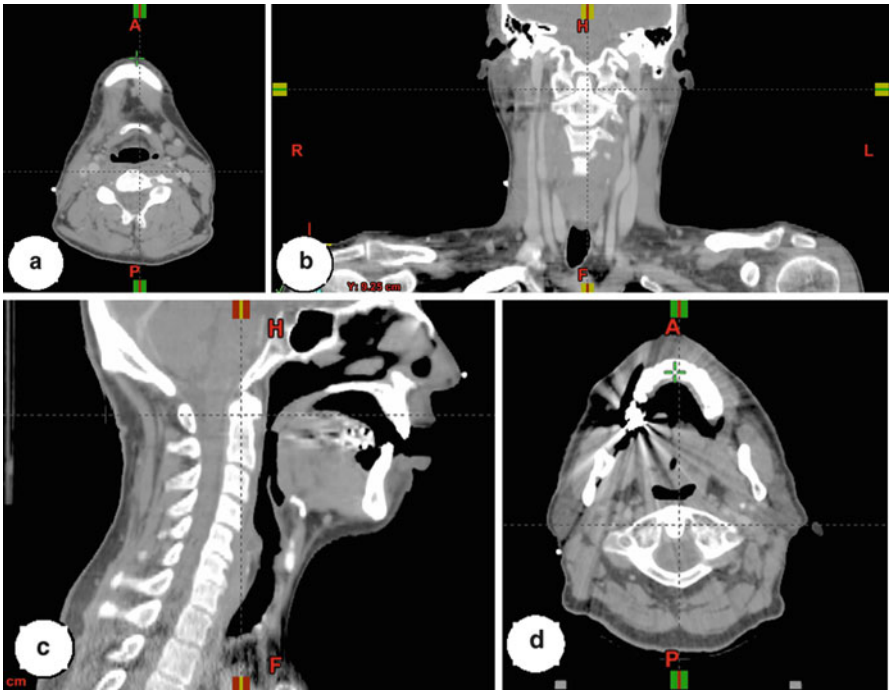

Fig. 19.4 (**a**) Axial contrast-enhanced CT image showing outstanding anatomical details of bony structure and enhanced soft tissue details. (**b**) Coronal CT image showing the anatomical details of the neck in a patient with a T3 N2 right aryepiglottic fold (supraglottic) squamous cell carcinoma. (**c**) MidSagital contrast enhanced CT image showing the anatomical details of head and neck. (**d**) Axial CT image (with contrast agent enhancement) showing an artifact arising from metallic dental restoration fillings (amalgam) which causes rarefaction and inability to evaluate the obtained image

19.3.2.2 Spiral Computed Tomography

Spiral CT imaging is a relatively new development. This technology is similar to standard CT but with a few new twists. In helical or spiral CT, the patient continuously moves through the gantry while the x-ray tube continuously encircles the patient. This combination of the patient and x-ray tube continuous movement results in a spiral configuration. This technology can produce 1 slice per second, and the slice can vary in thickness from 1 to 10 mm. The resolution and contrast of these images are better than standard CT images. In the helical or spiral CT scanner, the x-ray tube continuously circles the patient while the patient couch moves continuously through the opening in the x-ray tube gantry. The combination of continuous patient and x-ray tube movement results in a spiral configuration; hence the name "helical." In a standard CT or nonhelical scanner, the patient couch moves in short increments toward the gantry opening and stops intermittently to allow the x-ray tube to move around the patient. Thus, the x-ray tube moves around the patient only when the couch is stationary.

19.3.2.3 Multislice Computer Tomography

Conventional CT scanners have a single row of detectors; thus only one tomographic slice is generated for each rotation of the x-ray tube around the patient. In multislice CT there are multiple contiguous rows of detectors that yield multiple tomographic slices or images with each rotation of the x-ray tube. There can be as many as 16 detector rows in one CT machine, resulting in reduced acquisition time.

19.3.2.4 Computed Tomographic Angiography

This term refers to imaging of blood vessels using either a multislice or a helical CT scanner. The procedure produces 3-mm slices during the rapid injection of contrast media.

19.3.2.5 Three Dimensional CT Images (3D CT)

This format of CT is usually done to study and evaluate the bony structures of the maxillofacial skeleton. This technique does not show the adjacent soft tissues. In oncologic lesions with extensive bone destruction, 3D display can help the surgeon to determine the outlines the margins of bone resection in relation to the tumour and the normal adjacent tissues [22].

19.3.2.6 Requirements for Optimal CT Diagnostic Study

Patient Positioning

The patient should be comfortably positioned in a supine position during quite respiration. The supine position with slightly extended neck is needed in order to compare symmetric structures. Malposition may result in disease simulating appearance. The patient should be comfortable during the study; this will help the patient, dropping the shoulders to a position as low as possible which is applicable for all indications if multidetector spiral CT (MDCT) is used, as this modality allows retrospective high quality reformatting in every spatial plane.

Contrast Agent Injection

CT imaging is accomplished with and/or without intravenously injected contrast media. The intravenous contrast media enhance or increase the density of blood vessels, vascular soft tissues, organs, and tumors as in a radiograph. This enhancement assists in distinguishing between normal tissue and a pathologic process.

Injection of iodinated contrast agents is *essential* to obtain state of the art CT images. Optimal tissue enhancement allows correct differentiation between tumoral and normal tissue. For all practical purposes, a single bolus technique with an injection rate of 1 cc/s is appropriate on modern CT machines. A total amount of 100 ml is adequate. To some extent, a higher volume (up to 150 ml) may be required when an incremental or single slice spiral CT technique is used. It is essential to wait 60 s before starting the image acquisition, to give the contrast media a chance to diffuse throughout the body. A subsequent saline injection at the same injection rate is recommended [23]. Currently, in most patients computed tomography (CT) or magnetic resonance imaging (MRI) is performed for pre-therapeutic staging of a head and neck malignancy. Based on the information obtained from those techniques, treatment planning strategies are more clearly defined. A common question is which of these techniques should be used on a particular patient. The most widely used technique is CT, as it has a number of important advantages over MRI.

19.3.2.7 Advantages of CT

- Wide availability
- Relative low cost
- Easy to execute
- Rapid scan acquisition
- Short examination time, less image quality degradation caused by motion, such as swallowing and respiration
- Superior quality for bone details (Fig. 19.4c)
- Demonstration of calcifications
- High quality multiplanar imaging on multidetector CT systems
- Easy extension of the study into the upper thoracic cavity or intracranial cavity, if needed
- Easier interpretation

The new technological advances in CT have led to an increase of its use. However, there is a high radiation dose exposure while the examination is carried out. CT accounts for more than 40% of all radiation exposure to patients from diagnostic imaging. There may be as many as 65 million CT examinations performed each year in the United States and as many as 260 million CTs performed yearly worldwide. Many (up to 11%) of these examinations are performed on infants and children, who are more susceptible to the adverse effects of radiation. These considerations put a great responsibility on the radiologist and physicians to limit CT use to definitive indications; provide dose-efficient CT imaging protocols; suggest other imaging techniques, especially for young children, who are at the greatest risk from radiation; work with manufacturers to limit radiation dose; and educate patients and health care providers about the potential risks of radiation. In addition to that, CT also has a number of disadvantages compared to MRI.

19.3.2.8 Disadvantages of CT

- Relatively low soft tissue contrast resolution.
- Administration of iodinated contrast agent is necessary to enhance the resolution.
- Severe image quality degradation by dental restorations or other metallic foreign objects (Fig. 19.4d) [6].

19.3.3 Magnetic Resonance Imaging (MRI)

After 10 years of the emergence of CT, Magnetic resonance imaging (MRI) applications in the medical field revolutionized diagnostic imaging and provided a great leap forward in diagnostic imaging of the whole body and specifically imaging of head and neck pathologies. MRI can provide critical information in detection of neoplastic lesions either clinically detected or not. It has added value in depiction of anatomical details of soft tissues, marrow involvement, and perineural spread (invasion of nerve tissue). The excellent tissue characterization and multiplanar imaging capability of MR imaging resulted in more accurate diagnosis of neoplastic and benign processes [24].

MR is a technique producing tomographic images by means of magnetic fields and radio waves. The physics of MRI is complicated and beyond the scope of this chapter. To make it simple, MR is based on the ability of a small number of protons within the body to absorb and emit radio wave energy when the body is placed within a strong magnetic field.

Different tissues absorb and release radio wave energy at different, visible, and characteristic rates. MR scans are acquired by placing the patient in a static magnetic field 0.02–4 tesla (T). Low field strength systems are less than 0.1 T, midfield systems range between 0.1 and 1.0 T, and high-field systems range between 1.5 and 3.0 T. MR analyzes multiple tissue characteristics, including hydrogen (proton) density, T1 and T2 relaxation times of tissue, and blood flow within tissue. A small number of tissue protons in the patient align with the main magnetic field and are subsequently displaced from their alignment by application of radiofrequency (RF) gradients. When the RF gradient is terminated, the displaced protons realign with the main magnetic field, releasing a small pulse of energy that is detected, localized, and then processed by a computer algorithm similar to that used in CT to produce a cross-sectional tomographic anatomic image.

Standard spin-echo sequences produce a batch of images in 10–20 min. Rather than obtaining data for each image one slice at a time, many spin-echo MR sequences obtain data for all slices in the imaged tissue volume throughout the entire imaging time. Consequently, patient motion caused by breathing, cardiac and vascular pulsation may degrade the image considerably. MR has advanced to rapid-imaging breath-hold techniques. Continuing technologic improvements are making MR acquisition times comparable to those for CT [25].

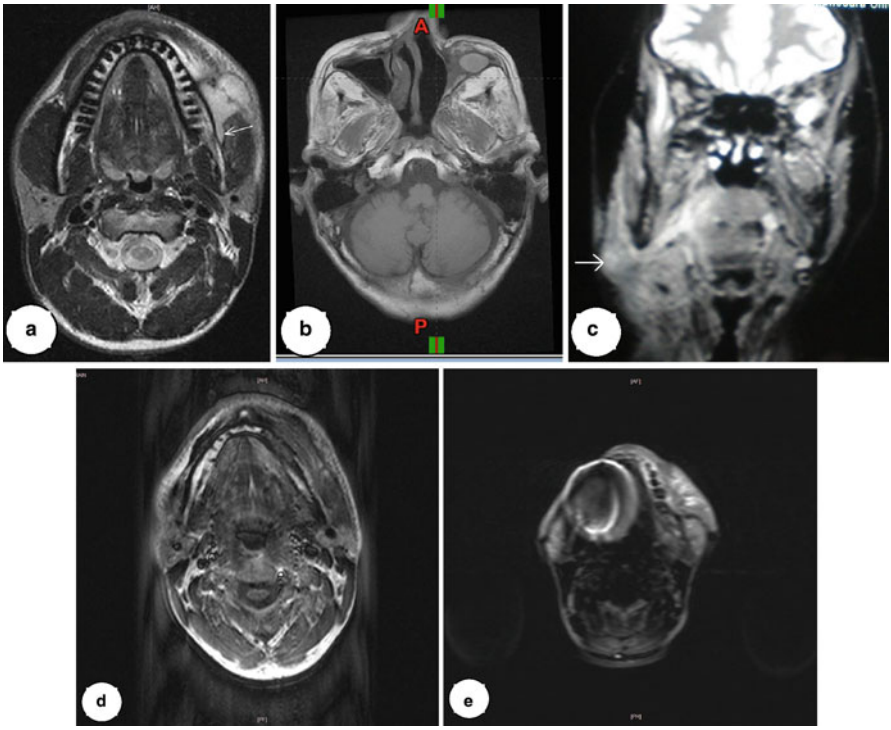

Fig. 19.5 (**a**) Axial T2- weighted MR image showing excellent anatomical details of soft tissues and demonstrate a mass in the *left side*. The lesion is clearly delineated from surrounding structures and extending under the masseter muscle which does not display intrinsic changes. (**b**) Axial T2- weighted MR image showing a mass in the nasal sinus area. (**c**) Coronal STIR MR image (with contrast enhancing agent) showing a mass the submandibular region appearing with higher signal intensity (*arrow*). (**d**) Axial MR image shows artifact hindering the ability to evaluate the obtained image caused by a large fixed metallic restoration in the oral cavity. (**e**) Axial MR image with artifact due to the movement of the patient during the examination study in the MRI unit leading to inability to evaluate the hazy obtained image

19.3.3.1 Advantages of MRI

One of the outstanding advantages of MR is its excellent soft tissue contrast resolution (Fig. 19.5a–c). Also, it has the ability of providing images in any anatomic plane without exposure to ionizing radiation. Image quality is not hindered by small metallic dental fillings like CT, but image artifacts can still result with big restorations.

19.3.3.2 Disadvantages of MRI

MRI is relatively expensive, and therefore it is less available. MR is limited in its ability to demonstrate dense bone details or calcifications, it has long acquisition time, making this technique sensitive to motion artifacts. It is not easy with MRI to

properly stage both primary tumor and neck nodal disease in a single study. Also, because of the physically limited space for the patient within the magnet, a number of patients may suffer from symptoms of claustrophobia and necessitate sedation or are simply unable to tolerate MR scanning. "Open" magnet design can be helpful in the MR imaging of obese and/or claustrophobic patients, but these units have lower field strength and lack the resolution of the high-field strength "tube" magnets.

There is no agreement regarding the use of CT or MRI as primary imaging tool, although most of radiologists prefer to use MRI because of its high ability in depicting anatomical structures without exposure to any radiation doses. It is quite hard to define the ideal imaging protocol depending upon the availability, cost, presence of prosthetic implants etc [2].

19.3.3.3 MR Artifacts

Artifacts in MRI may result from distortion of the magnetic field due to the presence of ferromagnetic objects such as orthopedic devices, surgical clips and wire, and metallic foreign bodies in the patient. The artifact is seen as areas of signal void (Fig. 19.5d) at the location of the metal implant with a rim of increased intensity and a distortion of the image in the surrounding area. Also, motion artifacts are common in MR because of the long image acquisition time which results in blurred images (Fig. 19.5e). So, patients are advised to hold his breath periodically to avoid the artifact [6].

19.3.3.4 Requirements for Optimal MRI Diagnostic Study

Magnetic resonance imaging (MRI) has been extensively used in the assessment of head and neck cancer. Accurate determination of tumor extent is of utmost importance in head and neck cancer because it has important consequences for staging of disease, choice of treatment, and prediction of prognosis. Magnetic resonance imaging is superb in detecting submucosal and perineural tumor spread, skull base invasion, and nodal metastases.

Patient Positioning

Similar to CT, image acquisition is performed with the patient in the supine position, and during quiet respiration. The head and neck should be aligned and symmetrically positioned. The patient should be instructed not to move, cough and swallow during the image acquisition.

Coils

The choice of the receiver coil depends on the localization of the disease process. If the tumor is localized in the oral cavity or the lower part of the neck (infrahyoid),

the neck coil should be used. When the neoplasm is at the level of the base of the skull, sinonasal cavities, face, parotid glands, or nasopharynx, the head coil should be selected. However, when head and neck region needs to be covered in one exam, as in nasopharyngeal cancer where neck adenopathies are usually involved, the head and neck coil can be both used together, allowing detailed evaluation of the entire head and neck region. On the other hand, in the absence of a dedicated neck coil, one can choose to stage the primary tumor with MRI, using the head coil, and perform an additional CT or Ultrasonography of the neck to stage neck disease.

A standard examination of the head and neck should start with a T2-weighted spin echo. The high signal intensity of fat on a T2-weighted sequence can be a disadvantage because it may reduce the contrast between a tumor and the surrounding tissues. This low contrast can be enhanced by applying an additional "inversion recovery preparation pulse" (a short inversion time known as STIR) (Fig. 19.5a, b).

Repetition of this sequence after injection of gadolinium-DTPA (contrast media), and comparison with the pre-injection sequence helps to outline the areas of contrast enhancement and to differentiate these areas from fat. A fat-saturated T1-weighted SE sequence after injection of gadolinium-DTPA may be helpful, as the contrast media enhances resolution of tissues and fat. Yet, such a sequence has some drawbacks too. A fat-suppressed sequence is susceptible to artifacts, which is more observed in the head and neck region because of the presence of different types to tissues (soft tissue-bone and tissue-air interfaces). Furthermore, the depiction of anatomical structures is reduced, and the acquisition time is longer. The selection of the plain of imaging is selected according to the location of the lesion [25].

Contrast Agent

Most neoplasms will show increased signal intensity after contrast agent injection. In MR studies for head and neck neoplasms, acquiring sequences before and after injection of gadolinium-DTPA (at a dose of 0.1–0.2 mmol/kg body weight) is mandatory. This will usually increase the contrast between the tumor and the surrounding lesions. Tumor necrosis becomes more visible after injection of gadolinium which is important in staging the neck nodes. On the other hand, tumors infiltrating bone marrow may become less well visible after contrast injection, as their signal intensity may become similar to that of the surrounding bone marrow. Ultra-small super paramagnetic iron oxide (USPIO) particles are captured by macrophages in normally functioning lymph nodes. As a result, signal intensity reduction is observed in tissues accumulating these particles, because of the susceptibility effects of iron oxide. Metastatic lymph nodes show increased intensity on sequences weighted to these effects [6].

19.3.3.5 Additional MRI Techniques

The flexibility of MRI may provide each patient a tailored study that fits his condition. Although the standard sequences solve the diagnostic questions in most cases,

in some instances additional sequences can further characterize pathological tissues. MRI is considered as a gold standard in structural imaging of the head and neck, particularly for the deeply located lesions as the skull base and related regions, oral cavity, larynx and hypopharynx. In addition to its excellent anatomical depiction, it has other functional imaging characteristics. MRI may investigate some functional aspects of disease using the recent developments in diffusion and perfusion MRI techniques.

Diffusion-Weighted (DW) MRI

Diffusion-weighted (DW) MRI is an imaging technique showing molecular diffusion, corresponding to the Brownian motion of the spins in biologic tissues. The apparent diffusion coefficient (ADC) is a parameter used to quantify DW-MRI. The ADC is in part determined by the molecular diffusion of water, the microcirculation of blood and the presence of structures on a microscopic scale (microvessels, tubules, and others) [26]. Cell size, cell density and cell integrity influence the signal intensity seen on DW images, as well as the value of the ADC. This technique shows potential to distinguish benign and malignant tumour. Volumetric interpolated breath-hold imaging (VIBE) is a 3D fat-saturated gradient-echo T1-weighted sequence that can be optimized for short acquisition times, providing high-quality MR angiograms if acquisition and contrast injection are properly synchronized. It can also be used to evaluate tumor perfusion, or as an alternative to T1-weighted SE sequences, as it combines excellent image contrast with minimal partial volume averaging [27]. These sequences provide high-resolution anatomical images of the cranial nerves; however, involvement of the nerves by neoplasms is often best detected on gadolinium enhanced images.

Recently, many reports have been published which investigated the capabilities of Diffusion-weighted imaging (DWI) as a functional diagnostic tool for detection and characterization of tumors. Technical improvements and higher magnetic fields (with wider use of 3 T systems) enhanced research in diffusion techniques. The principle of diffusion weighted imaging (DWI) is based on exploring the motion of the free water molecules in tissue, including intracellular and extracellular motion. Diffusion-weighted MRI in combination with size and morphological criteria of the tumor are a strong predictor of presence of malignant lymph nodes. It is also indicated to assess response to chemoradiotherapy as early as 1 week after beginning of treatment [6].

Perfusion Techniques

Perfusion techniques are mostly used for the assessment of the tumour response to treatment with antiangiogenic (prevention of formation of new blood supply to the tumour cells) and vascular-disrupting agents. Many chemotherapeutic agents and radiotherapy are targeting angiogenesis. Perfusion imaging estimates local blood volume variations and capillary permeability. Tissue characteristics such as

blood flow, blood volume and transit time parameters have been related with tumour vascularization and microvascularization. It thus provides information for tumor classification and in T1-weighted dynamic contrast-enhanced Perfusion MRI is studied to measure the drug effects on tumour microvascularity and capillary permeability [28].

19.4 Nuclear Imaging

Nuclear radiology is a functional imaging technique that includes both therapeutic and diagnostic modalities. Many techniques are available for nuclear imaging diagnosis such as single photon emission computed tomography (SPECT) and positron emission tomography (PET) which is progressively being used in the evaluation of head and neck cancer. PET and PET-CT, using fluorine-18-labeled 2-fluoro-2-deoxy-D-glucose (18FDG) as a tracer, have received a lot of consideration recently. This modality can be used in pretreatment staging of the neoplasm, during therapy, and in the post treatment follow-up. Radiographic anatomic imaging depicts and measures the dimensions of a lesion, but functional imaging shows the activity related to malignant changes. PET-CT has greatly improved patient diagnosis, tumor staging, and post treatment evaluation of tumour therapy. Also PET-MRI is a new technology which is recently introduced and showed promising results in follow up and detection of recurrent disease.

Nuclear imaging studies provide high functional resolution, physiologic and functional information not otherwise obtainable by other modalities like Ultrasonography, CT, and MRI.

Although PET is considered the best modality in detection and staging of cancer, it still has some drawbacks. PET has a higher sensitivity but lower specificity in detecting tumors in comparison with CT and MRI. The low spatial resolution and lack of tracer uptake in some neoplasms can cause false-negative results. Also, tracer accumulation in inflamed tissues may cause false-positive results. The high cost of PET imaging is also an important drawback [29].

19.4.1 Imaging Principles of Nuclear Imaging

The basic principles of diagnostic nuclear imaging are simple. Comparing the normal patterns of uptake, distribution, and excretion with the abnormal patterns leads to diagnosis of presence or absence of disease. External detection and mapping (image formation) of the biodistribution of radiotracers that have been administered to a patient either orally or parentally is the basic foundation for nuclear imaging. Sometimes a radionuclide or radioisotope is used alone or in combination with other physiologically active compounds. Usually, a radioactive isotope is combined with a physiologically active compound to create a di-pharmaceutical.

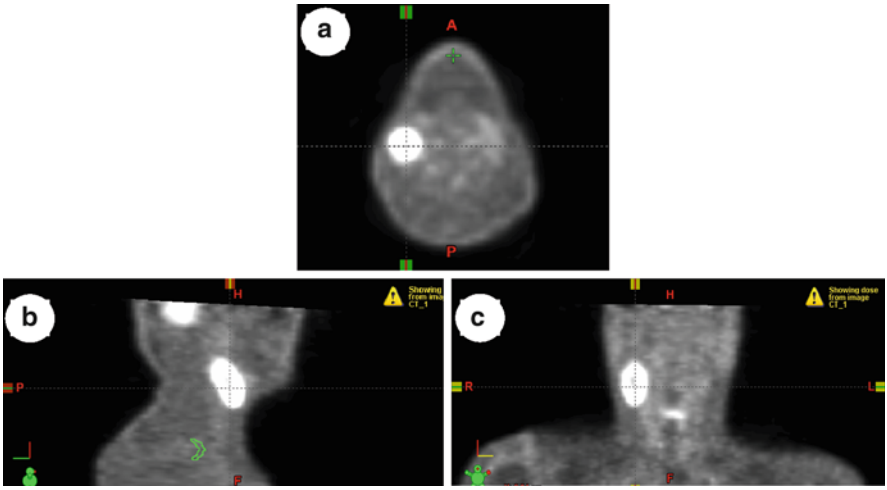

Fig. 19.6 (**a**), (**b**), (**c**) Axial, Sagittal, Coronal PET images showing a mass at the *right side* of the neck with high uptake of 18 F-FDG. Note poor anatomical details with PET alone

19.4.2 Image Interpretation

In order to interpret the obtained nuclear images, a basic knowledge of anatomic, physiologic, and nuclear imaging principles is necessary to make accurate diagnosis based on nuclear medicine studies.

When preparing a case for nuclear imaging, determination of the radiopharmaceutical isotope is important. Also, age, gender, the site of injection, patient orientation during imaging, the type of study, and the type of images (planar or tomographic, static or dynamic) should be considered.

Therefore, a basic knowledge of the normal biodistribution of the radiopharmaceutical and the usual indications for performing the study are needed. This information is critical to image interpretation. One approach to enhance and speed detection of abnormalities and asymmetries is to study the first frame (image) or two very closely and then move directly to the last frame. Direct comparison of early and late images will show changes between the two images.

19.4.3 Positron Emission Tomography (PET)

PET is considered the technique of choice for metabolic and molecular imaging of cancer (Fig. 19.6a–c) and is now widely available. PET scanning with 18fluorodeoxyglucose (18FDG) can be used for staging and evaluation of recurrence for primary head and neck tumors. 18F-FDG, is used as a marker of glycolysis. It has excellent intrinsic molecular sensitivity. For that reason, PET can be used

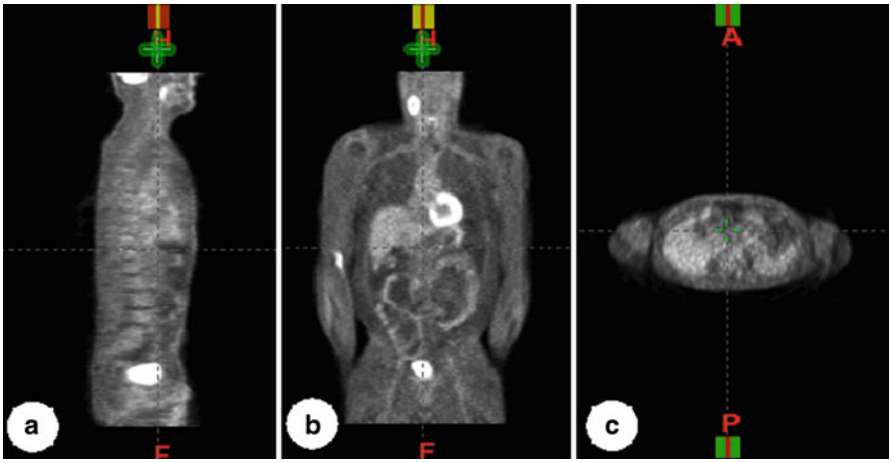

Fig. 19.7 (**a**) Sagittal PET maximum intensity projection (MIP) image. (**b**) Coronal PET maximum intensity projection (MIP) image. (**c**) Transverse PET. All images show no distant metastatic lymph nodes

for detection of nanomolar concentrations of molecules. This prospect of molecular applications (e.g. receptor expression, integrines and apoptosis) give it a lot of credit to be used in the future. PET has recently been improved by the combination of a CT scan, leading to the integration of morphological and anatomical information of CT with the metabolic and molecular information of PET [30].

Since 1970, Positron emission tomography (PET) started to be utilized for clinical imaging. It is more sensitive than CT or MRI for T1-staged lesions. The most recent advances in PET systems are the hybrid PET/CT scanners. The use of this modality was limited to specialized research institutions and was focused on the physiology and pathophysiology of the brain, heart, and then the use of PET in oncology has considerably increased [31].

Recently, several authors have shown the high negative predictive value and accuracy of PET for the follow-up after radiotherapy of head and neck tumors [32]. In case the PET scan is negative, further investigations are not needed according to most authors. PET may be performed within 4 weeks after the completion of chemotherapy, chemoimmunotherapy, or chemohormonal therapy. In contrast, PET is normally not performed until 2–3 months after radiation or chemoradiation or 1–2 months after surgery, because acute inflammatory changes that are commonly seen in the first few weeks after radiation or surgery can result in false positive PET scans.

However, PET evaluation of distant metastatic disease should be reliable even during this time. PET uses positron-emitting radioisotopes of natural elements, oxygen-15, carbon-11, nitrogen-13, and fluorine-18. These radioisotopes can keep their normal biologic function. So, they are used for the combination of many positron-emitting radiopharmaceuticals. 18fluoro-deoxyglucose- FDG-CT when used in combination with CT or MRI, the diagnostic efficacy increase to detect metastases. So it can be used for pre and post-treatment follow up. In addition, it may be used for cancer screening [33]. PET is a true whole-body imaging technique; modern scanners

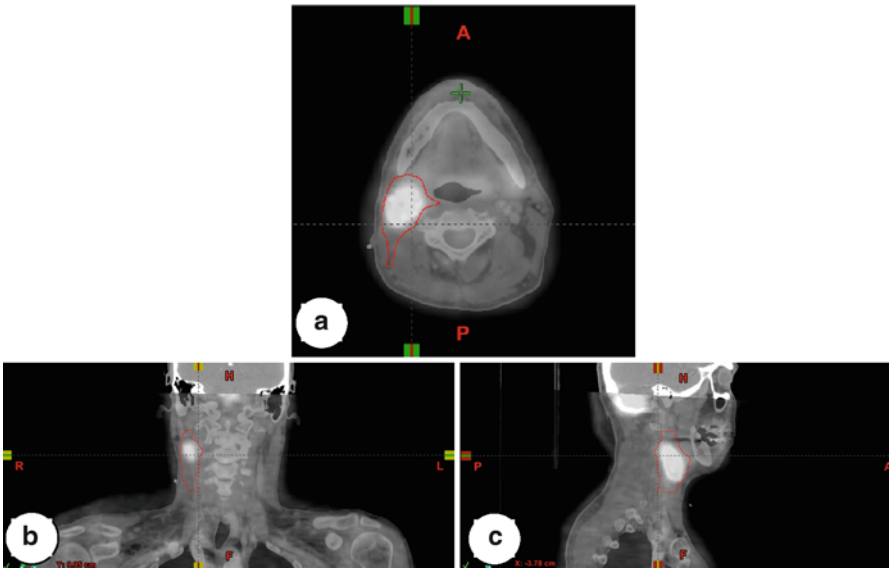

Fig. 19.8 (**a**), (**b**), (**c**) Axial, coronal and sagittal coregistered PET-CT showing a mass at the *right side* of the neck (outline with *red color*). Note the fusion of PET with CT provides enhanced anatomical details and accurate localization of 18 F-FDG uptake in comparison with PET alone

can acquire studies covering from head to knee area within 25 min or less (Fig. 19.7a–c). Therefore, PET is not limited to the depiction of one target lesion, but can be used to assess multiple tumor sites and to monitor their responses to different therapeutic choices. The spatial resolution of PET has improved during the recent years, and under optimal conditions, state-of-the-art PET scanners now provide a resolution of 3–4 mm. In routine clinical protocols, the spatial resolution is in the range of 5–6 mm. in consequence, PET is still limited in the detection and characterization of small lesions and in the evaluation of tumor heterogeneity in larger lesions [34, 35, 36].

19.4.4 Positron Emission Tomography-Computed Tomography PET-CT

Recently, PET-CT was introduced in oncology of head and neck. This modality allows direct image fusion between PET and CT and improves the ability to anatomically localize foci of fluorodeoxyglucose (FDG) uptake (Fig. 19.8a–c). The potential of PET-CT to evaluate malignancies of the head and neck, specifically squamous cell carcinoma is considerably high. It can be used for pretreatment staging, treatment monitoring, and post-treatment evaluation. It can identify lesions even 1 mm in volume. PET also has the ability to detect metastatic cervical lymph nodes, which may be both clinically occult and not detected by CT or MR. False-negative results may be obtained in patients treated with radiotherapy if the study is performed within 3 months of the completion of treatment. Also, false-positive results for treated oral

and pharyngeal malignancies may be obtained due to artifact from tongue uptake after radiotracer administration, lingual tonsil uptake, retained salivary uptake in the oral cavity, or post treatment granulation tissue. Similar false-positive findings can be seen in laryngeal carcinomas treated with combined chemotherapy and radiotherapy, and may be due to evaluation in less than 3 months period after completion of chemo-radiotherapy. Several studies have assessed the diagnostic accuracy of PET-FDG for detecting recurrent HNSCCA. PET-FDG has a higher diagnostic accuracy compared to cross-sectional imaging. It must be noted that the most accurate PET results will only be obtained if the information is interpreted in relation to clinical findings as part of a multidisciplinary head and neck oncology team.

Also, PET-CT was able to detect unknown primary tumors of the upper aerodigestive tract. PET-CT is mostly performed after confirming the presence of metastatic HNSCCA and following a negative endoscopy. PET is usually performed before endoscopic biopsies to help improve the yield of the speculative tissue sampling. The diagnostic findings will likely increase with PET-CT because this technique improves accurate anatomic localization of areas of abnormal FDG uptake [31].

PET-CT is currently under investigation in determining response to nonsurgical treatment modalities; either chemotherapy and/or Radiotherapy. Comparison of pretreatment standardized uptake values (SUVs) to SUVs 2 weeks into treatment can allow measurement of the speed of response and the sensitivity of the tumour to the treatment modality. Poorly responsive tumours can then be treated to higher doses of radiation or shift to perform surgery. PET-CT is very promising, and it will most likely be the modality of choice for both pre-treatment and post-treatment assessment in head and neck cancer in the future [33].

19.5 Molecular Imaging in Cancer

Molecular imaging in cancer has made great progress in the capabilities of conventional anatomical imaging methods. Molecular imaging will allow clinicians to not only localize tumors in the body, but also to depict the expression and activity of specific molecules (e.g. proteases and protein kinases) and biological processes (e.g. apoptosis, angiogenesis, and metastasis). Therefore, it can be used in monitoring the response to cancer therapy. This information is expected to have a major impact on cancer detection, individualized treatment, and drug development [37].

19.5.1 PET as a Biomarker

PET biomarkers allow noninvasive serial studies of the whole tumor mass. The most unique characteristic of PET-based biomarkers is that they are measuring a biologic process and not the concentration of a particular cellular protein. This differs in several ways from biomarkers derived from tumour biopsies or plasma samples. In biopsies, only small parts of the tumor can be evaluated [38].

The intratumoral heterogeneity can significantly affects the analysis of biomarkers derived from tumor biopsies which is really important in evaluating changes in a biomarker during treatment because it is difficult to ascertain that different parts of the tumor demonstrated the same expression of the biomarker before therapy. Serum biomarker studies are noninvasive and can easily be used to measure changes in multiple biomarkers over time. Yet, the results may be baffled by the metabolism and excretion of tumor derived biomarkers. Imaging of these biomarkers allows direct assessment of the tumor tissue without interfering with the metabolic processes in plasma or normal organs. The imaging signal in PET studies is the result of the functional interaction of multiple proteins. This is illustrated by studies that have correlated tumor FDG uptake with the expression of glucose transporters and hexokinase, the two classes of proteins involved in the intracellular uptake and trapping of FDG [39, 40].

19.6 Neoplasms of Head and Neck

In squamous cell carcinoma of the head and neck, CT, MRI and PET-CT play a critical role in pre-treatment staging of tumors.

19.6.1 Maxillary Sinus, Nasal Cavity, Nasopharynx

Determination of early stage disease (T1 and T2) is based on clinical assessment of disease spread. T3 disease is based on spread of the disease to involve the thin bony component that comprises the soft tissue structures immediately adjacent to the primary site. Early cortical erosion is better detected on CT and PET-CT compared to MR (Fig. 19.9a–g). However; MRI is still the imaging method of choice by most radiologists for bone marrow involvement, intracranial extension, and perineural extension (Fig. 19.10a–f) and should be performed when attempting to distinguish between T4a and T4b disease. For that reason, MRI is recommended for all sinonasal carcinomas if there is a doubt of intracranial spread of the tumor.

Cross-sectional imaging is critically essential for accurate staging of nasopharyngeal carcinoma. It is important to understand the anatomy of this region to be able to localize the neoplasm in fascial spaces of head and neck like parapharyngeal (PPS), masticator (MS), and retropharyngeal (RPS) spaces. When lesions are limited to the PPS, they are T2 lesions, but lesions that involve the masticator space are T4 lesions. For advanced staging, early cortical erosion (outer layer of compact bone) is better detected on CT compared to MR 2. However, MR is superior to CT for evaluation of bone marrow involvement. A noncontrast axial T1-weighted (T1 W) image is the most reliable sequence to determine if there is marrow involvement, looking for replacement of high-signal marrow by intermediate signal tumor in the untreated patient. MR is clearly superior to CT for detecting perineural extension (extension to nerve sheath). As a result, all patients with nasopharyngeal carcinoma should undergo thin-section contrast-enhanced MR of the skull base and cavernous sinus.

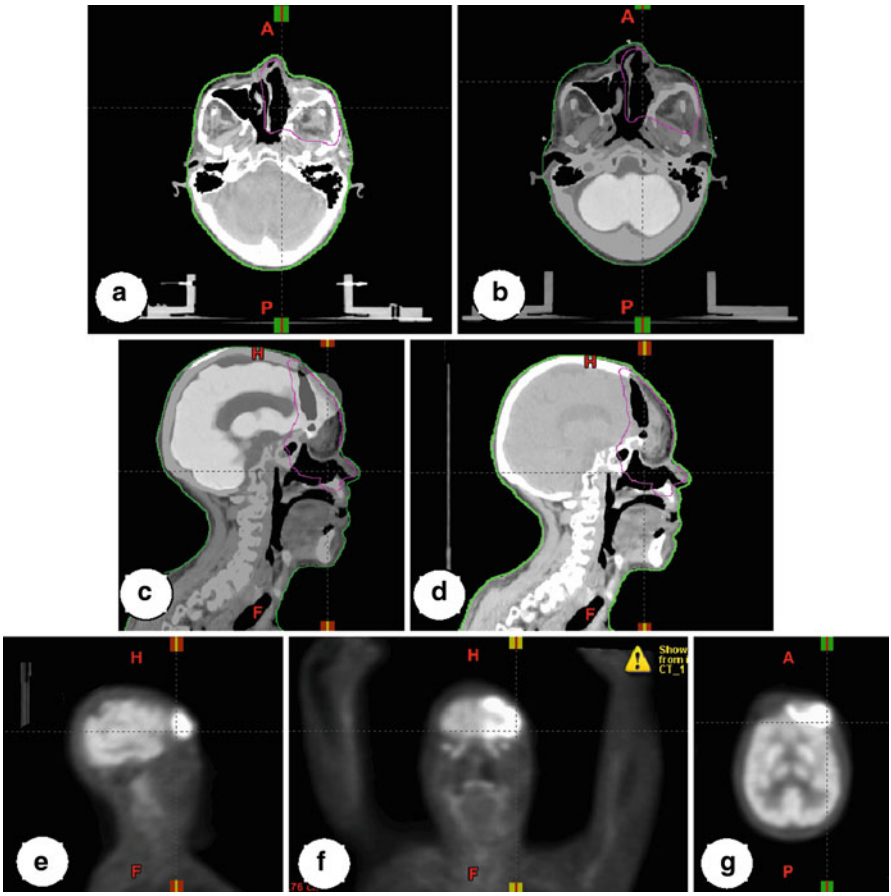

Fig. 19.9 (**a**) Contrast enhanced axial CT image. (**b**) Coregistered PET-CT image at the level of the maxillary sinus of a recurrent nasopharyngeal squamous cell carcinoma with superior spread and bone erosion. (**c**), (**d**) Contrast enhanced sagittal CT and coregistered PET-CT of the recurrent tumor showing the recurrent tumor (outlined in *purple color*) and destruction of cortical bone (appears as *black* area in the skull anterior part). (**e**), (**f**), (**g**) Sagittal, coronal and axial PET images showing a high uptake of 18 F-FDG in the forehead area with close proximity of the tumor to brain tissues

19.6.2 Laryngeal Carcinoma

Laryngoscopy plays a great role in diagnosis of laryngeal carcinomas and should be performed with clinical examination. It can detect any mucosal abnormalities. However, when these tumors spread submucosally which takes place with a high tendency, this extension into the deeply located tissue planes is frequently

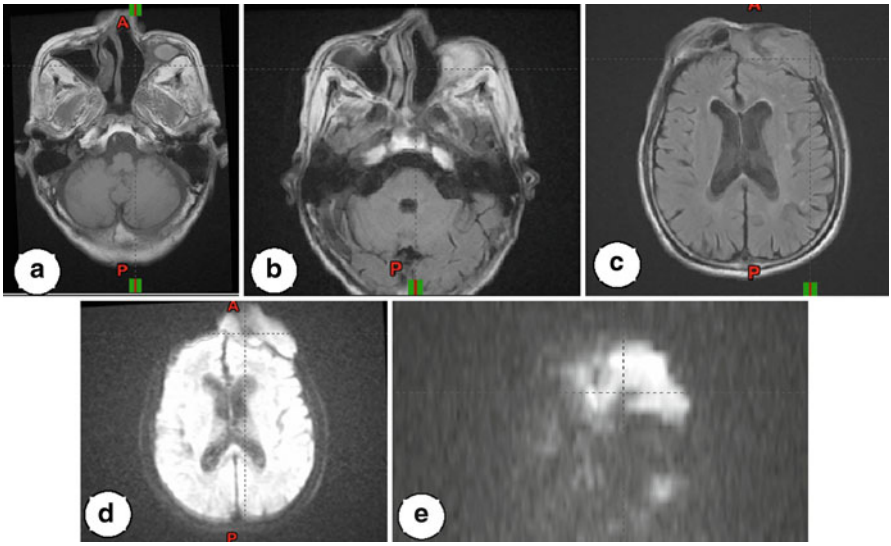

Fig. 19.10 (**a**) Axial T2-weighted contrast-enhanced MR image shows moderate enhancement in left maxillary sinus (**b**) Axial T2-weighted contrast-enhanced MR image shows dense enhancement in the left maxillary sinus (**c**) Axial T2-weighted contrast-enhanced MR image clearly identifies dense enhancement at the level of the frontal sinus crossing the midline. (**d**) STIR MRI image showing intracranial extension of the tumour, (**e**) STIR MRI image showing the recurrent tumor

difficult to evaluate by clinical examination alone. In that condition MRI and CT play a role revealing the spread away from the mucosal lining. The site of the tumour is considered the first clinical criteria used for giving a tumor a particular T-classification. Involvement of different laryngeal anatomical subsites and limited vocal cord mobility in the larynx are important criteria of staging. About 65–70% of laryngeal cancers originate at the glottic level (Fig. 19.11a–d), and about 30% at the supraglottic level. Laryngeal cancer originating from the subglottic region is rare. Classification of laryngeal cancer based only on clinical findings alone is insufficient when compared with pathologic classification. Diagnostic accuracy is markedly improved when the results of CT or MRI are added to the clinical findings [41]. Findings from imaging studies frequently result in an upstaging of the disease. In order to evaluate the accuracy of the CT and MR imaging, many studies compared the findings of imaging with the whole organ sectioning after total or partial laryngectomy, which confirmed that both techniques are accurate methods to visualize laryngeal pathology [41]. Erosion or lysis has been found to be a specific criterion for neoplastic invasion in all cartilages. The positive diagnosis of neoplastic invasion of the thyroid cartilage should be made with extreme caution on MRI [42].

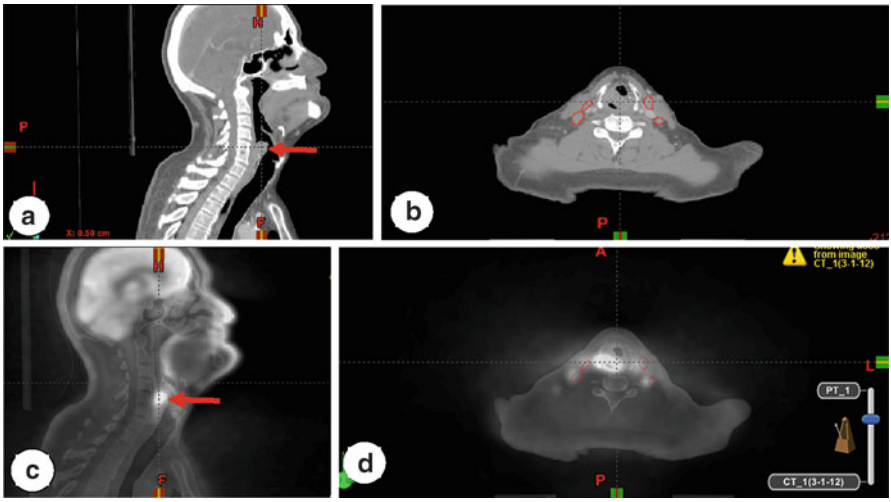

Fig. 19.11 (**a**) Sagittal contrast enhanced CT image of a patient with supraglottic squamous cell carcinoma (*arrow*). (**b**) Axial contrast enhanced CT Image showing the tumor and metastatic lymph nodes on both sides of the neck (outlined in *red*). (**c**) Sagittal coregistered PET-CT image showing the tumor and its high uptake of 18 F-FDG (*arrow*). (**d**) Axial coregistered PET-CT image clearly depicting the primary tumor (high uptake of 18 F-FDG) and the metastatic lymph nodes (moderate uptake of 18 F-FDG) which are outlined in *red color*

19.6.3 Supraglottic and Subglottic Carcinomas

The site of involvement is the main criterion for Primary site staging in clinical diagnosis (Fig. 19.11a–d). Involvement of various subsites of the supraglottic larynx and vocal cord mobility should be carefully assessed. Imaging can aid to a great extent to identify occult submucosal transglottic extension. Imaging criteria that define T3 lesions are extensions into the pre-epiglottic space (paralaryngeal fat) or erosion of the inner cortex of the thyroid cartilage [6].

Tumors that erode through the outer cortex of the thyroid cartilage are defined as T4a tumors. Stage T4 (a&b) tumors are difficult to identify based on clinical examination alone because most of the criteria cannot be assessed by endoscopy and palpation. Tumor limited to one subsite of supraglottis with normal vocal cord mobility are classified as T1, Tumor invading the mucosa of more than one adjacent subsite of supraglottis, glottis or region outside of supraglottis, without fixation of the larynx are T2. Vocal cord fixation or invasion of postcricoid area, preepiglottic and/or paraglottic space, and/or minor thyroid cartilage erosion is classified as T3. T4 tumors are: extralaryngeal tumor spread T4a: tumor invading through thyroid cartilage, or tissues beyond the larynx (e.g. trachea, soft tissues of the neck, strap muscles, thyroid gland, and esophagus) andT4b: tumor invading prevertebral space, mediastinum, or encasing carotid artery.

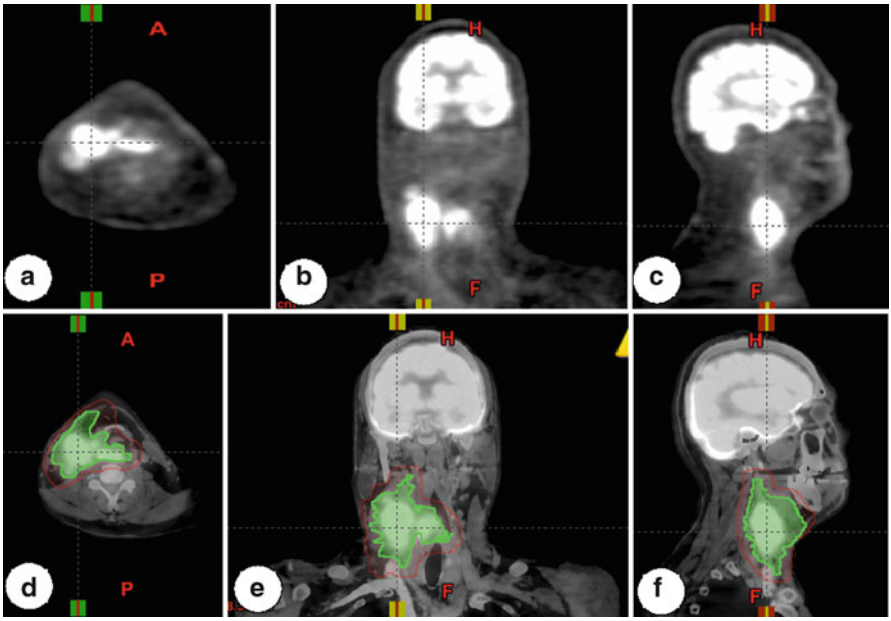

Fig. 19.12 (**a**), (**b**), (**c**) Axial, coronal, sagittal PET images showing a high uptake of 18 F-FDG by a mass in *right side* of the neck and the primary laryngeal tumor. (**d**), (**e**), (**f**) Coregistered PET-CT images clearly identifying in axial, coronal and sagittal planes the primary tumor and the metastatic lymph nodes (outlined by *green color*)

19.6.4 Glottic Carcinoma

Clinical diagnosis can identify T1 and T2 tumors. To confirm the clinical diagnosis, cross-sectional imaging may be used to prove that the clinical diagnosis of early stage lesions is correct. Also, cases with submucosal extension is identified using the cross sectional Imaging. Imaging may also identify glottic carcinomas that have occult transglottic or subglottic spread. Tumor erosion limited to the inner cortex of the thyroid cartilage indicates a T3 lesion, whereas carcinomas which erode through the outer cortex of the thyroid cartilage describe a T4a tumor. To make such an accurate imaging diagnosis, High-resolution Computed Tomography (Fig. 19.12a–g) is used where the slice thickness does not exceeding 2.5 mm. Both MR and CT may be used to detect cartilage invasion. However, there will be cases that MR may detect cartilage invasion not seen on CT and vice versa. CT is preferred over MR due a shorter scan time and lower costs. Staging of glottic carcinoma is as following: T1 Tumor limited to vocal cord(s) with normal mobility (may involve anterior or posterior commissure), T1a: limited to one vocal cord, T1b: involving both vocal cords. T2 Extension into supra and/or subglottis, and/or with impaired vocal cord mobility. T3 Vocal cord fixation and/or invasion of paraglottic space, and/or minor thyroid cartilage erosion. T4 Extralaryngeal tumor spread T4a: tumor invading

through thyroid cartilage or tissues beyond the larynx (e.g. trachea, soft tissues of the neck, strap muscles, thyroid gland, and esophagus) T4b: tumor invading prevertebral space, mediastinum, or encasing carotid artery [2].

19.7 Assessment of Metastatic Spread of Head and Neck Cancers

Accurate assessment of tumor spread affect the staging, prognosis, and treatment options of the disease. It determines whether conservative surgery and/or radiation therapy can be performed or a more radical technique is necessary. It guides the physician and surgeon to choose the best treatment choice for the patient starting with radiotherapy, radiochemotherapy and/or surgery. The assessment of the extent of the lesion can also identify other factors that may prevent surgical resection. These factors include encasement of the carotid artery (invasion of the tumour to the carotid artery), fixation to the base of the skull, intracranial extension. Also, involvement of the prevertebral fascia or direct invasion of the prevertebral space eliminates the option of tumor resection and consequently predicts a poor prognosis. Therefore, in patients who are surgical candidates, it would be practically useful if preoperative imaging could reliably assess the absence of prevertebral compartment involvement. As a result, this would reduce the need for intraoperative assessment in these patients [43].

The improved soft-tissue resolution and multiplanar capabilities of MRI make it a more accepted diagnostic tool for detection of tumor spread into the deep spaces of the head and neck. In cases with large nasopharyngeal, large pharyngeal and laryngeal cancers, surgery is not a recommended option because it would be difficult to obtain tumor-free margins. For example, surgical resection of the prevertebral muscle or debulking of the tumor in cases of prevertebral space involvement is coupled with poor outcomes on both clinical and functional levels. Therefore, patients with prevertebral involvement can be treated with other treatment choices as radiotherapy and complementary chemotherapy [43, 44].

Enlarged lymph nodes are usually due to either inflammation or hyperplasia. In the assessment of cervical lymph nodes, imaging plays a major role. It is used mainly for (N staging). Also, imaging plays an increasing role in evaluating the degree of extension and spread of the disease. Most metastases originate from malignant neoplasms of the mucous membranes in head and neck, skin, thyroid and salivary glands follow certain pathway in spread. Metastatic adenopathies can be identified even when still in a subclinical stage or at places not accessible for clinical examination, such as the retropharyngeal or paratracheal lymph nodes. Imaging is needed in submucosal lesions, covered by an intact mucosa.

Assessment of the nodal status is an essential procedure in patients of head and neck cancer, not only for treatment planning but also for prediction of treatment outcomes. Malignancy involved lymph nodes from head and neck cancers usually follow a certain pattern of spread with respect to the location of the primary tumour. Consequently, that assessment of the distribution of metastatic nodes in patients

with unidentified primary can indirectly help, revealing the site of the primary tumor [19, 45, 46].

Additionally, metastatic nodes in an unpredicted site may point to the fact that the primary tumor is biologically more aggressive [47, 48].

Together with metastases, lymphoma is also a common malignant disease and head and neck involvement is very common. Clinically, lymphoma of the cervical lymph nodes is difficult to differentiate from other causes of lymphadenopathy including metastatic nodes. Metastatic cervical lymph nodes from head and neck primaries are site specific [49].

The common nodal metastaic sites for head and neck primaries are:

- Tumours of pharynx, larynx, oesophagous, and papillary carcinoma of thyroid metastasize along internal jugular chain.
- Tumours in the oral cavity metastasize to the submandibular and upper cervical lymph nodes, although carcinoma of the tongue may give rise to skip metastases to the lower neck.
- Infraclavicular primaries from breast and lung metastasize to supraclavicular fossa and posterior triangle nodes.
- Nasopharyngeal carcinomas commonly spread to upper cervical nodes and posterior triangle nodes [50, 51].

19.7.1 Lymphadenopathy of the Neck

The causes of enlarged cervical lymph nodes are usually due to one of the following reasons:

19.7.1.1 Reactive Inflammatory Enlargement

The reactively enlarged lymph nodes are most often due to bacterial or viral infections (Fig. 19.13a–c) When a patient presents with enlarged lymph nodes, differential diagnosis should be done to determine the cause behind the adenopathy. History, clinical examination, and microbiological tests can confirm the differentiation that the adenopathy is due to exposure to an infection and not as a result of metastases of malignancy originating in the region of head and neck. Cat scratch disease (mycobacterial infection), suppurative bacterial lymphadenitis, Castleman's disease, tuberculosis, mononucleosis, herpes, cytomegalovirus infection, rubella, or seldom HIV should be included in the differential diagnosis [6].

In suppurative bacterial lymphadenitis Ultrasonography can be used to determine inflammatory changes [52]. Ultrasound examination is helpful in diagnosis of enlarged lymph nodes [19]. Viral infections usually cause bilateral diffuse lymphadenopathy without necrosis of the central part. Sarcoidosis and toxoplasmosis, rarely cause diffuse, multiple nodal enlargement. In these cases, the salivary glands

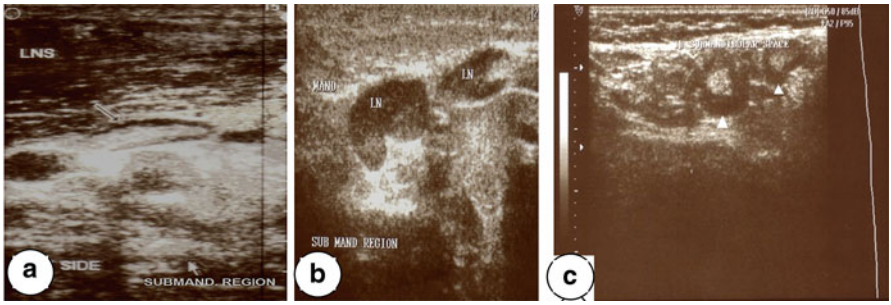

Fig. 19.13 (**a**) sonogram showing the normal oval shaped elongated LN (normal appearance) (*arrow*) in the submandibular region. (**b**) Sonogram showing enlarged oval shaped lymph nodes (*LN*) (inflammatory) in the submandibular region. (**c**) Sonogram showing enlarged round shaped Lymph nodes (*arrow heads*) with internal enhancement) suspecting inflammatory reaction or neoplastic change

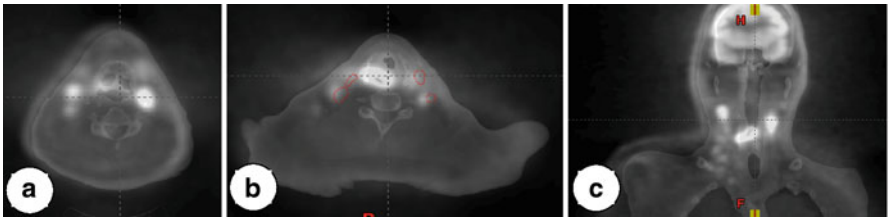

Fig. 19.14 (**a**) Axial PET showing high FDG uptake of cervical lymph nodes on both right and *left sides*. (**b**) Coregistered PET-CT showing the primary tumor and the metastatic spread to cervical lymph nodes (outlined in *red color*). (**c**) Coregistered coronal PET-CT showing the primary tumor and metastaic lymph nodes

can be swollen as well as mediastinal lymph node enlargement. Carotid body paragangliomas can mimic lymphadenopathy. Imaging is helpful in these cases by showing the vascular nature and exact location of the lesion; however, Median (thyroglossal) or lateral (brachial) cervical cysts have a typical low-density center and sometimes rim enhancement appearance on enhanced CT. T2-weighted MR imaging shows the typical cystic appearance. However, squamous cell metastases rarely appear as cystic lesions (Fig. 19.14a–c). The exact localization and extent of a lesion is also critical when surgical treatment is considered in order to know the extension and the relation of vital structures to the neoplasm such as the carotid artery, the prevertebral fascia, and base of the skull [6].

19.7.1.2 Metastatic Lymphadenopathy

In 1932, Rouvière came up with a classification of the regional lymph nodes of the neck bases on the anatomical relation. Recently, the American Academy of

Otolaryngology developed a new classification that most clinicians are using now based on both clinical and radiographic examination. One of the major reasons for using the new classification is that almost all of patients with head and neck malignancies undergo cross-sectional imaging before treatment.

According to this classification neck is divided into levels:

1. **Level 1A**: it includes all submental nodes that are between the medial margins of the anterior bellies of the digastric muscles below the mylohyoid muscle.
   Level 1B: it includes the submandibular nodes. These are above the hyoid bone, below the mylohyoid muscle, in front of the posterior belly of the digastrics muscles and around the submandibular glands.
2. **Level 2**: it includes the upper internal jugular nodes. This level extends from the skull base to the level of the bottom of the body of the hyoid bone. Lymph nodes in this level are posterior to the back of the submandibular gland and anterior to the back of the sternocleidomastoid muscle. Level 2 nodes can be subclassified into levels 2A and 2B. Level 2A nodes are situated around the internal jugular vein; level 2B nodes are posterior to the internal jugular vein, separated from the vein by a fat plane. Nodes medial to the internal carotid artery are called retropharyngeal lymph nodes.
3. **Level 3**: it includes the mid-jugular nodes. They extend from the level of the bottom of the hyoid bone to the level of the bottom of the cricoid cartilage. They lie anterior to the back of the sternocleidomastoid muscle. They are located lateral to the carotid arteries.
4. **Level 4:** it includes the low-jugular nodes. They extend from the level of the bottom of the cricoid bone to the level of the clavicle. They lie anterior to a line connecting the back of the sternocleidomastoid muscle and the posterolateral margin of the anterior scalene muscle. They are also lateral to the carotid arteries.
5. **Level 5:** it includes nodes in the posterior triangle. They are posterior to the back of the sternocleidomastoid muscle from the skull base to the clavicle. Level 5 is also divided into level 5A and 5B. Level 5A extends inferiorly toward the bottom of the cricoids bone whereas 5B extends from the bottom of the cricoids cartilage to the clavicle. They are also anterior to the anterior edge of the trapezius muscle.
6. **Level 6**: it includes the visceral nodes which are inferior to the lower body of the hyoid bone, superior to the top of the manubrium sterni muscle, and between the left and right common carotid arteries or the internal carotid arteries.
7. **Level 7**: it includes the superior mediastinal nodes. They are between the carotid arteries below the level of the top of the manubrium and above the level of the innominate vein [51].

For consistency with the prior classifications, the following nodal groups, as well as the other superficial nodes, are referred to by their anatomical names as retropharyngeal, parotid, facial, occipital, and postauricular. Most tumors originating from the mucosal lining of the upper aerodigestive tract have a well-defined and more predictable pattern of metastasis to the neck.

The classification of neck levels of lymph nodes of the neck depicts the map of surgical removal of the involved nodes in neck dissection according to the N staging. This clinical classification leads to improved management of patients which could be followed by radiation therapy depending on histological findings to confirm the presence of extra nodal spread or presence of multiple metastases. This line of treatment (surgery and radiation therapy) still has a considerable morbidity and mortality. Therefore, imaging assessment of the lymph node status is critically significant for the choice of treatment. So, making the decision for such a radical treatment should be fully supported by the obtained findings of a highly accurate radiographic modality. For example, ultrasonography (USG) that has the advantage of Ultrasound guided fine needle aspiration cytology (USgFNAC) which is considered highly accurate and has the best diagnostic value for the detection of cervical lymph node metastases. Ultrasound alone is also associated with high diagnostic odds ratio (DOR). The DOR is a single indicator of test performance. It varies between 0 and infinity [53]. Whereas computed tomography (CT) and magnetic resonance imaging (MRI) perform less well. The nature and internal structure of small lymph nodes (≤5 mm) may not be readily assessed by them. Also, MRI may not identify intranodal calcification which is a feature used in prediction of metastatic nodes from papillary carcinoma of the thyroid gland [54]. The main advantages of CT and MRI are the lower inter-observer variation (not highly dependent on the operator), and less time consuming compared to USgFNAC and USG. Furthermore, CT and MRI are relatively standardized techniques that can be interpreted by general radiologists, whereas USG and USgFNAC should be performed by a well experienced radiologist in Ultrasonography. Detection of occult lymph nodes by imaging can guide the treatment choices according to its findings in cancer patients. It has been proposed that a minimally invasive approach concerning management of the clinically negative neck could be allowed, if the risk of occult lymph node metastases is less than 20% [6].

Cross-sectional imaging has been shown to be superior to clinical examination for staging of cervical lymph nodes. The diagnostic accuracy of cross-sectional imaging is based on cross-sectional diameter and presence of internal abnormalities. The reader is referred to the prospective study of Curtin et al., which reports the diagnostic accuracy of CT and MR based on these criteria. The advent of multidetector imaging now permits rapid reconstruction on imaging studies in the sagittal and coronal planes. Curtin's classic work only evaluated axial dimensions. There have been no large-scale randomized prospective trials that have been performed to determine if sagittal or coronal measurements will improve the diagnostic accuracy of CT for detecting metastatic lymph nodes. Extracapsular penetration can be detected on cross-sectional imaging and is defined by reticulation of the fat adjacent to the outer margin of a lymph node. These findings are not pathognomonic, as similar findings can be seen in inflamed lymph nodes due to adenitis. However, the presence of such findings in a patient with head and neck cancer, in the absence of an infection, should be considered highly suspicious for extracapsular penetration.

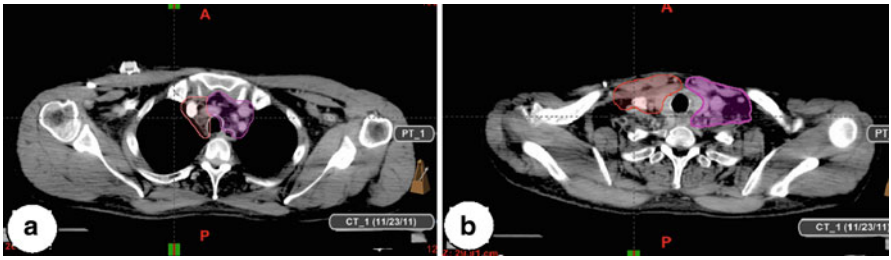

Fig. 19.15 (**a**), (**b**) Coregistered PET-CT images of a patient with multiple neck lymph node metastases at Level II under the sternocleidomastoid muscle. PET revealed high FDG uptake in the *right side* which was enlarged on CT images (outlined with *red color*) and moderate FDG uptake in the lymph node in the *left side* (outlined in *purple*)

19.7.1.3 PET-CT and Lymph Nodes

With the development of new technologies, additional criteria are added that improved the diagnostic performance of existing techniques. Positron emission tomography-computed tomography (PET-CT) imaging is a valuable addition to the diagnostic armamentarium in the diagnosis of metastases to lymph nodes (Fig. 19.15a, b) [53].

One of the potential applications of PET-CT is using it in advanced stage head and neck squamous cell carcinoma to evaluate for occult distant metastases to the lungs or bones. The presence of pulmonary metastases upstages a patient from M0 to M1 and alters treatment plan. However if a solitary nodule is identified, it is often unclear if this is a separate primary, metastasis, or a granuloma. PET may help in this evaluation because an FDG-positive nodule will likely require biopsy, whereas an FDG-negative nodule (>8 mm) likely indicates a granuloma and a biopsy may be avoided. Knowledge of these patterns of metastases is important for radiologists and surgeons. The most frequent source for metastases to lymph nodes in the head and neck region is from squamous cell carcinomas of the mucous membranes of this region as it comprises more than 90% all head and neck tumors. The presence of one isolated lymph node metastases (stage N1) lowers the prognosis with 50%, where as multiple metastases worsen the prognosis even more. Therefore, prediction of prognosis in head and neck tumors is usually based on the lymph node staging [55, 56].

19.8 Imaging Accuracy of Diagnostic Modalities

Accurate staging of head and neck cancers represents a great challenge to radiologists because of the anatomical and functional complexity of this region of the human body. The introduction of CT and MRI has renovated head and neck radiology.

Modern radiological modalities can provide a reliable image of the head and neck structures with extraordinary level of details. These techniques can provide a comprehensive evaluation of the location and extent of neoplastic lesions. The introduction of new developments like diffusion-weighted MRI, PET-CT, and PET-MRI has intensified the accuracy level of imaging in addition to monitoring tumor response to treatment [55]. The main tasks of imaging in management of patients with head and neck cancers are:

1. Identification of the neoplasm and its extent in the initial or pre-treatment diagnosis in order to outline the possibility of complete surgical resection.
2. Assessment of lymph nodes for metastatic spread.
3. Monitoring tumour response to the appropriate therapy.
4. Assessment of disease recurrence after treatment.

Positron Emission Tomography CT (PET-CT) is now competing with the CT and MRI and gaining more acceptance in imaging of head and neck neoplasms. PET-CT major advantage is the ability to provide information about both the anatomy and metabolism of examined area. It can identify metastatic cervical lymph nodes with a negative predictive value up to 90%. It can also detect the primary tumor in patients with metastatic squamous cell carcinoma of the head and neck with unknown primary lesion in 30–50% of cases. Further advances in the technology of PET-CT can promote its role to provide optimal diagnostic quality [55].

PET-CT provides high quality images which can be used to detect pathological lesions and differentiate between malignant and physiological uptake. There are many reports on the clinical usefulness of PET-CT system for head and neck cancer with promising diagnostic accuracy; on the other hand, there are some patients who do not tolerate iodine-based IV contrast media used in PET-CT [57, 58]. Nakamoto et al, 2009 tried to use MRI instead of CT because of the higher tissue contrast by MRI in head and neck cancers than with CT and because it could be used in patients allergic to contrast media used in PET-CT. They found that the fusion of MR and PET images resulted in some clinical advantages for head and neck cancers over PET/CT. However, the clinical application of MR and PET fusion imaging of the whole body is still limited [59].

Ultrasonography is also a strong player in the diagnosis of metastatic cervical lymph nodes. It has the highest accuracy among all modalities especially with the evolution of endoscopic Ultrasonography (EUS) which overcame the drawback of the inability to pass through dense structures. Ultrasonography guided needle biopsy enables identification of the nature of pathological processes. Ultrasonography can diagnose not only cervical metastatic lymph nodes but can also be used to evaluate treatment-induced changes in lymph node metastases after chemoradiotherapy. Ultrasonographic assessment of the presence or absence of metastases is directly associated with the decision of removal of the involved lymph nodes by neck dissection. Ultrasonography allows the evaluation of lymph nodes that are 10 mm diameter or more, which can be diagnosed as cervical lymph node metastasis-positive by computed tomography (CT) or magnetic resonance imaging (MRI). It also can evaluate lymph nodes of less than 10 mm diameter, based on sufficient image information.

All lymph node metastases less than 10 mm in diameter are considered as "potential lymph node metastases" and radical dissection is recommended. Although radical neck dissection can decrease the rate of secondary lymph node metastases or relapse, it may induce various postoperative pain and disorders due to cervical dysfunction. Using combination therapy chemotherapy/ radiotherapy even in metastatic lymph nodes may lead to organ preservation. The number of patients in whom satisfactory efficacy has been obtained even with cervical lymph node metastases by combining chemotherapy with radiotherapy is continuously rising. Ultrasonographic evaluation of therapeutic effects on cervical lymph node metastases is significantly necessary to choose the patients who do not need additional neck therapy, to avoid shoulder dysfunction or swallowing disturbance caused by excess neck therapy. So, it is important to perform pretreatment ultrasonographic assessment of lymph nodes less than 10 mm in diameter which cannot be assessed by CT or MRI in diagnostic procedures for cervical lymph node metastases of head and neck cancer. This can lead to more conservative surgeries or even prevention of surgical treatment [60].

Tumor resectability is the major challenge that faces the surgeon. The translation of diagnostic images to the operative field is the key to obtain a successful treatment. The high accuracy of imaging modality helps the surgeon to adequately discriminate between tumor and normal tissue. This has a role in determining the healthy margins. However, the only way to do this during surgery is by visual appearance and palpation. Introduction of real-time imaging technologies into the operating room has the potential of cross the gap between radiology and surgery, resulting in intraoperative image-guided surgery. Optical imaging is currently considered the optimal technique for intraoperative image-guided surgery. In optical imaging, the properties of light are exploited to image anatomic or chemical characteristics of tissue. Imaging of optical contrast can be performed either using the properties intrinsic to the tissue, or, analogous to many radio-labeled agents, using antibodies or ligands conjugated to an optically active reporter to target a recognized disease biomarker [59, 61]. Accurate assessment of tumor spread leads to accurate staging; therefore the treatment outcomes and prognosis can be predicted more accurately. It determines whether conservative surgery and/or radiotherapy can be performed or whether more radical surgical intervention is necessary. In addition to guiding the surgeon, imaging has been used to recognize other reasons that may interfere with surgery and redirect the treatment plan to another choice. These reasons include encasement (involvement) of the carotid artery, fixation of the tumor to the base of the skull, intracranial (inside the skull) tumour extension, extension to the nasopharynx, or invasion of the brachial plexus (network of nerve fibers, running from the spine). Prevertebral space involvement defined as fixation to or direct invasion of the prevertebral fascia eliminates the option of surgical resection and predict very poor prognosis. The 2002 American Joint Commission on Cancer (AJCC) revised the T-stage classification of head and neck cancers recommending that advanced (T4) stage cancers to be subdivided into T4a and T4b categories. T4b tumors were categorized as surgically unresectable; T4a lesions are still classified resectable although they may require extensive surgery. The criteria of T4 according to the AJCC for most aerodigestive

system locations are: (1) Vascular encasement and invasion, (2) Prevertebral space invasion and (3) Invasion of mediastinal structures [62].

MRI can be particularly helpful in assessing carotid encasement. If the vessel shows greater than 270° of circumferential encasement, it usually cannot be resected from the artery at surgery. Tumors that surround the artery by less than 180° can be readily resected; most tumors showing 180–270° encasement can also be resected [1, 62, 63].

Based on the previous discussion of different diagnostic modalities, each case is unique and needs a specific study to address it carefully. Once a lesion is identified, there are two questions needed to be answered: (1) where is it located? And (2) what is its nature? To answer these questions other factors should be included which are epidemiologies, clinical presentation, and pathological findings. The imaging findings consist primarily of CT and MRI because these are the most commonly used modalities for evaluating the extracranial head and neck lesions. So, in summary, each modality has its advantages and disadvantages. No modality can provide everything needed in every study; however some modalities can be more superior to another and provide more information. Also, combinations between these imaging modalities can provide a complementary evaluation by covering the drawbacks in each modality.

19.9 Role of Imaging in Treatment Planning of Head and Neck Cancer

Recent and continuing research is empowering the impact of imaging in health care of patients with cancer. Consequently, the radiologist is now considered to be an important member of the multidisciplinary team managing head and neck cancer patients.

Imaging of tumours and surrounding normal tissues is used for several purposes related to treatment, this includes:

- Cancer screening and surveillance.
- Initial or pre-treatment radiographic diagnosis which comprise detection, staging, location, relations, metastases and resectability.
- Planning for therapy to determine the treatment of choice with consideration to the age or the patient and his general health.
- Evaluation of treatment outcomes during the treatment period and that includes observation of changes in tumour size and shape in response to treatment and
- Finally post-treatment follow up of the patient to examine the signs of the cure of the disease and /or recurrence of the tumour.

Although head and neck cancer can be successfully managed with a combination of surgical and chemoradiotherapeutic interventions, the disease should be well characterized both radiographically and histopathologically before carrying out surgical or medical management of the patient. Radiographic imaging is a fundamental part of the initial staging process for head and neck cancer and plays an important

role in identifying the locoregional extent of the tumor, localization of an unknown primary site, and the presence of distant metastases which in turn guide the surgical planning.

Several imaging modalities are recommended for the pretreatment evaluation of head and neck tumors. The most commonly used are magnetic resonance imaging (MRI) and computed tomography (CT). Computed tomography is a well-established diagnostic tool in the initial staging and surgical planning for head and neck cancer since it provides structural information at a high spatial resolution. However, it does not always provide additional needed information. Suspicion for nodal disease is mainly based on size, which can be due to inflammatory reaction or due to metastases. Ultrasonography and Positron emission tomography (PET) using the radiolabeled glucose analogue fluorodeoxyglucose F 18 can be used in both the initial evaluation and in the detection of recurrent lesions after treatment. Positron emission tomography provides metabolic information of the tumor by showing the metabolically active tissues. PET can be used for initial staging, for detecting regional or distant nodal disease (metastases), for localizing unknown primary tumors, and for identifying recurrent disease. With all these advantages, it lacks of perfect anatomical resolution which is necessary for surgical and radio/chemo therapeutic planning. This limits its usefulness as a single diagnostic modality. So, combinations with other modalities like CT and MRI are now applied to improve the technology of PET imaging. A newer imaging modality, PET and CT fusion (PET-CT), allows for simultaneous image acquisition and co-registration of metabolic and anatomical data, expanding the benefits of PET or CT alone. This relatively new diagnostic imaging modality, PET-CT plays a valuable role in the initial staging and in the therapeutic management planning for untreated head and neck cancer patients in both early and advanced stages of the disease. Patients with early-stage disease can benefit from the detection of regional metastases, and those with advanced-stage disease can benefit from the detection of distant metastases. They can also benefit from a well defined extension of regional spread of the tumor and its relationship to the surrounding normal tissues [64, 65].

Treatment strategies of squamous cell carcinoma of the head and neck is planned with respect to many considerations that include: site, stage of the disease, age and general health of the patient. In most cases of early stages (stage I, II) the modality of choice is surgery or radiotherapy as initial treatment. Before 1980, the initial treatment of patients with locally advanced stage III or IV was also surgery and/or radiation therapy, a choice that also depended on the site of the disease, the resectability of the cancers. The obtained poor results in these advanced stages with the "traditional" therapy led to introduction of systemic chemotherapy in the mid 1970s as part of combined modality treatment. Later, chemotherapy was used in patients with earlier disease stages and with resectable disease for organ preservation and better cure rates. Advanced squamous cell cancers of the head and neck are usually associated with high rates of morbidity and mortality with predicted prognosis of less than 30% 5 year survival rates. The introduction of new active chemotherapeutic agents and combinations with radiotherapy, targeted treatments, and better sequencing of treatment options, it is expected to promote the improvements in treatment

results. Organ preservation is more commonly achieved. Newer targeted therapies will also add to the progress that has already been achieved in the multimodality management of patients with head and neck cancers. New standards of care have been defined for patients with nasopharyngeal cancer and for those with advanced unresectable disease [59].

In head and neck cancer patients, it is essential to monitor the response of the tumor to radiotherapy, and to determine whether the chosen treatment regimen is effective so that an ineffective Treatment approach or drug regimen can be changed. After irradiation therapy, clinical examination of the head and neck is difficult and residual or recurrent tumor cannot be detected. Post-radiotherapy, residual tumor and post-radiation changes may show contrast enhancement. Post treatment MR imaging is inaccurate in the differentiation of residual tumor from post-radiation changes, as fibrous tissues may be enhanced, simulating a tumor, and residual tumors may show insignificant contrast enhancement and may be mistaken for post-treatment fibrosis. Diffusion-weighted MR imaging has been applied to differentiate residual or recurrent tumors from post-treatment changes in head and soft-tissue masses. Functional imaging like Diffusion-weighted MR and PET-CT could identify nonresponding tumours early, which allows for a switch in therapy [66, 67].

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Chapter 20
Radiotherapy of Head and Neck Cancers

Bulent Aydogan

Contents

Abstract Radiation therapy has played principal role in the treatment of head and neck cancer. Treatment capabilities have steadily improved with the improvement in technology and our knowledge regarding the disease and clinical outcomes. In this chapter we will first present an overview radiation therapy in head and neck cancers. We will then present a historical review of radiation therapy of head and neck cancers from three dimensional conformal radiotherapy (3DCRT) approaches to intensity modulated radiotherapy (IMRT) to image guided radiation therapy (IGRT). Details and important aspects of imaging, both the target and critical organs contouring and treatment planning will be demonstrated with examples. Treatment

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planning, setup, and organ motion and their impact for sample cases will be compared for 3DCR and IMRT techniques. A brief summary and discussion of future direction will conclude this chapter.

Keywords Head and neck cancers • Radiotherapy • Intensity modulated radiotherapy • Image guided therapy • Proton beam therapy

Abbreviations

IMRT	Intensity modulated radiotherapy
IGRT	Image guided radiotherapy
3DCRT	Three-dimensional conventional radiotherapy
IMPBT	Intensity modulated proton beam therapy
Linac	Linear accelerator
MLC	Multi leaf collimator
kV	Kilo voltage
MV	Mega voltage
CT	Computed tomography
CBCT	Cone beam computed tomography
DRR	Digitally reconstructed radiograph

20.1 Introduction

The head and neck comprises of elusive, complexly spread radiation sensitive organs in a very small body area that are fundamental for physiologic functions, appearance, expression, and communication [1]. Although representing less than 5% of all cancers and 3% of all cancer deaths, quite a few of cancers with varying origins and histories can be observed in the head and neck region [2]. Site-specific head and neck neoplasms can be categorized under cancers of oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, nasal cavity, paranasal sinus, salivary glands, thyroid, skin, neck node metastasis from unknown primary. Depending on the site, size, and pattern of spread, management of head and neck cancers demonstrate fundamental differences and may induce injuries and deteriorating quality of life. These features make head and neck cancers very difficult to manage and require an interdisciplinary team approach. A strong collaboration between surgical, radiation, medical, and dental oncologists is essential [1]. In addition, support and cooperation between the oncologists, pathologists, plastic surgeons, nurses, speech pathologists, and other health care personnel is the key for a successfully integrated management of head and neck cancers patients for an optimal outcome [1–3]. Likewise, to deliver high-quality and accurate radiation treatment well structured collaboration between radiation oncologists, dosimetrists, medical physicists, radiation radiotherapists and oncology nurses is imperative.

Fig. 20.1 A Varian Trubeam STX linear accelerator featuring cone beam computed tomography (CBCT) and *Brainlab ExacTrac* patient positioning system

20.2 Radiotherapy

Radiation therapy has played a principal role in the treatment of head and neck cancer since it was first used decades ago. Advancement in computer technology led enhanced radiotherapy planning and delivery technologies that have gradually improved the outcome in most head and neck cancer patients. From the early experiences with treatment of head and neck cancers using less penetrating orthovoltage radiation with up to 500 keV we learned that tumors could be eradicated but the major problem and often dose limiting factor was the side effects [3]. Even with the availability of deeply penetrating radiation therapy modalities such as Cobalt-60 and linear accelerators (linacs), advanced treatment planning algorithms, brachytherapy or electron boost the side effect remained as the main concern and limited the dose that can be safely delivered without major complications.

Recent advances in technology in the last two decade have significantly transformed the treatment of head and neck cancers by improving our ability to maximize tumor dose while minimizing the dose to adjacent normal critical structures. The most common radiation therapy delivery modality for head and neck cancers is external beam irradiation using high energy photons produced with linacs. This device make use of microwave technology to accelerate electrons then force them to collide with a heavy metal target to produce high-energy x-rays (Fig. 20.1). These high energy x-rays are

Fig. 20.2 Multi leaf collimator (MLC) is used for sculpting the radiation beam to conform to the shape of the tumor

then shaped as they exit the Linac gantry to conform to the shape of the tumor. The beam traditionally shaped by special blocks cut from custom made alloys and mounted in the exit window of the beam in the gantry. Multi-leaf collimators (MLC) shown in Fig. 20.2 replaced the custom-made alloy blocks. The MLC is a device made up of individual "leaves" of a high atomic numbered material that can move independently in and out of the path of radiation beam in order to shape it to conform to the tumor.

20.2.1 Treatment Planning

Image-based treatment planning using computed tomography, delivery of three-dimensional conformal radiation therapy (3DCRT) and the use of multi leaf collimators facilitated advanced treatment techniques to be implemented. More recently, the advances in computer technology allowed development of inverse planning algorithms and very fast delivery of small beamlets of radiation. With this technique known as intensity modulated radiation therapy (IMRT), the radiation intensity of each beamlet is controlled and the beam shape is changed hundreds of times during each treatment to create the desired dose distribution that conforms tightly to the shape of the target. Outside of the target, a steep dose gradient is created to protect the surrounding healthy tissues, which is almost impossible with other techniques. Radiation treatment is planned on the computed tomography (CT) images of the patient using computerized dose calculation algorithms to determine the dose intensity pattern that will best conform to the tumor shape while avoiding the surrounding healthy

organs and tissues. Typically, combinations of five to nine intensity-modulated fields aimed from different beam directions produce a dose distribution that maximize the target dose while also minimizing the dose to the nearby health tissues and more importantly to the organs at risk.

Because the ratio of tumor dose to normal tissue is optimized with the IMRT technique, higher and more effective radiation doses can safely be delivered to tumors with fewer side effects compared with conventional radiotherapy techniques. Due to its complexity, IMRT does require slightly longer daily treatment times and additional planning, quality assurance, and safety checks before the patient can start the treatment. For instance, the accuracy of dose distribution of each treatment plan is required to be verified before the patient is treated. This is generally done by delivering the treatment plan to a phantom and measuring the dose distribution with appropriate dosimeter(s) including film, ion or diode arrays. The measured dose or dose distribution is then compared with that calculated by treatment planning computer.

IMRT due to its superior dose distribution has become the standard treatment technique in head and neck radiotherapy within the past decade. Steep dose gradients of IMRT around the target offer the potential for limiting the high dose to target and sparing the noninvolved tissues as much as possible. This offers substantial gains in limiting dose to salivary glands, oral cavity, mandible, and the noninvolved parotid in addition to dose limiting organs including brain stem and spinal cord [4]. IMRT eliminates the dose deficiencies of conventional radiation therapy as such eliminates the need for posterior electron field. This not only improves the dose distribution but also simplifies the radiation treatment. One major disadvantage of the IMRT is that it is very sensitive to changes in the anatomy, organ motion and reproducibility of the treatment position. Organ motion in the head and neck being negligible, only factor to be considered is the patient setup uncertainties making the IMRT to be the choice of treatment modality in this site [5].

Earlier efforts to rationalize the use of IMRT in head and neck cancers were primarily in the form of treatment planning studies comparing this new technique with conventional 2D and 3DCRT. These studies were all concluded that IMRT exhibited significant potential for normal organ sparing. For instance, the first study that investigated the dosimetry of IMRT in patients with head and neck cancer concluded that IMRT was capable of producing dose distributions with invaginations, bifurcations, and internal voids, thus exhibiting substantial potential for healthy tissue sparing [6]. As early as the beginning of millennium, clinical studies demonstrated improved outcome and quality of life with IMRT in patients with head and neck cancers. For instance, Eisbruch et al. reported an improvement over time in xerostomia, occurring in tandem with rising salivary production from the spared major salivary glands, suggests a long-term clinical benefit from their sparing with IMRT compared with 3DCRT [7].

20.2.2 Imaging

For IMRT to be efficacious, the 3D localization and definition of the tumor and its relation to surrounding healthy tissues must be accurately obtained. While Computed

tomography (CT) provides the essential 3D anatomical information, magnetic resonance (MR) and positron emission tomography (PET) imaging offer physiological and molecular information that may be very important not only in staging but also in planning and delivery of radiation treatment.

20.2.3 Immobilization and Simulation

Accurate immobilization and positioning of the patient during the treatment simulation, imaging, and treatment is crucial. In order to reduce the geometric errors and limit motion during the simulation and treatment, head-and-neck cancer patients are immobilized using custom designed immobilization treatment devices. Thermoplastic masks are the most commonly used immobilization for head and neck patients (Fig. 20.3). In our center we also use a light cast immobilization system shown in Fig. 20.4. Our extensive analysis (unpublished) demonstrated that our set up uncertainty is less than 3 mm using this immobilization system. Common practice for head and neck treatment set up is that the internal bony structures visible within the portal images are aligned with those in the reference images for accurate positioning of patient. A potential shortcoming of this procedure is that the delineation and matching of bony structures is relatively time-consuming. Furthermore, the projection of bony structures can sometimes be difficult to interpret, especially when these structures are rotated relative to the reference position and/or the field size is relatively small. Gold markers are successfully used for localizing moving organs

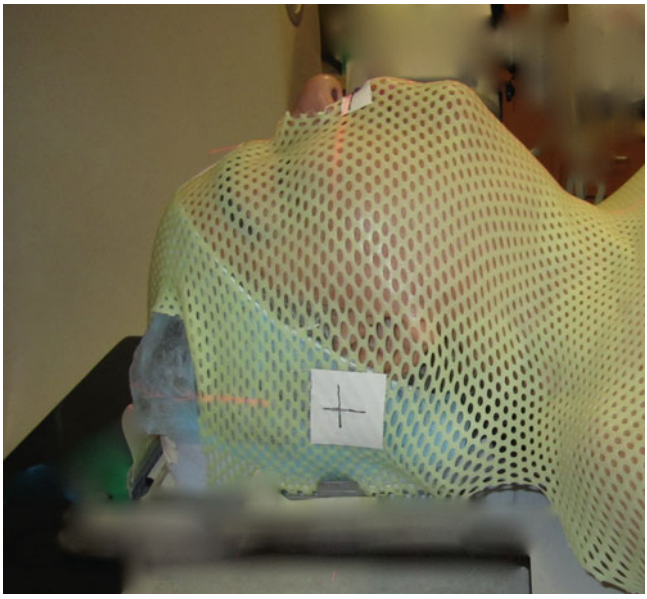

Fig. 20.3 Thermoplastic mask in a supine position

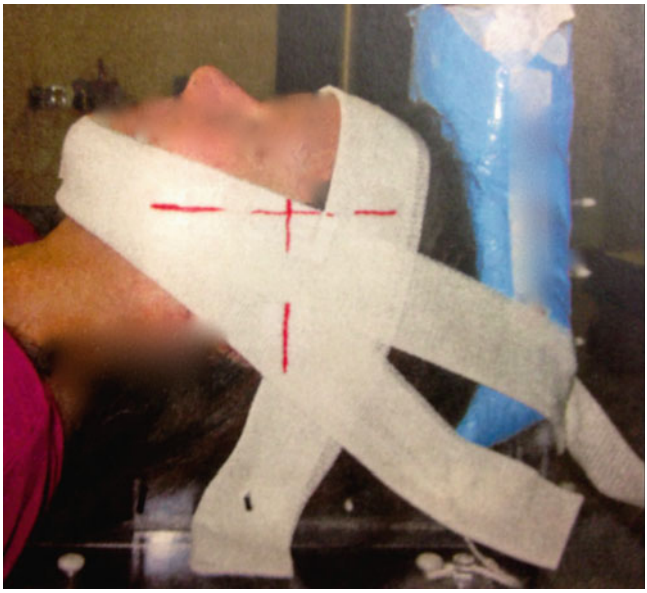

Fig. 20.4 Light cast head and neck immobilization

such prostate and lungs. The use of gold markers is proposed to overcome above-mentioned shortcomings in head and neck cancer treatments [8]. The use of gold markers in head neck cancer treatment is not very common. This may be considered mainly because of complex geometrical spread of cancer around critical organs and the invasive nature of seed placement. Also bony structures can be considered, in majority of the cases, as a good surrogate for accurate positioning of head and neck patients for radiation treatment delivery.

20.2.4 Image Guided Radiotherapy (IGRT)

More recently, advances in radiation technologies led to image guided radiation therapy (IGRT). IGRT is the process of using frequent or continuous two and three-dimensional imaging such as CT scanning, ultrasound, or x-rays, during a course of radiation treatment in order to accurately deliver radiation therapy utilizing the imaging coordinates of the patient specific radiation treatment plan. This is of outmost importance since tumors can move between treatments or during the treatment due to many reasons including the differences in organ filling or movements while breathing or patient discomfort. Radiation therapy requires that the patient be localized in the same position during each and every treatment as planned using the reference imaging dataset. This is verified by matching 2D planar kilovoltage (kV) radiographs, fluoroscopy or megavoltage (MV) images with digital reconstructed

radiographs (DRRs) from the planning CT. This allows radiotherapy technician to position the patient accurately using the bony anatomy but does not provide information regarding the whereabouts of the tumor. Consequently, large geometric margins around tumors are added to the tumor in order to compensate for possible tumor motion and setup uncertainties. This results in delivering high doses to surrounding healthy tissues. The invention of cone beam computed tomography (CBCT) allowed 3D IGRT, which involves localization of a CBCT dataset with the planning CT dataset from planning. CBCT imaging allows setting the patients up using the location of the tumor right before the treatment as such improves the accuracy of targeting.

20.3 Case Studies

In this section we will present two case studies to demonstrate, planning, patient setup and delivery of radiation therapy using 3DCRT and IMRT as well as the rational for radiotherapy and choice of treatment technique.

20.3.1 Case Study 1: 3DCRT

A 67-year old patient presented to the ENT clinic with hoarseness and pain when swallowing. He noted intermittent early morning odynophagia. Subsequently, he has developed dysphagia and dry throat for more than a month. His physical revealed irregular lesions on the anterior true vocal cords; however both vocal cords were mobile. The anterior commissure and ventricle were also involved. His biopsy revealed well-differentiated squamous cell carcinoma. Patient was staged as T1N0 limited to supraglottis with normal vocal cord mobility and with no regional lymphatic node involvement. The advantage of radiation therapy for this patient is that any failures can be salvaged with partial laryngectomy and still have a third chance with total laryngectomy [9]. There are several studies that suggested different dose fractionation. Yamazaki et. al. randomized to 2 Gray radiation dose per fraction (Gy/fx) to total 60 Gy or 66 Gy vs. 2.25 Gy/fx to total 56.25–63 Gy. The 2.25 Gy/fx arm improved 5-year local control from 77 to 92%, but not the cause-specific survival or toxicity [10]. The dose prescription preferred for treating T1-T2N0 cancers is 2 Gy/fx to a total dose of greater than 66 Gy [9].

The patient is simulated in the supine position with the head hyperextended using a light cast immobilization system shown in Fig. 20.4. Shoulders are pulled down with straps to move them away from the radiation field. A bolus material made of water equivalent gel is added in order to increase the dose coverage to the skin for anterior commissure tumors. A CT scan of the patient at 3 mm slice thickness is obtained for radiation therapy planning. Treatment plan for T1N0 cancer is fairly simple since there are no involvements of lymph nodes and organs at risk

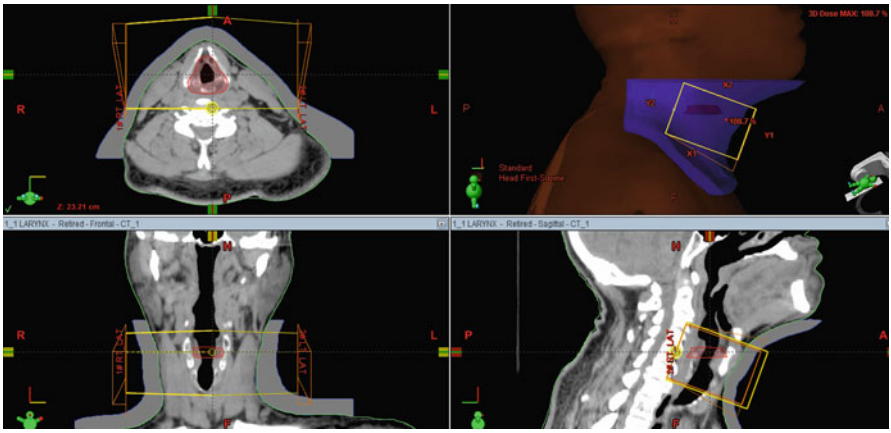

Fig. 20.5 Axial, sagittal, and coronal CT slices showing the larynx in *bright red*, bolus in *blue*, the body contour in order to increase dose homogeneity

are reasonably away from the cancer. Preferred treatment method is the simple parallel-opposed radiotherapy technique with wedges. Figure 20.5 shows the axial, sagittal, and coronal CT slices showing the larynx in bright red, bolus in blue and the treatment field in yellow. It can be seen that only nearby critical tissue is the cord, which can be easily protected by appropriately choosing the treatment field border. Shown in orange are the wedges used to compensate the shape of the body contour in order to increase dose homogeneity.

Figure 20.6 shows the radiation dose distribution. Intended 100% isodose line shown in yellow covers the volume including the larynx shown in red and extends to the skin with the help of the use of bolus.

Figure 20.7 displays the daily verification of treatment using electronic portal imager (EPID). The EPID image is the lower right corner and the digitally constructed image (DRR) from CT images shown on the upper right corner. Both images are co-registered and displayed on the right window demonstrating a good setup with a very minimal error in positioning using the patient's bony anatomy.

20.3.2 Case Study 2: IMRT

A 51 year old man, long time smoker, was diagnosed with head and neck cancer. Biopsy of the primary tumor was positive for squamous cell carcinoma of the supraglottic larynx and the patient was staged as having a T2N2 carcinoma. Due to the proximity of the planning target volume (PTV) to normal and critical structures and to the geometry of the PTV, IMRT is indicated in order to decrease the dose to these dose-limiting structures while maintaining adequate dose and coverage to the PTV.

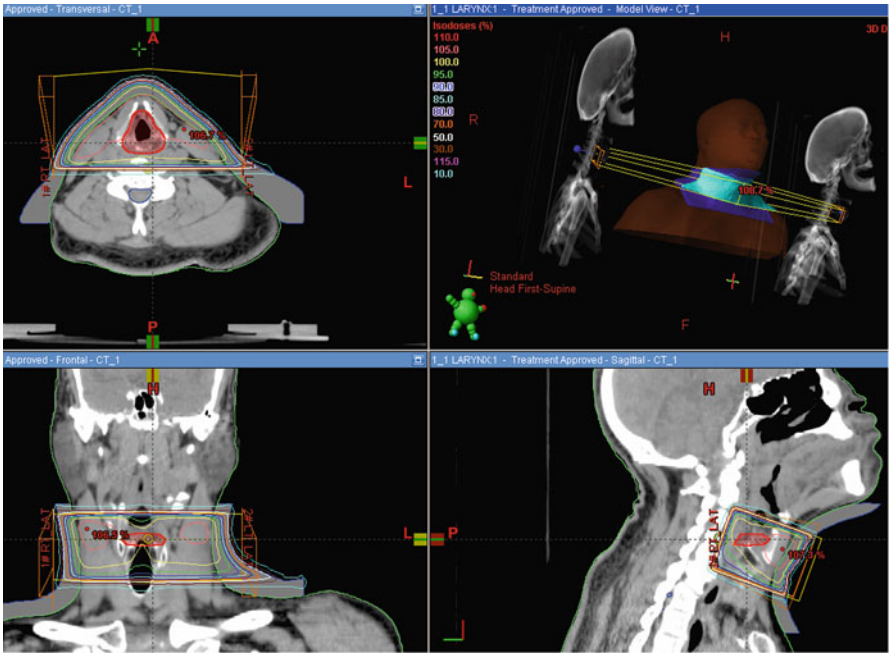

Fig. 20.6 Radiation dose distribution. The 100% isodose line covering the larynx volume (*red*) is shown in *yellow*. The cord is shown in *blue* being outside of the irradiated field did not receive any dose

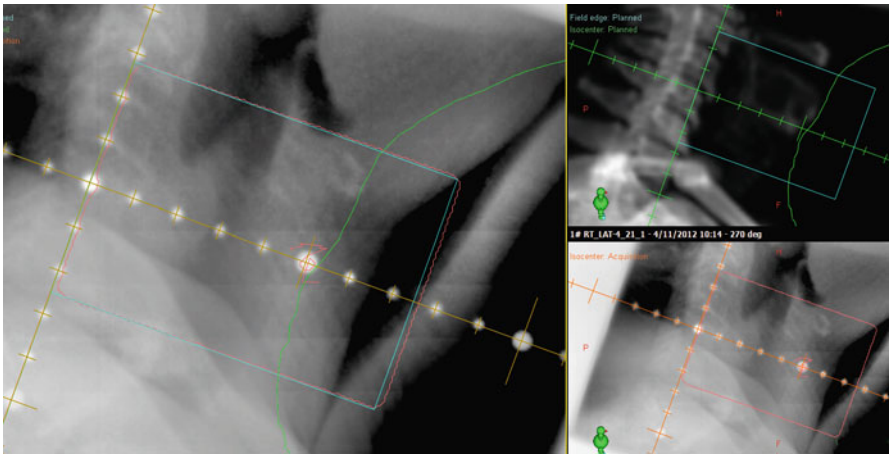

Fig. 20.7 Daily treatment verification with electronic portal imager (*EPID*). The EPID verification and the digitally constructed radiograph (DRR) images are shown on the *upper right and lower right corner, respectively*. Both images are co-registered and displayed on the left demonstrating a good setup with a very minimal error in positioning using the patient's bony anatomy

Table 20.1 Treatment planning goals for the case study 2

Organ	Planning goal
PTV	$V_{Prescription} = 95\%$[a]
Esophagus	$V_{50} < 50\%$[b]
Left parotid	$V_{26} < 50\%$ and $V_{30} < 45\%$
Spinal cord	$D_{max} < 45$ Gy[c]
Brainstem	$D_{max} < 50$ Gy

[a]$V_{50} < 50\%$: Volume that receives 50 Gy must be less than the 50% total esophagus volume
[b]$D_{max} < 50$ Gy: Maximum dose should be less than 50 Gy
[c]$V_{Prescription} = 95\%$. A minimum of 95% of the PTV volume must receive the prescribed dose

The goal is to achieve tumor control while minimizing the risk of both acute and late toxicity greater than grade 2.

As part of the planning process, we have obtained a simulation CT scan of the patient in the treatment position and immobilized with the same light cast immobilization device shown in Fig. 20.4. The images have been entered into the treatment planning system and treatment volumes and normal structures are defined as following:

The initial clinical target volume (CTV) consisted of the tumor and involved nodes with a margin. The planning target volume (PTV) is obtained by expanding this CTV by 5 mm all around. The PTV is treated to a dose of 50 Gy in 25 fractions. An additional 20 Gy in 10 fractions is delivered conning down to the primary tumor (red) (Fig. 20.8). Organs at risk around the tumor identified are esophagus, oral cavity, spinal cord and brainstem. To avoid unnecessary dose to these organs and limit radiation induced acute and chronic side effects treatment planning goals are given in Table 20.1.

The inverse planning technique IMRT is used in order to achieve the complex dose requirement necessary to improve the tumor control and reduce the radiation induced toxicity. The dose criteria given in Table 20.1 for the PTVs and ORS are used in the treatment plan optimization. Figure 20.9 displays the dose distribution in axial, sagittal an coronal view demonstrating the ability of IMRT in sculpting the dose to the target while sparing the nearby critical organs including the spinal cord, brainstem, and oral cavity. Shown in red is the planning target volume (PTV1) for the primary tumor and receives 70 Gy while the PTV2 for the nodes receives 50 Gy. The oral cavity in lime gray, spinal cord in blue and brain stem in brown are all kept under the specified threshold dose criteria.

The dose volume histogram (DVH) is widely used to evaluate dose distribution. The purpose of a DVH is to summarize 3D dose distributions in a graphical 2D format. The "volume" referred to in DVH analysis is the target of radiation treatment, a healthy organ nearby a target, or an arbitrary structure. Shown in Fig. 20.10 is the DVH for the patient presented here demonstrating that almost 100% of the PTV1 and PTV2 received the full prescription dose of 70 and 50 Gy, respectively, while the dose to the nearby critical organs including brainstem, spinal cord and oral cavity were minimized without compromising the target coverage. The maximum tolerance dose above which likelihood of complication increases for spinal cord and brain stem are 45 and 50 Gy, respectively.

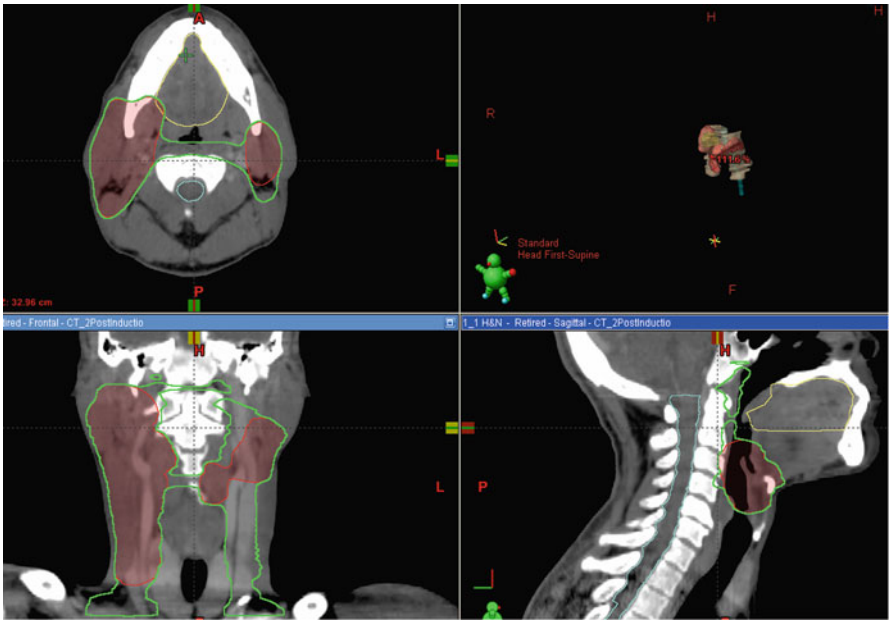

Fig. 20.8 Axial, sagittal, and coronal CT images of the patient. Shown are the planning target volumes (*PTV*) for primary tumor in *red*, PTV for nodes in *green*, and organs at risk (*OAR*) including oral cavity in *yellow* and spinal cord in *light blue*

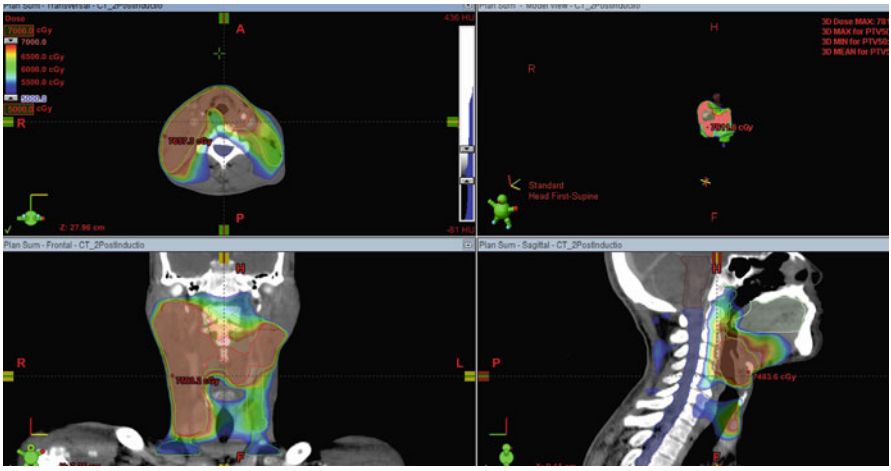

Fig. 20.9 Dose distribution in color-wash displaying the dose between 50 and 70 Gy in axial (*upper left*), sagittal (*lower right*) and coronal (*lower left*). Spinal cord, oral cavity, and brain stem are shown in *blue*, *lime green*, and *brown color*, respectively

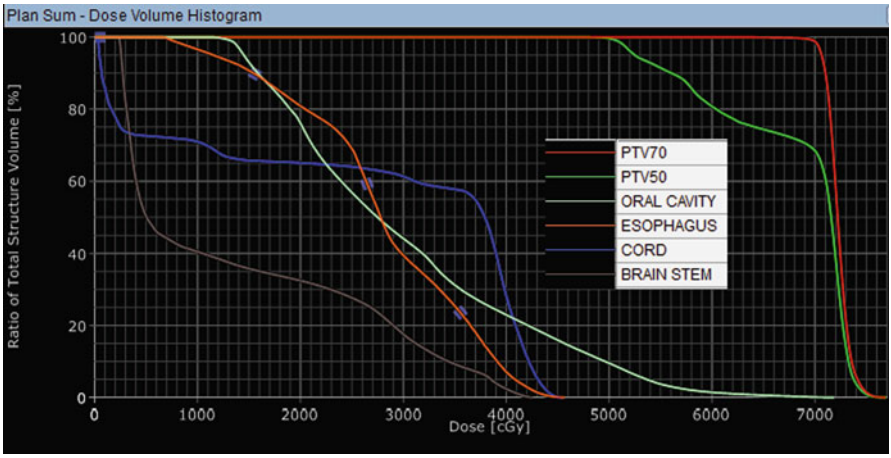

Fig. 20.10 Dose volume histogram (*DVH*) for the patient presented in Case 2. Shown in *red* and *green* are PTV1 and PTV2 receiving almost full prescription dose of 70 and 50 Gy respectively. Organs at risk displayed are oral cavity (*lime green*), esophagus (*orange*), cord (*blue*) and brainstem (*brown*). Shown in Figure is the DVH for the case presented here demonstrating that almost 100% of the PTV1 and PTV2 received the full prescription dose of 70 and 50 Gy, respectively, while the dose to the nearby critical organs including brainstem, spinal cord and oral cavity were minimized without compromising the target coverage

20.4 Summary

The complexity of tumor volumes in addition to being in the close proximity of normal tissues make head and neck cancers very challenging for radiation treatment delivery. IMRT with its ability to target the tumors while sparing the surrounding healthy tissues has become the standard of care for many head and neck cancers despite the increased complexity and time required for planning. It has reported to improve tumor control and to reduce radiation related toxicities. Added benefit of IMRT can be also seen in recurrent diseases. For patients who are not surgical candidates, re-irradiation is possible using IMRT. A thorough evaluation of the patient's condition is very important for the tolerability of the treatment and the treatment related complications. Different imaging modalities including MRI and PET should be used to limit the treatment volume with a high level of confidence that the disease is contained with the planning target volume. The radiation dose to central nervous system should be carefully analyzed and kept below threshold doses to avoid complications.

20.5 Future Direction

To fully benefit from the IMRT technique further development is needed in several areas including functional and molecular imaging to better define tumor margin, the better determination of day-to-day anatomic variation, and adapting the radiotherapy to this change. This would allow furthering the healthy tissue sparing allowing dose escalation to improve the therapeutic ratio.

The limitations of photon radiation delivery technique may be significantly improved by the use of protons beams. Proton beam therapy (PBT) is a novel method for treating malignant diseases and has been gained popularity within the last few years with new centers opening in the USA. The combination of the physical properties of protons and IMRT called Intensity modulated proton beam therapy (IMPBT) has been proven to yield better dose conformity and to significantly reduce dose to surrounding health tissue. IMPBT has been shown to improve dose distribution for targets near critical structures, especially at the base of the skull [11]. Data for other head and neck tumors treated with IMPBT are encouraging, but further data are needed [12]. However, until our experience with IMPBT matures, it will be difficult to establish whether IMPBT may be equivalent or better than the photon IMRT for head and neck cancers. Further prospective clinical trials are needed before IMPBT can be recommended for routine head and neck radiation therapy outside of clinical trials.

Data from clinical trials have demonstrated that concurrent-chemotherapy regimens improve the local and regional control of locally advanced head and neck cancers and some regimens also improve survival rates over those of radiation alone [1]. However, higher normal tissue toxicity is often a limiting factor and might effect overall survival [13]. Future development of targeted radiotherapy techniques that may further reduce radiation dose to surrounding normal tissues is highly desirable.

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Chapter 21
Laser Treatment for Head and Neck Cancer

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Contents

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Abstract This chapter reviews the history of how lasers came to be and how they came to be used in medicine and, specifically, for head and neck malignancies. We will review the scientific principles that lead to the development of the maser, followed by the laser [1, 2]. Next, we will review the effects that laser energy has on organic tissue and how this information influences both the selection of an appropriate laser and our ability to design laser to accomplish specific tasks. We will, then, apply this knowledge to the physician patient interaction. A clear understanding of the mechanism of action of the laser aids in informing a patient about laser surgery prior to obtaining informed consent. After reviewing selection of appropriate lasers for specific tasks, we will look at four selected pathologies: (1) Laryngeal/Glottic malignancies (2) Epiglottic/Supraglottis masses (3) Oral cavity lesions and (4) Tracheal tumors. We will conclude with future directions that include office based surgery for (1) Premalignant and early malignant laryngeal tumors (2) Transnasal and transoral biopsy (3) Fiber laser devivery and (4) Photodynamic therapy. Finally we will briefly discuss robotic assisted procedures as the most recent area of advancement.

Keywords Cancer • Larynx • Laser • Office based procedures • Minimally invasive surgery

Abbreviations

CO2	Carbon dioxide
Nd:YAG	Neodymium:Yttirum-Aluminum-Garnet
KTP	Potassium Titanyl Phosphate
PDL	Pulse Dye Laser
TLM	Transoral Laser Microsurgery
TOS	Transoral Surgery
TORS	Transoral Robotic Surgery
HP	Hypopharynx
OC	Oral Cavity
OP	Orophyarnx
SG	Sublgottis

21.1 Introduction

Cancer is the unifying term we use to describe unregulated cell growth within a living being. Cell behavior, however, is tremendously varied and there are multiple pathways for caregivers to accomplish desired goals. In order to address cancer treatment, clinicians must embrace the concept of more than one pathway to success and the reality that success, itself, comes in many forms. One of the most enduring concepts in surgical oncology is en bloc resection of a tumor. Notwithstanding, current technology may allow us to challenge the idea and any breech to the integrity of a solid tumor

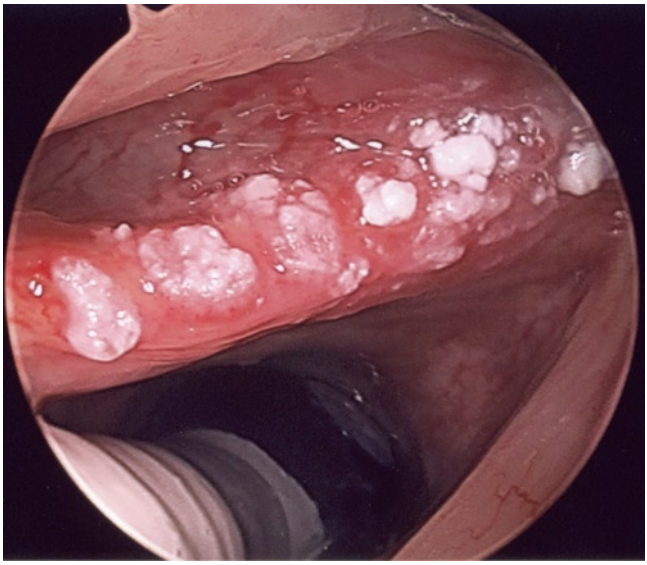

Fig. 21.1 Early glottic carcinoma amenable to laser resection. Under microscopic magnification, the junction between involved and normal tissue is more clearly seen

creates a source for malignant cell transplantation and seeding. Lasers both cut and seal mucosal surfaces in a way that may prevent tumor dissemination from cut edges [3].

The use of lasers in the larynx and pharynx offers several advantages. When coupled with an operative microscope and high magnification, the delineation between macroscopic tumor and normal appearing mucosa is much easier. Further, the surgeon can work with greater precision and challenge the venerable tradition of achieving large margins of resection to insure extirpation (Fig. 21.1).

We now have the benefit of nearly four decades of growth and maturation using laser surgery to address both benign and malignant lesions of the upper aerodigestive tract. Minimally invasive, endoscopic approaches with microscopic magnification have allowed greater preservation of normal tissue, normal physiologic function, and improvement in patient outcomes for speech and swallowing. These advances have not come at the expense of sound oncologic surgical principles. Rather, our ability to present varied approaches to varied tumor cell behavior has only increased our success.

21.2 Historical Perspective

Charles Townes was sitting in a park on a nice bright morning when he suddenly had an idea that helped him overcome the hurdle of shortening wavelengths in order to complete a project [2]. The maser (microwave amplification by stimulated emission of radiation) was the eventual result of his idea in the park. Einstein first postulated the theoretical foundation of laser action in 1917. In his Quantum Theory of Radiation,

he discussed the concept of stimulated emission of electromagnetic radiation from atomic transition (i.e. emission of energy in the form of a photon of light which occurs when electrons *spontaneously* drop from higher to lower energy levels). Einstein further postulated that an atom in a high-energy level could be *induced* to make a transition to a lower energy level if it interacted with a photon with an energy level that, after its collision with an excited atom, would result in two identical photons leaving the collision and traveling in the same direction. This is the underlying principle of laser physics [4].

It is somewhat poetic that experiencing nature helped Mr. Townes focus on a new way to harness natural energy. Once Townes and his partner, Schawlow, transferred the concept to optical wavelengths, light refraction replaced the microwaves and the blueprint for laser was finished. Theodore Maiman built the first laser using a ruby crystal in 1960. Only 2 years later, medical applications began, though the substitution of argon gas for the Ruby crystal was key in the development of medically useful lasers.

As Physicists in the United States were expanding the tools available to surgeons, surgeons were looking for ways to effectively treat cancer and minimized destruction of normal tissue. The concept of minimally invasive tumor extirpation was not far behind the dissemination of laser use in medicine. In 1962, Zaret and others examined the damage caused by lasers on the rabbit retina and iris. In 1964, the argon (Ar) and neodymium:yttrium-aluminum-garnet (Nd:YAG) lasers were developed. Ophthalmologists used the laser as a therapeutic tool prior to Otolaryngologists. In 1965, however, the carbon dioxide (CO2) laser was developed, which would later have widespread applications in medicine [5] and Otolaryngology. By 1971, there was large published report of the safety, efficacy and efficiency of carbon dioxide laser in Otolaryngologic Surgery [6]. The University of Illinois Eye and Ear Infirmary was a part of this groundbreaking trial and the carbon dioxide laser remains a work horse of head and neck surgical intervention.

The external approach for oral cavity and laryngeal surgery, while entirely effective, often carries grave cosmetic and function changes for the patient. The earliest reports of a less destructive approach came in the 1970s [7]. In 1980, Wolfgang Steiner published his early experiences in endoscopic laser manager of laryngeal lesions [8]. By 1987, McGuirt published a small series of cases using the carbon dioxide laser to manage pre-cancerous lesions, carcinoma in-situ and early glottic lesions and the marriage of technology with improved functional outcome was complete [9]. This alternative approach, however, gained its greatest popularity in Germany. Steiner's work has advanced the use of endoscopic approach even for larger glottic malignancies and other subsites including the supraglottis, hypopharynx and oropharynx. As all of these authors suggest, the transition from open procedures to minimally invasive, endoscopic approaches requires a paradigm shift.

Tumor margins are typically much closer for endoscopic procedures, on the order of 1–2 mm. En bloc resection is sometimes not possible and tumors are sometimes divided in order to be removed. Second look procedures are also recommended in addition to monthly surveillance. It is of great importance to return to John Kirchner's work about the patterns of tumor spread in the glottis when managing tumors of the vocal folds endoscopically [10]. Appreciation of inside out anatomy is invaluable for

management of oral cavity and oropharyngeal lesions. Further, each advance should prompt reflection on what we already know so that new information is incorporated rather than allowed to eclipse a dynamic body of information.

Head and neck cancer clinicians practicing in 2012 have a myriad of tools and techniques at their disposal. This history of lasers in medicine, Otolaryngology, and cancer management is rich. We continue to move forward by understand the basic, historical principles of how lasers work and how we can use stimulated emissions energy to our advantage.

21.3 Tissue Effects

There are three fundamental interactions between living tissue and laser energy. First, the laser energy can be absorbed by chromophores within the tissue. This process translates light energy into heat energy and the thermal effect is the primary tool harnessed by the surgeon using the laser. Second, there are photochemical reactions when the laser energy specifically interacts with molecules within a cell. This is the basis of photodynamic therapy. The patient's cells are exposed to a photosensitive agent prior to the application of laser energy. Upon exposure, the pharmaceutical agent is transformed into an active state by laser energy. Third, the energy deposited by the laser can be increased to high wattage, elicit acoustic energy and create a mechanical disruption of the cell. This is, perhaps, on of the least predictable interactions in terms of post-operative healing [6]. We will keep these principles in mind as we discuss further.

Tissue is affected by the amount of radiant energy *absorbed* by a laser. Energy that is reflected, transmitted, or scattered is not taken into account. The radiant energy of a laser varies among the different types of lasers used in otolaryngologic surgery. The wavelength of a laser also affects the degree of absorption by tissue, where lasers with longer wavelengths exhibit less tissue scatter and more absorption. The pioneering work on the first laser had a prominent element of trial and error, by necessity. As with most discoveries, however, successive work builds on a new foundation and higher heights are reachable. Lasers can now be developed to affect specific tissues. For example, the tunable Q-switch and pulse-dye laser (PDL) were designed to be absorbed by color pigments and hemoglobin, respectively. Additionally, the KTP, Argon, and PDL lasers all have frequencies near the absorption of hemoglobin and these tissue interactions make them quite suitable for use on vascular lesions. The role of these lasers in addressing head and neck lesions is expanding, but the carbon dioxide laser is still considered the work horse.

The properties of the CO2 laser, which has the longest wavelength of any laser commonly used in medicine, make it an extremely comfortable fit for head and neck surgery. It works by increasing the temperature of its target tissue to between 60 and 65°C, at which point protein denaturation and disturbance of the deep structural integrity of the tissue occurs. Further heating results in vaporization of intracellular water and tissue shrinkage. Adjacent to the targeted area is a zone of thermal necrosis, where small vessels, nerves, and lymphatics are sealed. The parameters of this

zone are regulated by wattage, pulse time and application time, all of which can be at least partially controlled by the surgeon. In general, shorter pulsed, high peak power lasers minimize the extent of collateral thermal damage. This effect likely contributes to the lack of postoperative edema seen in wounds post laser therapy. Studies on the healing properties of laser compared to traditional incisions have yielded conflicting results: some noted impaired wound healing among the CO2 laser incisions compared to those of the scalpel, while others [11] noted equivalent results between these groups of wounds. These discrepancies are likely result from a lack of uniform standards for application time, debridement of char tissue and the use of cooling agents on the tissues, all of which can impact post-operative results.

21.4 Applied Knowledge

21.4.1 Preoperative Discussion

Optimal surgical management begins with preoperative education of the patient and their family as well as evaluation of the patient to determine the appropriate plan. Specifically for laser surgery, it is best to transmit as much information as possible about the potential risks of laser surgery that are not present using external, conventional approaches. While surgical fires are, thankfully, rare, it behooves the surgeon to make the patient away of this potential complication and reassure them that preoperative recognition of potential complications is essential to preventing their occurrence. The use of the laser intra-operatively may require intubation with a laser resistant, and more expensive, laser tube. Alternatively, Venturi jet ventilation is sometimes used and the increased risk of pneumothorax associated with high positive pressure, jet ventilation should be shared with the patient. In addition, the placement of a metal laryngoscope to expose the larynx or hypopharynx an result in cracked or chipped teeth, tongue numbness, or a disturbance in the taste buds (Fig. 21.2). Placement of a laryngoscope can be difficult, and rarely, only a monocular, Holinger anterior commissure scope can be place. Use of the laser would be contraindicated. The use of mouth retractors, including the Crowe-Dawis, McIvor, Dingman, and Feyh-Kastenbauer (FK), can also result in injury to lips, teeth, gums and tongue (Fig. 21.3). We recommend discussing the major and minor complications with the patient, again, from the standpoint of reassuring the patient that everything possible will be done to prevent this events.

The next step in preparation is communicating with colleagues. It is policy at the University of Illinois for the surgeon to mark the surgical site in the pre-operative area. Prior to incision, the proposed surgery, operative site and correct side are also confirmed. Specifically for laser cases, the airway fire triad is reviewed. The laser can serve as a spark. Agents that support combustion should also be minimized. We prohibit the use of nitrous oxide and favor oxygen saturation low. There are surgeons who argue that if the fraction of inspired oxygen (FiO2) is always kept below 21%, ignition is impossible. However, the median patient who requires head

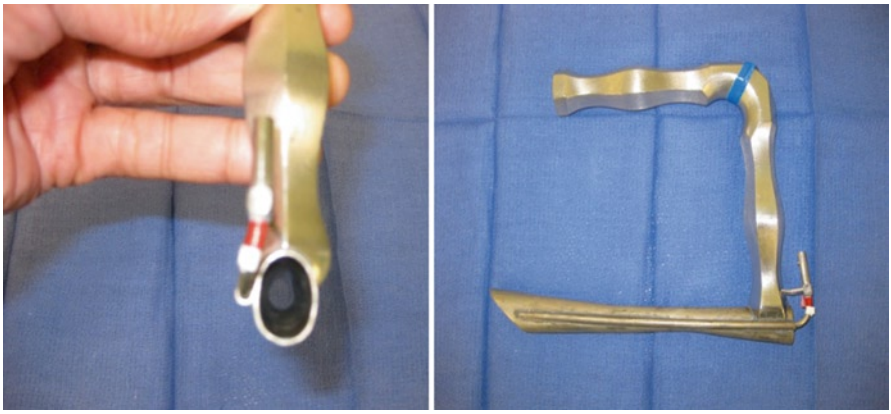

Fig. 21.2 Holinger anterior commissure laryngoscope. Note narrow design, monocular vision

Fig. 21.3 Feyh-Kastenbauer™ Laryngopharyngoscope

and neck cancer surgery is likely to have diminished pulmonary capacity and reserve that may make keeping inspired oxygen below 21% a challenge and we prefer to use less than 30% and as close to air as the patient can tolerate as our guideline. The endotracheal tube most often serves as the source of fuel. A laser-safe tube is commonly used [12–15]. Additionally, some procedures can be done with apneic technique or jet ventilation. As we mentioned earlier, each of these decisions should prompt preoperative discussion of attendant risks and common complications.

Informed consent highlights
Risks of anesthesia (Jet Ventilation/apneic technique/shared airway)
Risk of collapsed lung
Risk of scar tissue (depth of penetration of laser energy)

Risk of fire
Risk of recurrence/need for second look surgery
Risk of conversion to open procedure

21.4.2 Potential Dangers to Patient

Although its occurrence is rare, the most feared, commonly written-about, and potentially devastating complication of laser surgery of the aerodigestive tract is airway fire. For this reason, all persons in the operating room at the time of laser surgery need to be educated on how to prevent and treat airway fires. Overall complications in laser surgery of the upper aerodigestive tract are also rather uncommon: Healy and his colleagues reviewed 4,416 head and neck cases performed using the CO2 laser at their institution over the 11 year period from 1971 to 1982, and found only nine (0.2%) complications [16].

A recent questionnaire designed to elicit the frequency and characteristics of operating room (OR) fires among 349 Otolaryngologists surveyed revealed that 25% had witnessed at least one OR fire during their career. While 27% of these occurred during endoscopic airway surgery, the rest occurred during oropharyngeal, cutaneous, or tracheostomy surgery. There are three basic requirements for a fire: an ignition source, fuel, and an oxidizing agent. In endoscopic airway surgery these requirements are met with the laser (CO2 or KTP reported in this study), an endotracheal tube, suction tubing, or pledget, and oxygen or nitrous oxide.

In oropharyngeal surgery, fires most commonly occurred in the setting of monopolar cautery, an endotracheal tube, tonsil sponge, or red rubber catheter, and oxygen. This study concluded that monopolar cautery devices and lasers represent the most common ignition sources of fires experienced by otolaryngologists [17]. Notably, no airway fires were reported in this survey in the setting of laser-protected endotracheal tubes, so these protected tubes should always be utilized in cases of laser surgery of the aerodigestive tract. Another report of fire during the se of Nd-Yag laser for repair of congenital subglottic stenosis occurred in the setting of a non laser protected ETT [18]. Ahmed and his colleagues reported in 2010 about the safety of lasers in head and neck cancer surgery. They looked at various laser settings to underscore the point that continuous wave and super pulse modes should be viewed separately. They confirmed that the use of higher wattage setting increased risk of ignition, which should be intuitive [12]. Taking a slightly more comprehensive view, Dhar looked at the correlation between wattage setting on the laser, oxygen concentration and the use of dry versus wet cottonoids [19]. The use of dry cottonoid with the laser at 5 W of power and 50% oxygen caused ignition in less than 3 s. Summary knowledge of all these reports underscores the importance of a continuous triad of communication between the surgeon(s), OR staff, and anesthesiology personnel. This is even more critical during work breaks and meal breaks.

Structure and developing a uniform patter are two of the best barriers to mishaps using lasers in surgery. We follow an operative room laser protocol and formal checklist (see Fig. 21.4).

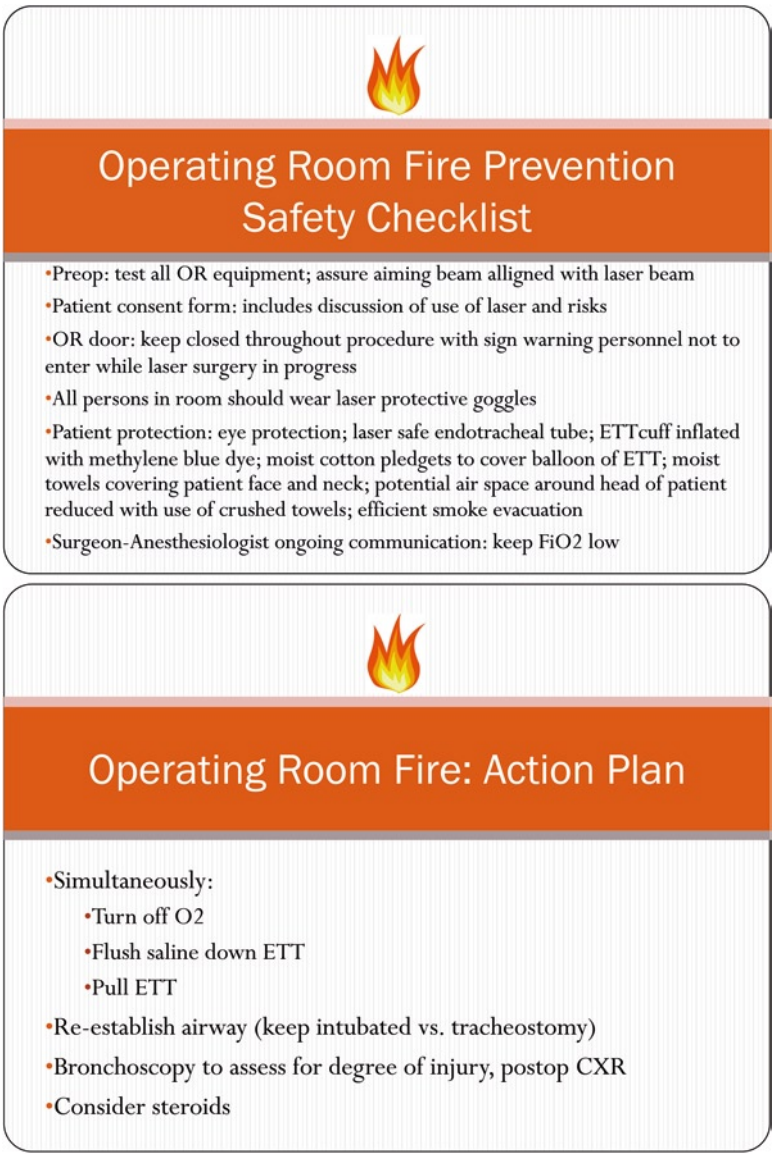

Fig. 21.4 Laser safety protocol

21.4.3 Potential Dangers to Staff

All lasers destroy human tissue to some degree. The result is that all laser surgeries create particulate matter in a gaseous state we call a plume. By definition, a plume is not the same as smoke. Lasers and ultrasonic devices produce larger particles, a plume, that the particulate matter found in smoke. Smoke and plume both can contain

noxious chemical in addition to matter than can be inhaled and cause harm to professionals that work with these instruments. As a result, the association of operating room nurses (AORN) is specific in its recommendation that evacuation systems be used whenever surgical smoke or plume is generated [20]. The University of Illinois at Chicago School of Public Health recently published a comprehensive review on this issue. They found that the surgeon are at greatest risk of exposure to laser-generated air contaminants (LGACs). They looked at chemicals, particulate matter, viruses, and bacteria all of which have been discovered in a surgical plume [21].

The results of the University of Illinois study confirm the recommendations of AORN. They specifically recommend an air exchange rate provided by dilution ventilation of 15 air changes per hour. They further recommend that all rooms should be maintained at positive pressures though dilution ventilation seems sufficient to effectively control smoke generated from the surgical site.

Obviously, it is prudent for healthcare providers to wear protective masks. It remains unclear which device offers the greatest protection, but the N95 respirator appears to be the consensus recommendation. Taping the mask to the fact to improve seal is also recommended.

There are two reports from Europe in 2003 of OR personnel developing laryngeal papillomas after working with a laser surgeon to treat HPV associated lesions. By report, a case in Germany was treated as an occupational disease [22]. A dearth of systematic analysis to establish causation, however, still exists.

21.4.4 Risk/Benefit Assessment

Oncologic efficacy of transoral laser microsurgery has been best supported in cases of early glottic cancer. Specifically, deglutition and speech functions appear to be better preserved with surgical approaches. Transoral laser surgery has also been shown to be more cost effective than primary radiotherapy for all upper aerodigestive tract subsites, with chemoradiation therapy reserved for salvage cases [23]. This may become increasingly important in an upcoming era of more cost- and limited-resource conscious medicine.

Ellies and colleagues reviewed 1,528 patients with carcinomas of the aerodigestive tract found in several subsites: oral cavity (OC), oropharynx (OP), hypopharynx (HP), subglottis (SG) and the glottis. When they looked at patients that underwent CO2 laser surgery as a primary mode of treatment with curative intent (excision of primary tumor), they found that postoperative bleeding, although not common in absolute numbers, was the most common postoperative complication observed in this group [24]. This complication was more common among patients with more advanced stage primary tumors, as well as those whose primary tumor site was the SG. This group of patients did, however, enjoy a less extensive surgical resection than were they to have undergone an open surgical resection of their tumors.

In the era of chemoradiation, however, it may be more appropriate to compare outcomes of laser surgery vs. chemoradiation treatment as opposed to laser surgery

vs. open surgery, as the latter is a less commonly pursued therapeutic route [25, 26]. Also important in the preoperative discussion with the patient is the possibility of the need to convert to an open procedure despite initiating surgical therapy via the laser surgery route. It is also fair to broach the subject of long term sequelae and look discuss function outcomes including speech and swallowing, need for tracheostomy, need for alternative feeding methods and quality of life measures.

Other post-CO2 laser surgery complications cited in the review included laryngeal edema, synechiae formation, pneumonia, pneumothorax (especially when jet ventilation is employed), perichondritis, temporary or permanent tracheostomy, laryngeal stenosis, dysphagia, aspiration, and orocutaneous fistula [24]. A risk:benefit analysis may still favor surgical approaches empirically though available data is conflicting. No prospective randomized controlled studies were encountered on a literature review comparing complications rates between open procedures and their laser surgery counterparts in the aerodigestive tract. Optimizing patient care, however, will likely thwart attempts to conduct that type of study.

We recommend that healthcare providers share as much of this information as possible in a concise manner. We have also found it helpful to present the information in written form, give it to the patient to review and, in some cases, have the patient return for an office visit and have all questions answered prior to proceeding. While the last step may not always be prudent or practical, equipping the patient and family with more information tends to aid in establishing better relationships and lays a foundation for outcomes that are favorable for all.

21.5 Selecting the Appropriate Laser

Any skilled craftsperson must possess the ability to select the appropriate tools and use them wisely. The high energy density of laser light is important in medicine because it is the high density that allows the surgeon to use the laser to ablate and remove diseased tissue. It is important to understand, however, that focusing the energy to a small point that keeps the absolute intensity low while creating a high density energy field in a specified location [6]. Several types of lasers are commonly used in otolaryngology, including the argon (Ar), Neodymium:Yttrium-Aluminum-Garnet (Nd:YAG), Potassium-Titanyl-Phosphate (KTP), pulsed dye (PDL), and CO2 lasers. They vary mainly by their wavelength and specific tissue-absorptive characteristics. Lasers can be thought of in several binary categories: cutting vs. ablative, gaseous state vs. solid state, contact vs. non-contact. The CO2 and Thulium are commonly used cutting lasers while the KTP and PDL are commonly used ablative lasers. The argon laser is a gas state laser whereas the ruby laser relies on a solid state crystal as a means of amplification. The CO2 laser requires a mirror reflection system for delivery and has limitations as to how far in will reach to the target tissue (Fig. 21.5). The KTP laser, in contrast is delivered via a fiber than can be placed in direct contact with the tissues (Fig. 21.6).

The CO2 laser has several applications in otolaryngology, including the management of malignant oropharyngeal or laryngeal tumors, recurrent respiratory papillomatosis

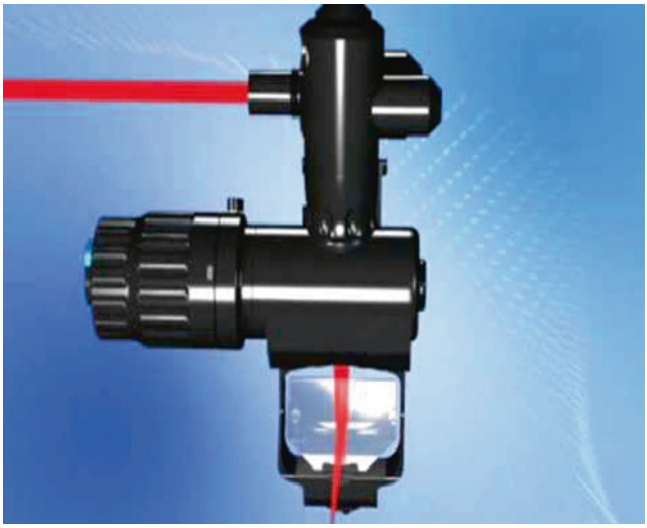

Fig. 21.5 Micromanipulator mirror system for CO2 Laser delivery

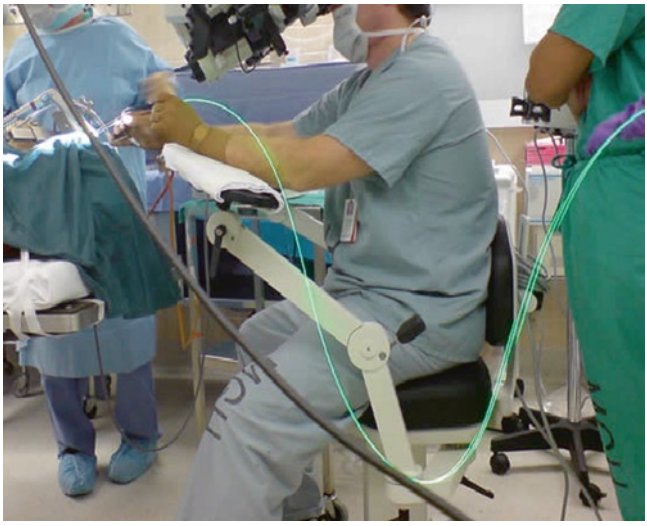

Fig. 21.6 KTP laser with visible *green* light, fiber delivery

(RRP), laryngotracheal stenosis, vocal fold motion impairment (i.e. laser cordotomy, medial arytenoidectomy), otosclerosis (laser stapedotomy), and skin conditions (laser resurfacing for hyperpigmentation and scarring). CO2 lasers produce light with a wavelength of 10.6 μm in the infrared, or invisible, range of the electromagnetic spectrum. Because the CO2 laser is invisible, it is coupled to a helium-neon laser, whose visible, red light acts as an aiming beam for the CO2 laser. It is strongly absorbed by the water content of biologic tissue, and reflection and scatter is minimal.

Recently, flexible scopes and handheld devices have been adapted to transmit the CO2 laser (OmniGuide™, FiberLase™ see Figs. 21.15 and 21.16), which have allowed for increased applications of this laser.

Like the CO2 laser, the Nd:YAG laser is useful in treating patients with obstructive tracheal or bronchial lesions, especially if there is a significant ulcerative component or if active bleeding during lesion (tumor) resection is anticipated. The effective coagulating properties of the Nd:YAG laser is useful in these scenarios. The Nd:YAG lasers have a wavelength of 1,064 nm in the near infrared range. Water weakly absorbs this laser, making it useful in the eye or bladder, where it can be transmitted through liquids. One of its primary uses in otolaryngology is photocoagulation: control of hemorrhage associated with laser bronchoscopy is facilitated by its deep tissue penetration. However, a negative aspect of this laser is its large zone of collateral damage (up to 4 mm deep and lateral from a target surface), which makes precise control impossible, but its use for tracheal neoplasms has yet to be supplanted by a more favorable device.

The Argon lasers produce blue-green light in the visible range, with primary wavelengths of 488 and 514 nm. It is readily transmitted though clear aqueous tissues (cornea, lens, vitreous humor), and is absorbed by hemoglobin and pigmented tissues (i.e. port-wine stains, hemangiomas, telangiectasias). Bone, being a white tissue, reflects most of the incident energy from an argon laser. As such, a small drop of blood or tissue which can absorb the energy of laser must be placed atop the bone in order to make use of the energy of the argon laser.

The KTP laser has a wavelength of 532 nm, and is comparable to the Argon laser. The laser light from a 1064 Nd:YAG is passed through a KTP crystal to produce a double frequency and half the wavelength. The visible KTP laser is more strongly absorbed by hemoglobin, and can be applied for selective photoangiolysis of laryngeal lesions. This property has been exploited to introduce a new modality in cancer therapy, but his will be discussed in greater detail later in the chapter.

The 585 nm PDL is mainly used as a photoangiolytic laser for the larynx, and causes the involutions of lesions through disruption of vascular supply rather than immediate removal of the lesion. Compared to the CO2 laser, the PDL induces less collateral thermal injury. It is also able to be used in the office setting and current applications to address pre-cancerous and early cancer lesions will be discussed. Please see Table 21.1 for a review of the several types of lasers commonly used in otolaryngology. They vary mainly by their wavelength and specific tissue-absorptive characteristics. (See Table 21.1 for summary).

21.6 Selected Procedures

1. Laryngeal Carcinoma in-situ and early glottic carcinoma
2. Epiglottic/Supraglottic carcinoma
3. Oral cavity lesions
4. Tracheal tumors

Table 21.1 Summary of lasers commonly used in medicine

Laser type	Wavelength (nm)	Depth of Penetration (mm)	State
Argon fluoride (UV)	193		Gas
Krypton fluoride (UV)	248		Solid
Xenon chloride (UV)	308		Gas
Nitrogen (UV)	337		Gas
Pulse Dye	**532, 585**	**0.9**	Solid
Argon (blue)	**488**		Gas
Argon (green)	**514**	**0.8**	Gas
KTP	**532**	**0.9**	Solid
Helium neon (green)	543		Gas
Helium neon (red)	633		Gas
Rhodamine 6 G dye (tunable)	570–650		Solid
Ruby ($CrAlO_3$) (red)	*694*		Solid
Yttirium Aluminum Garnet (YAG)	**1,064**	**4**	Solid
Nd:Yag (Neodymium)		**0.4**	
Tm:Yag (Thulim)	**100**	**3 μm**	
Ho: Yag (Holmium)			
Er:Yag (Erbium)			
Carbon dioxide (CO2)	**10,600**	**30 μm**	Gas

21.6.1 Laryngeal Precancerous Lesions and Early Carcinomas

Forty years ago, Geza Jako published his experimental work applying the carbon dioxide laser to laryngeal tissue in a canine model. Early on, the large wavelength (10.6 μm) of the CO2 laser was thought to allow precise removal of tissue that was practically bloodless. However, this mode of thought translated into using the laser at settings of 20–40 W of power with 0.1 s exposure durations and between 6 and 25 exposures [27]. Translating this work to human subjects, the laser was coupled with an operating microscope fitted a 400 mm front lens to provide a binocular view with the appropriate laryngoscope. During these pioneering surgeries, 15 W of power was still in rather common usage [7, 27].

As technology improved and our experience increased, more refined protocols were developed. In 1995, Rudert reported on the comparison of endoscopic laser resections to radiotherapy [28]. They reviewed results from 1979 to 1993 and looked at 161 patients at the University of Kiel. Using a power setting of 1–2 W, they specifically looked at early stage (T1a, T1b, and T2) lesions. They found that the oncologic outcome was at least equal to open partial resection. Though there was no direct comparison, they found their results superior to those achieved with radiotherapy alone [29].

With the patient equipped with preoperative knowledge, the reasonable options include the KTP laser in the office setting, the pulse-dye laser coupled with inhaled 5-amino-leuvulinic-acid (ALA) in the office setting, or the carbon dioxide laser used with or without 5-ALA in the outpatient surgery suite. It is somewhat rare for these procedures to require an inpatient hospital stay.

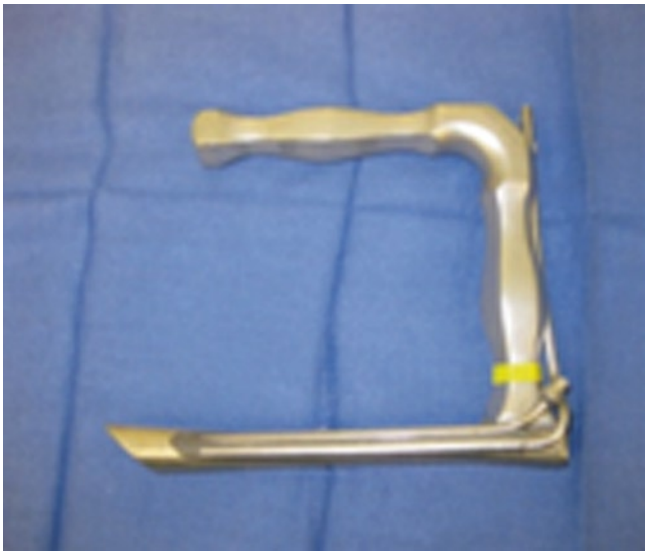

Fig. 21.7 Ossoff-Pilling binocular laryngoscope. Binocular vision with anterior flare for easy placement

One of the important parameters is surgical exposure. While the Holinger anterior commissure laryngoscope can typically be placed in nearly every patient, it is a monocular scope through which the laser cannot be used.(see Fig. 21.2) The Ossoff-Pilling is the laryngoscope of choice for the authors as it offers ease of placement, excellent visualization, and binocular optics for the microscope (see Fig. 21.7).

Once the glottis is exposed, the carbon dioxide laser can be used as a scalpel to perform a biopsy by tightly focusing the Helium-Neon (HeNe) beam for precision work. To address the possibility of field cancerization, the laser can be defocused to re-surface the vocal fold epithelium in a field of absorption. We favor using cold knife technique to collect deep biopsies for frozen section margins to confirm the absence of cancer prior to performing laser resurfacing.

The optimal management of early glottic carcinoma remains a matter of debate [30]. However, it is certainly not entirely clear that radiotherapy should be the primary choice. Surgical options, specifically, laser surgery still has a role in the management of glottic tumors (see Figs. 21.8 and 21.9).

21.6.2 Epiglottic/Supgraglottic Lesions

One of the first reported surgeries for epiglottic cancer is from 1859. Chevalier Jackson, however ushered in the use of a laryngoscope and the endoscopic approach [31]. Ogura's standardized procedure has been refined as the selectivity of neck dissection has increased [32, 33]. Supraglottic cancer as a subset of laryngeal cancer

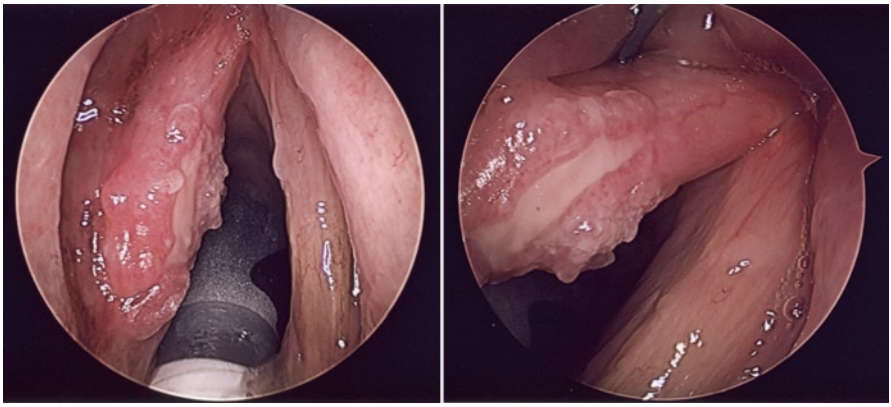

Fig. 21.8 Preoperative view. Magnification and angled telescopes allow for assessment of tumor

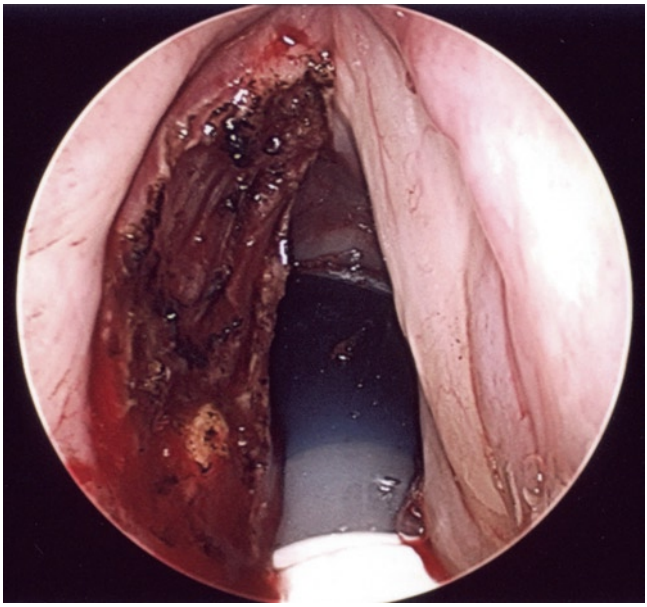

Fig. 21.9 Postoperative view after laser resection. Muscle preserved

is relatively rare. However, this location is particularly amenable to a transoral approach as a means to improve outcome and preserve function.

The Lindholm laryngoscope offers optimal exposures for lesions above the vocal folds (see Fig. 21.10). It rests against the base of tongue and provides superior access to the supraglottis to perform an endoscopic supraglottic laryngectomy (see Fig. 21.11). This approach minimizes hospital time and patients have superior preservation of function for swallowing [34–37]. Thumfart and Eckel published one

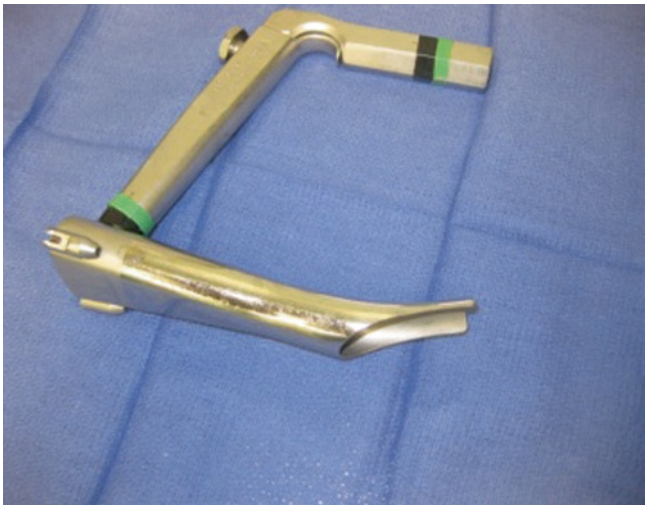

Fig. 21.10 Lindholm laryngoscope for exposure of the epiglottis, petiole

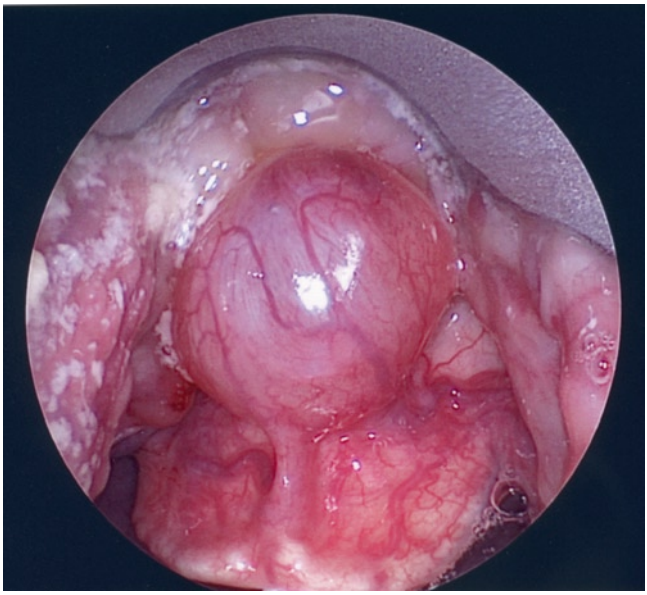

Fig. 21.11 Supraglottic mass exposed with Lindholm scope

of the early reports describing four approaches that continue to inform the surgeon in terms of which lesions are appropriate for an endoscopic approach [36].

As with glottic lesions, the concept of 1 centimeter (cm) margins must be adapted to an area that is only several centimeters in total area. So, close margins are common

and the use of biopsies after tissue resection is, again, encouraged. Also, the idea of bisecting a tumor and "tumor mapping" directly challenge the idea that en bloc resection is oncologically superior. Haughey and Hinni have suggested that a detailed, magnified view of the invasive front of a tumor achieve by cutting through a tumor may provide an advantage over the time honored en bloc resection [26].

The Omni-Guide laser may offer the advantage of improved visualization and precision to remove supraglottic tumors. The Olympus FiberLase system is also an option. The DaVinci robot may also offer superlative operative characteristics and may allow for decreased morbidity from surgical removal of hypopharyngeal and oropharyngeal tumors.

21.6.3 Oral Cavity/Oropharyngeal Lesions

Oral cancer is the sixth most common cancer in the world. Recently, there is evidence that the already high incidence may be increasing. As such, a management strategy is a necessity. The traditional approaches to malignancies in the anterior tongue, floor of mouth, buccal mucosa, retromolar trigone and palatine arch all heal with appreciable disfigurement. Midline sagittal mandibulectomy with mandible swing allows access to the oropharynx, but with a visible cosmetic cost. Though King's report was the first published Strong and Jako were among the first to consider using the laser for oral cavity and oropharyngeal lesions [38]. The initial reception appears to have been cool, since from 1972 to 1979 only 57 cases were completed using laser surgery. Thumfart and Eckel's work, however, lead to our current paradigm [39–41]. It is now universally accepted that T1 and T2 malignancies of the oral cavity can be addressed by laser surgery [30, 42] (see Fig. 21.12). There is persistent discussion as to when a lesion is too big to be appropriate and adequately address by a transoral approach, but bone involvement remains the most universally agreed upon absolute contraindication.

Human Papilloma Virus has been recovered from oral cavity tumors and, indeed, the increase in incidence of oral cavity malignancies has been referred to as a viral epidemic by some. It is also a commonly presented opinion that HPV positive tumors should be managed with radiotherapy because of studies that suggested that HPV and p16 were prognostic factors that favored radiotherapy [43–45].

However, there is some literature to suggest that quality of life trajectory is not improved by radiotherapy. Further, there is evidence and p16 positive malignancies are more responsive to surgery as well and the improved outcomes are not limited to radiotherapy [25]. In short, people with HPV associated tumors are likely to do better with either treatment modality. This perspective helps reinstate surgical therapy as a viable alternative and it is prudent for clinicians to consider the reduced morbidities and a minimally invasive surgical approach can offer [30]. Surgical options for advanced staged disease are also likely to have benefit [26, 46]. Our understanding of

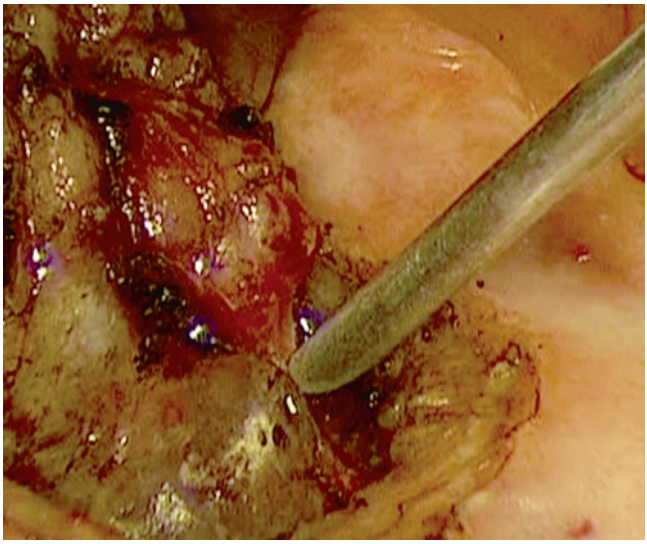

Fig. 21.12 Omniguide laser intraoperative resection of oral cavity (right tonsillar fossa) tumor

long term outcomes for swallowing, speech, and function continues to evolve, but transoral laser surgery does appear to have some advantages [47, 48].

21.6.4 Tracheal Lesions

Use of the CO2 laser in the tracheobronchial tree actually preceded Jako's work in the larynx. In 1970, T.G. Polanyi published work from American Optical Research Laboratories giving the basic design and mechanical embodiment of a system that would allow the laser to be attached to a rigid endoscope/bronchoscope [49]. They addressed three central issues: (1) positional control (2) dosage of the laser beam and (3) visualization of the operative site. A system to manipulate the laser beam through mirrors to focus the energy at the distal portion of the endoscope was detailed. The evolution and refinement of these concepts introduced the CO2 laser (rigid) bronchoscope. In 1982, Ossoff and Karlan made a substantial improvement in the delivery system and introduced the universal coupler [50]. These allowed for the use of a HeNe aiming beam ushering in greater precision and control of the instrument. In 1985, they reported on the use of a universal l coupling device for a multi-institutional trial. 70 patients were enrolled for a total of 118 procedures. 79% of patients with a tracheal malignancy (N = 24) were successfully palliated by CO2 laser bronschopy and removal of obstruction [51]. One year later, they reported on safety precautions [52].

The Neodymium: Yttirium-Aluminum-Garnet laser was the first to offer a fiber that could be place through a flexible bronchoscope. Our French colleagues provided the first report in 1979 [53] and touted the advantages of using a fiber to reach previously inaccessible areas in the distal trachea and mainstem bronchi. Perhaps more importantly, the laser offered a more effective means to control hemorrhage that had made prior approaches to tracheal tumors rather dangerous [54]. Cavaliere reported the successful management of 649 tracheal tumors over a 5 year period in 1988 [55]. Some were even treated with local anesthesia. Squamous cell carcinomas were amenable to this therapy, but they also managed sarcomas, plasmacytomas, malignant lymphomas and thyroid and renal metastatic lesions.

Obstructing tracheal and proximal endobronchial cancers may also be treated with laser surgery either through a microscopeor bronchoscope for the CO2 laser or using a handheld, flexible laser device. primarily with the Nd:YAG or KTP lasers. Depending on the vascularity of the lesion, the coagulating properties of the Nd:YAG laser may be advantageous in combination with the vaporizing properties of the CO2 laser [56]. Hujala reviewed 102 patients treated between 1987 and 1999 for tracheal or endobronchial tumors, 83% of which were deemed malignant upon pathologic review, with either the CO2-Nd: YAG combination laser via a rigid bronchoscope or the fiberoptic Nd:YAG laser. The fiberoptic Nd:YAG laser was mainly used distally in the bronchial tree when direct visualization of the tumor using the rigid bronchoscope was deemed suboptimal. Treatment was considered successful in 77% of these cases (i.e. tumor was removed and ventilation was re-established) [57]. Those deemed unsuccessful were found to have tumors in unfavorable locations.

Otolaryngologists and Thoracic surgeons have advanced our knowledge about lasers in the tracheobronchial tree. Our success in this arena is not yet complete. However, significant palliation and restoration of relatively unlabored breathing with a minimally invasive approach dictate that laser management of endobronchial lesions should maintain its place in the scheme of surgical options.

21.7 Office Based Procedures

1. Precancerous lesions
2. Transnasal/Transoral Biopsy
3. Direct Fiber Laser
4. Photodynamic Therapy

21.7.1 Precancerous Lesions, Leukoplakia, Carcinoma-in-situ

One of the challenges faced by the Otolaryngologist is evaluation of the ‘little white spot’ visualized in the office during flexible fiberoptic exam or videostroboscopy.

Patients typically present with a history of tobacco and alcohol use as well as noticeable voice change. Direct microlaryngsocopy with biopsy allows superior control of the situation, but not every patient is a candidate for general anesthesia. Also, with an ever increasing percentage of surgical costs being passed on to patient as co-payments, the expense of the operative suite is not a negligible factor.

Advances in technology have made some lesions accessible in the non-sedated patient in the office. Our colleagues in Dermatology were pioneers in the use of photosensitizing agents to improve cell destruction and effectively treat cells based of cell phase/mitoses. Ramon Franco provided an early report of using inhaled 5-amino-levulinic-acid (5-ALA) coupled with the 585 pulse dye laser in the office setting [58]. This approach appears to be cost-effective and clinically important for the management of hyperkeratosis, parakeratosis, and other premalignant condition allowing close observation and analysis of tissue samples without necessitating general anesthesia and costs associated with the operating room [59].

21.7.2 Transnasal/Transoral Biopsy

Until recently, one limiting factor for in-office, endoscopic procedures was equipment. Multiple vendors make a flexible endoscope that has a side port (see figure) which will allow passage of injection needles and instruments to facilitate biopsy in the unsedated patient under local anesthesia. However, Infectious Disease guidelines have required gas sterilization of this equipment because the hollow bore working chamber can become a repository for microbes. This requirement pretty much erases the substantial decrease in turnover time that allows in office procedures to be cost effective.

Vision Sciences developed disposable endosheaths that also contain a working port and obviate the need for sterilization. These sheaths can be attached to a variety of flexible endoscopes and convert them into tools for endoscopic biopsy under magnified visualization. A microcup forceps can easily be passed via the working channel to collect an adequate specimen for tissue analysis. Currently, a large percentage of the upper to middle aerodigestive tract can be visualized in a minimally sedated or unsedated patient in the office [60, 61] (see Figs. 21.13 and 21.14).

Fig. 21.13 Endosheath™ slide on technology and schematic of working port

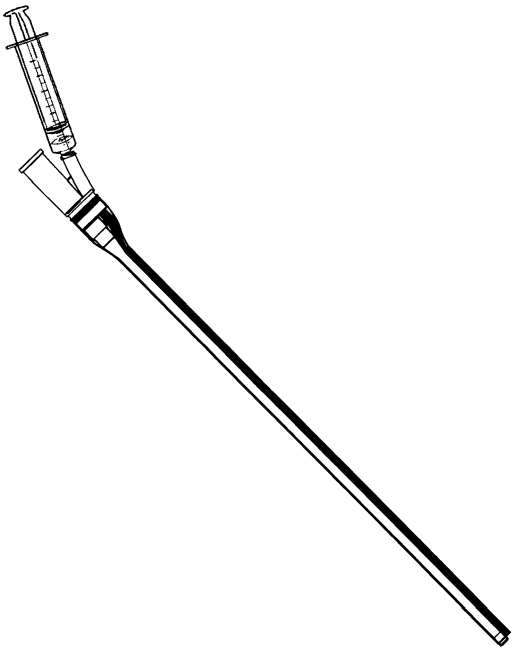

Fig. 21.14 Medications can be delivered through working port as well as passing instruments, e.g., micro-cup forceps, through it for access with visualization through the scope

21.7.3 Direct Fiber Laser

The advent of easy access to a working port has made the use of any of the fiber lasers a realistic possibility in the office setting. As such, we have already described the KTP and Pulse Dye Lasers. The other specific applications are for CO2 fiber delivery systems including the OmniGuide™ and the Lumenis systems (FiberLase™ and 40 W AcuPluse™).(see Figs. 21.15 and 21.16). Both of these delivery systems require that the surgeon understand the inherent loss of power by using a mirror reflection based system.

Laser technology continues to evolve and we are not able to be aware of what properties of lasers will be developed in the future. This wide open canvas will continue to allow scientists and clinicians to craft a wonderful picture of how we manage and often eradicate small malignant lesions in the aerodigestive tract.

21.7.4 Photodynamic Therapy

The KTP, 630 nm photodynamic therapy (PTD), and CO2 lasers (Omniguide® and FiberLase®) all have a means of delivery suitable for an office based approach. In addition, here are a variety of photosensitizing chemicals available for use specific

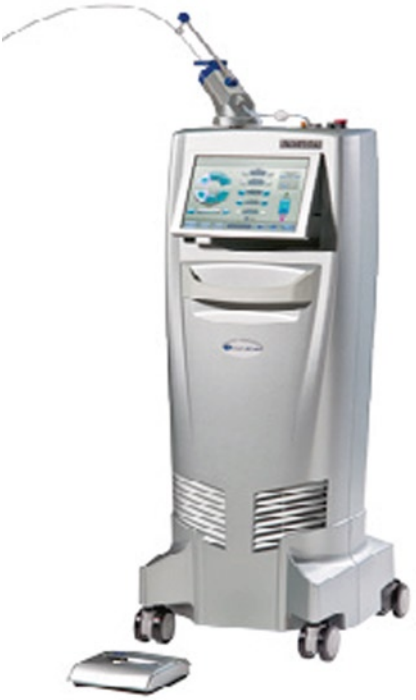

Fig. 21.15 Lumenis FiberLase 40 W CO2 Laser with fiber delivery

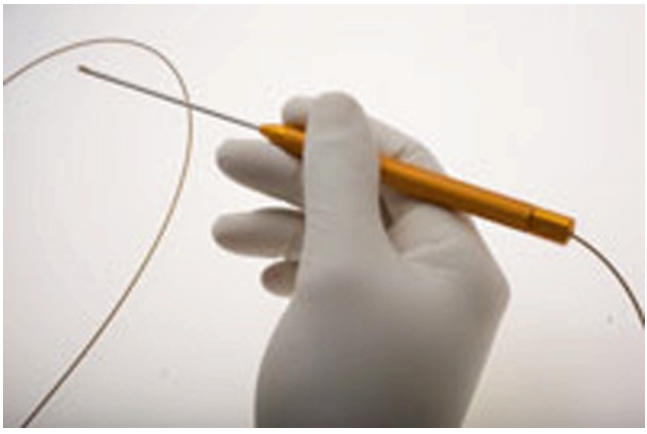

Fig. 21.16 Omni-Guide beam path system

to the absorption frequencies of the individual lasers. Much of the early work in t this field came from Dermatologists and applications for cutaneous lesions. However, the basic principles are appropriate for management of mucosal lesions as well [62, 63]. As mentioned early, 5-ALA can be inhaled in the office and, after waiting

approximately 30–45 min, activated by the PDL in the minimally sedated or unsedated patient [58, 64].

This is an encouraging area of research and progress. Hartnick and Zeitels have been at the forefront of looking at diverse applications for laser technology in the office setting [65, 66]. Currently, however, CPT coding and reimbursement have not mature at the same rate as technology. So, some of these procedures are difficult to submit to third party payors. The combination of the KTP laser with vascular endothelial growth factor inhibition is a recent advance that bears mentioning [67]. Avastin is given as a primer and then the KTP laser is used to ablate visible tumor and the complete disruption of blood supply essentially eradicates tumor and prevents recurrence, in theory.

Also, the 630-nm Photdynamic Therapy Laser is specifically designed to interact with Foscan, Photofrin or Photochlor to enhance cytotoxicity to malignant cells [62, 68–70]. There are emerging reports of creating highly selective photosensitizing agents to more specifically target certain cells. Verteporphin has been used to specifically ablate lymphatic channels to prevent metastasis [71].

21.8 Robotic Assisted Laser Surgery (RALS) in Head and Neck Cancer

The search for improvement and innovation lead to the development of a laser that was quickly applied to medicine.

In 1985, the PUMA 560 single arm robot was used to assist with a CT guided brain biopsy [72]. The new technology evolved rapidly with ZEUS, AESOP and daVinci developed in concert. Neurosurgery, Gynecology, Thoracic Surgery, and Abdominal Surgery/Surgical Oncology found applications for robotic surgery as the new millennium began.

Implementation for head and neck surgery is relatively new. Neil Hockstein and Weinstein have provided much of foundation for the application of robotic surgery to transoral, endoscopic work [73–76].

Use of the DaVinci Robot offers the advantage of virtually eliminating natural, human tremors and creating greater precision. For the patients, early results suggest that robotic surgery offers excellent cancer control, reduced risk of infection, potentially less painful surgery and reduced hospital stays [75, 77]. Harry Quon also suggests that in the age of robotic surgery, postoperative radiation therapy dosage may need to be modified [78]. Reduced radiation therapy dosing may reduce radiotherapy associated morbidity and, overall, the new paradigm of robotic surgery with modified post-operative radiation therapy protocols may produce equivalent or improved cancer control with appreciably improved quality of life measures. The applications of robotic surgery to endolaryngeal and supraglottic surgery will likely increase exponentially as smaller instruments are produced. This remains an area of excitement and interest.

21.9 Conclusions

To be sure, science and medicine continue to undergo metamorphosis. Current cancer management would have seemed impossible to Chevalier Jackson. The reality of constant change mandates that even what we understand now will someday appear ridiculously simple and antiquated. Issues of risk factors and nutrition that have underpinnings in culture will continue to influence outcomes and opportunities to improve patient care will continue [79]. The preponderance of mentholated cigarettes, fortified wines and food deserts in certain communities will likely continue to skew data regarding age at onset, stage at the time of diagnosis and response to therapy. The human condition will remain an entity that demands that we find new ways to address old problems and laser surgery for head and neck cancer will surely continue to mature.

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Chapter 22
Photodynamic Therapy (PDT): An Evolving Therapeutic Technique in Head and Neck Cancer Treatment

Benjamin J. Vesper and Michael D. Colvard

Contents

Abstract Photodynamic therapy (PDT) is a non-invasive therapeutic technique used in the treatment of many cancers, including head and neck cancers. PDT is a two-step process: the patient is first given a drug ("photosensitizing agent") that preferentially accumulates in the tumor. Light is then applied to the treatment site in order to active the drug, in turn leading to tumor destruction. A number of photosensitizing agents and light sources are used clinically for treating head and neck cancers. The PDT technique has been shown to be effective for treating premalignant

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lesions, early stage malignant tumors, and secondary or recurrent head and neck squamous cell carcinomas, as well as for aesthetic and cosmetic purposes. Additionally, a number of different head and neck tumor subtypes (larynx, oral cavity, neck, pharynx, etc.) have been successfully treated with PDT. This chapter serves to provide a general background of the PDT technique and discusses how PDT is currently used clinically to treat head and neck cancers. The future prospects of PDT in the treatment of head and neck cancers will also be discussed.

Keywords Early stage tumors • Head and neck cancer • Lasers • Photodynamic therapy (PDT) • Photofrin • Photosensitizer • Premalignant lesions • Recurrence • Secondary tumors • Squamous cell carcinoma

Abbreviations

5-ALA	5-Aminolevulinic acid
Chlorin e6-PVP	1,3,5,8-tetramethyl-4-ethyl-2-vinyl-klorin-6-carbonic-acetic-7-propion acid sodium-vapor salt
Cis	Carcinoma *in situ*
CO_2	Carbon dioxide
EU	European Union
FDA	Food and Drug Administration
H_2O_2	Hydrogen peroxide
H&N	Head and neck
HNSCC	Head and neck squamous cell carcinoma
HpD	Hematoporphyrin derivative
HPPH	2-(1-Hexyloxyethyl)-2-devinyl pyropheophorbide-a
InGaAlP	Indium-Gallium-Aluminum-Phosphide
IPDT	Interstitial photodynamic therapy
IPL	Intense pulsed light
KTP	Potassium-Titanyl-Phosphate
LEDs	Light emitting diodes
MAL	Methyl ester-aminolevulinate
mTHPC	*m*-Tetrahydroxyphenylchlorin
$O_2^{\bullet-}$	Superoxide anion radical
$^1O_2$	Singlet oxygen
$^3O_2$	Triplet ground state molecular oxygen
$OH^{\bullet}$	Hydroxyl radical
PDT	Photodynamic Therapy
PPIX	Protoporphyrin IX
PS	Photosensitizer
ROS	Reactive oxygen species
S_0	Ground state
S_1	Excited ground state

T_1 Excited triplet state
TNM Tumor, Node, Metastases
UV Ultraviolet

22.1 Introduction

While surgery, chemotherapy, and radiation remain the conventional methods used to treat head and neck cancers, other alternative forms of treatment are becoming more common. One of these alternative methods, photodynamic therapy (PDT), is a United States Food and Drug Administration (FDA)-approved treatment modality utilizing a photosensitizer (PS) and light source. In this technique, a patient is treated with a drug (the PS) that preferentially localizes in the tumor cells. A light source, consisting of a wavelength that specifically matches the excitation properties of the photosensitizer, is applied to the tumor. This excited photosensitizer reacts with oxygen in the tissue to produce reactive oxygen species (ROS) that result in cell death.

PDT has numerous advantages over the conventional treatment methods. Given that the photosensitizer is selectively incorporated into the tumor cells, and the light is applied locally to the tumor, PDT is a minimally invasive procedure that can spare the healthy tissue surrounding the tumor, thereby preserving the aesthetic nature of the patient. This targeted application of PDT minimizes the relative damage of nerves, large blood vessels, and collagen fibers in the normal tissue [1]. Furthermore, there are currently no lifetime limits on the amount of photosensitizer that can be given to a patient, so the treatment can be repeated as necessary, and there are currently no known interactions between PDT and chemotherapy or radiotherapy protocols [1].

The efficacy of the PDT treatment modality is highly dependent upon the properties of the photosensitizer and light source used, and many of the disadvantages associated with this technique arise from shortcomings of these inputs. Disadvantages include poor tumor selectivity of the photosensitizer, limited depth of tissue penetration, prolonged exposure time, prolonged photosensitivity, and pain. Recent research in this field has focused primarily on developing new photosensitizers with improved biological properties and improving the light sources used—either increasing the intensity output of currently used sources or developing and utilizing new light delivery methods.

PDT is clinically approved for use in the treatment of cancer in the United States, Canada, Russia, Japan, and European Union (EU) [1]; however, only a limited number of PDT agents are currently in clinical use. While the technique has found application in the treatment of a variety of cancers [2, 3], as well as other diseases such as macular degeneration [4], this chapter focuses on the use of PDT in the treatment of head and neck cancers. In particular, PDT has been used to treat pre-malignant lesions and early stage malignant tumors in the head and neck region, as well as secondary or recurrent head and neck squamous cell carcinomas (HNSCC). It has also been used for aesthetic and cosmetic applications [1].

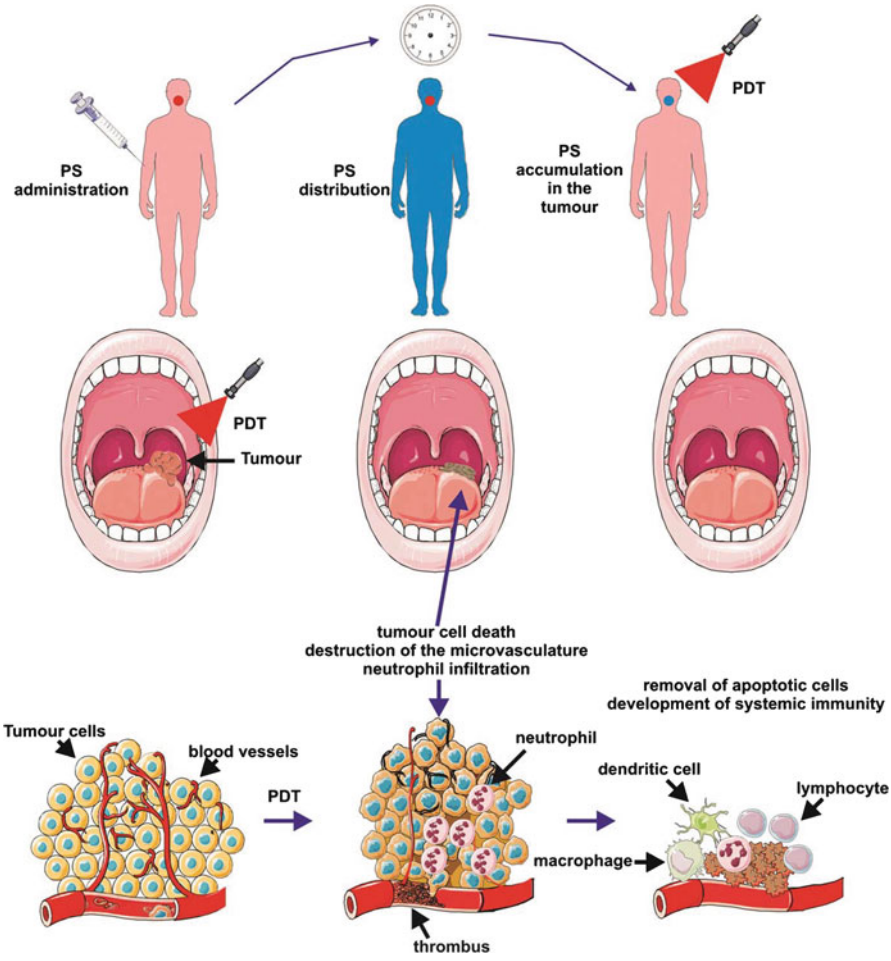

Fig. 22.1 Overview of the PDT process (Figure reprinted with permission from [2]. Copyright John Wiley & Sons, Inc., 2011)

22.2 PDT Mechanism

The PDT mechanism is dependent upon three factors: a photosensitizer, light, and oxygen. An overview of the treatment is provided in Fig. 22.1. A patient is given the PS either topically or systemically, and the PS is given time to distribute within the body and accumulate in the tumor. Once incorporated, the tumor site is irradiated with a light source, which in turn activates the PS. This activated PS reacts with molecular oxygen present in the tissue to produce a photochemical reaction resulting in the production of singlet oxygen ($^1O_2$), which in turns leads to cell death, destruction of the microvasculature, and neutrophil infiltration [2, 5, 6]. Additionally, an

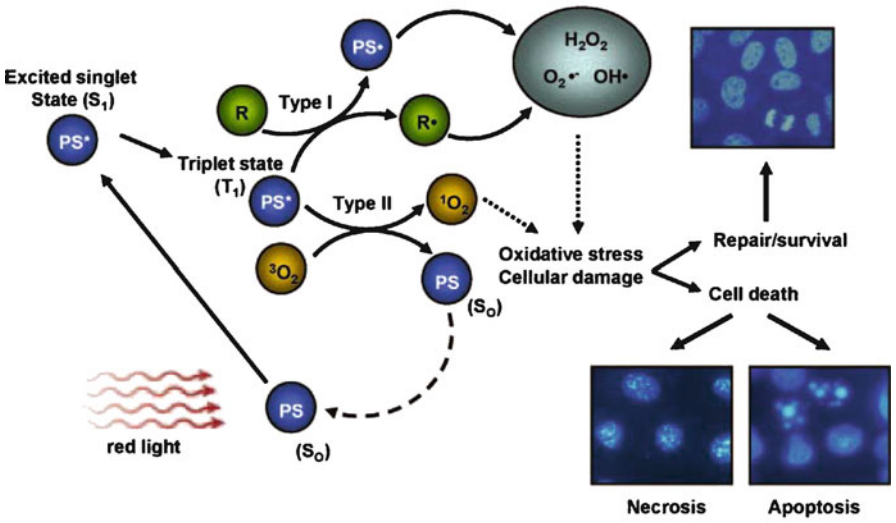

Fig. 22.2 Mechanism of photosensitizer excitation (Figure used with kind permission from Springer Science+Business Media: [7], Figure 1)

inflammatory response is initiated that assists in the removal of apoptotic cells and can, in some cases, lead to the development of systemic immunity [2, 6].

Figure 22.2 provides a more detailed explanation of how photosensitizer activation leads to cellular destruction. When electrons are paired (spins are opposite), the molecule is referred to as being in the singlet state. When the two electrons are unpaired (spins are the same), the molecule is referred to as being in the triplet state. Most molecules, including clinically used photosensitizers, are in their lowest energy state (e.g., "ground state") when they have two paired electrons; thus, these molecules are said to be in the singlet ground state. (In rare cases, the lowest energy state of a molecule occurs when the electrons are unpaired. The most notable molecule with such a triplet ground state is oxygen.) Upon light exposure, a PS in its singlet ground state (S_0) can absorb energy in the form of photons to activate an electron from its ground state to an excited state. The activated electron remains paired to the ground state electron; thus, the molecule is now in an excited singlet state (S_1). Molecules in S_1 are very unstable and therefore transition back to a more stable state through thermal decay, fluorescence emission, or a process known as intersystem crossing in which the spin of the excited electron flips to match that of the ground state electron, thus resulting in an excited triplet state (T_1). Molecules in T_1 are more stable than molecules in S_1, but are still in an excited state. As such, these molecules undergo further processes in order to reach a more stable state—either via direct radiationless decay to the ground state (phosphorescence), or through the formation of ROS via Type I or Type II chemical reactions. In Type I reactions, PSs in the T_1 state react directly with biomolecules in the cellular environment to gain a hydrogen atom

or electron, leading to the subsequent formation of either hydrogen peroxide (H_2O_2) or free radicals, such as the hydroxyl radical ($OH^{\bullet}$) or the superoxide anion radical ($O_2^{\bullet -}$). In Type II reactions, PSs in the T_1 state react with triplet ground state molecular oxygen ($^3O_2$) to form singlet oxygen ($^1O_2$). While it is widely believed that the $^1O_2$ generated in Type II reactions is the most common pathway utilized by clinically used PSs [2, 7], radicals generated by Type I reactions are of significant importance in hypoxic (lack of oxygen) conditions [7]. Regardless of the mechanism used, both Type I and Type II reactions lead to the induction of oxidative stress and cellular damage. The cells are either able to repair themselves and survive, or die via one of three pathways: apoptosis, necrosis, or autophagy-associated cell death [2]. This destruction process may take several weeks, and similar to what is observed from radiation treatment, the healing process occurs with normal mucosa advancing from adjacent tissue [8–10].

Given that $^1O_2$ is a highly reactive species and has an extremely short half-life (10–320 ns) [2], the cellular effects triggered by the production of $^1O_2$ are limited to a very short diffusion range, thus making the treatment highly localized. Dysart and Patterson report that $^1O_2$ can diffuse only 10–55 nm [11]. Given this limited range of treatment, it is imperative that the photosensitizer accumulates in the targeted tumor cells and that the light source reaches the targeted area.

22.3 Light Sources

The wavelength of the light source plays a critical role in the ability to activate the PSs and, thus, the efficacy of the PDT technique. In order to activate the PS, the light must first be able to reach the cells, and then be properly matched with the absorbance properties of the PS being applied in order to supply the energy needed to successfully excite the PS. Longer wavelengths are known to penetrate skin deeper than shorter wavelengths (Fig. 22.3). For example, wavelengths of 500–600 nm can penetrate tissue about 4 mm, while wavelengths of 600–800 nm can penetrate tissue about 8 mm [5]. Thus, PSs that absorb at longer wavelengths can be activated deeper within the tissue than PSs absorbing at shorter wavelengths, and therefore are able to treat deeper rooted tumors. However, wavelengths above ~800 nm, while being able to penetrate tissue even further than shorter wavelengths, are unable to initiate $^1O_2$ production due to a lack of sufficient energy [12]. Thus, most PSs that are currently approved for clinical use absorb within the red and far red spectral window (600–800 nm) [2], and this spectral range is typically targeted in the research and development of potential new agents. While the red and far red spectral ranges are the most commonly used, other wavelengths can still possess clinical significance.

As also shown in Fig. 22.3, light is either absorbed or scattered when it enters the tissue. Both the wavelength of the light source and the tissue type/size being treated will affect the relative amounts of absorption and scattering that occurs [13, 14]. Furthermore, tissue structures present in the treated area (including organelles,

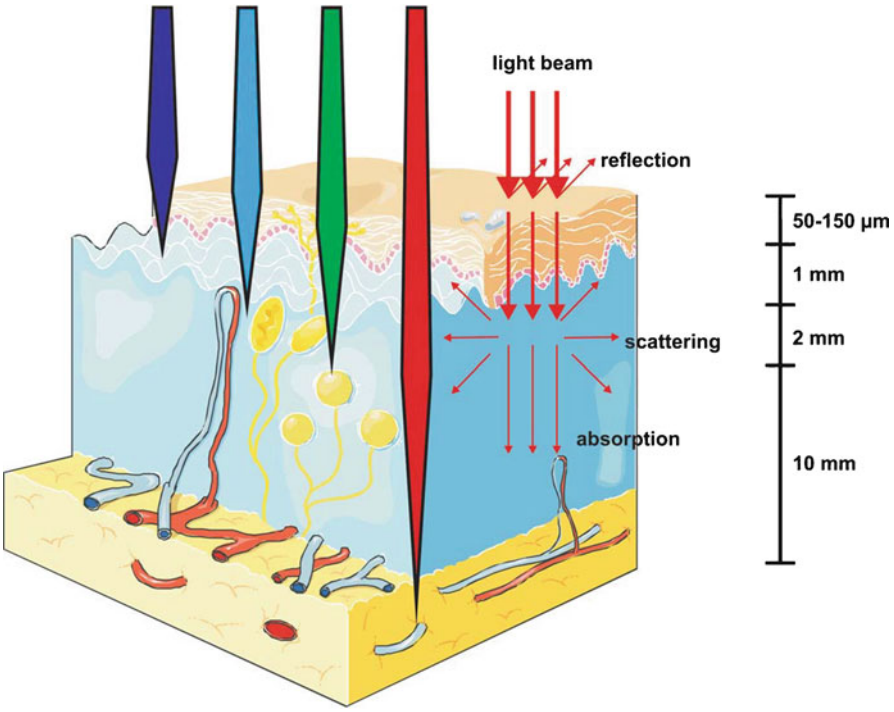

Fig. 22.3 Tissue penetration by various wavelengths of light (Figure reprinted with permission from [2]. Copyright John Wiley & Sons, Inc., 2011)

macromolecules, etc.) can lead to loss of directionality of light and additional light scattering [14], thereby decreasing the amount of light reaching the treatment site and potentially decreasing the effectiveness of the treatment.

In addition to matching the wavelength with the PS properties and ensuring the light reaches the treatment site, light sources vary in the amount of photonic energy they are capable of delivering to a target area [15]. (This measure of light delivery is termed "light fluence rate.") Other considerations for choosing a light source include practical limitations such as the size and cost of the device. Additionally, since different photoactive drugs require different excitation wavelengths, clinicians may desire to use a currently available light source, even if that light source is not the best option for the particular drug being used [16]. The optimized light source may provide only a minimal benefit over a currently available option.

Given the myriad of factors involved in the light delivery process, a number of different light sources are used in clinical PDT settings, including: lasers, ultraviolet (UV) lamps, intense pulsed light (IPL), and light emitting diodes (LEDs). Lasers are the most commonly used light source for PDT, primarily due to their ability to deliver a precise wavelength, often with high light fluence rates. The most commonly used

lasers in PDT include Indium-Gallium-Aluminum-Phosphide (InGaAlP) lasers (which emit at 630 nm), Potassium-Titanyl-Phosphate (KTP) lasers (which emit at 532 nm), and carbon dioxide (CO_2) lasers (which emit at 1,060 nm). (Please see Chap. 21 for a more detailed discussion of these and other lasers used in the treatment of head and neck cancer.) UV lamps, IPL, and LEDs are all forms of non-coherent light sources, in that they emit a range of wavelengths. These sources are widely available, are typically much cheaper than lasers, and are able to cover a larger surface area than lasers [17, 18]. UV lamps emit light within the 100–400 nm range; thus, due to poor tissue penetration at these low wavelengths, they are usually limited to dermatological treatments. IPL sources can emit light in the range from 500 to 1,300 nm, and have the added benefit of employing different pulse durations, pulse intervals, and fluence rates [19], thereby offering the clinician some additional flexibility in tailoring patient treatment. Specific wavelengths can also be obtained with IPL sources if cut-off filters are employed during use; however, the spectral resolution obtained with the cut-off filters is not nearly as precise as that which is found with lasers [19]. LEDs offer a combination of high fluence rates, narrow spectral bandwidths, small size, and low energy requirements [2, 20, 21]. However, LEDs are not commonly used in the clinic for PDT applications because they offer only limited tissue penetration and are more expensive than other non-coherent sources. To this end, some clinicians have argued that for dermatological applications at least, little difference exists among the different light sources, and that the non-coherent light sources offer a cheaper and more practical option than lasers, without sacrificing the effectiveness of the treatment [22, 23]. However, for the treatment of head and neck tumors, which routinely exist in the subcutaneous region, lasers are still the light source of choice for most clinicians.

22.4 Photosensitizing Agents

22.4.1 Photosensitizer Properties

As mentioned above, it is desirable that PSs absorb strongly in the red and infrared spectral region. Additionally, an ideal PS would possess the following properties: (1) selective accumulation and retention in tumor cells, (2) high molar absorptivity, (3) chemical pureness and stability, (4) little-to-no dark toxicity, and (5) high $^1O_2$ quantum yield.

In order for PDT to be effective, the PS needs to be present within the tumor cells, but not in the surrounding normal cells, at the time of light treatment. This can be accomplished by either selective uptake of the PS in tumor cells or, if the PS is incorporated into both tumor and normal cells, a difference in retention times between tumor and normal distribution. (For example, clinically used PSs are taken up by both tumor and normal cells, but reside in the tumor cells for a longer period of time. In this case, after the PS is given the patient, the drug is allowed to clear the normal cells before the light source is applied.) Preferably, the PS will localize

rapidly within the tumor cells, thereby minimizing the time interval between PS introduction and light treatment, and will be cleared rapidly from the body following the light treatment.

Additionally, differential uptake between tumor and normal cells can be achieved to a certain degree by adjusting the amphilicity of the PS [24]. Amphilicity refers to chemical species that have both hydrophilic ("water loving") and lipophilic ("fat loving") properties. In terms of PSs, drugs that are hydrophilic are able to travel through the bloodstream, thus aiding in distribution. Drugs that are lipophilic are able to be incorporated into tumor cells, since these cells have increased lipophilic receptors compared to normal cells [24]. Thus, ideally, PSs will strike a balance between hydrophilic and lipophilic properties, so that they can easily reach tumor cells, and then successfully bind to and/or enter the tumor cells once there.

The ability of a chemical species to absorb light at a specific wavelength is measured by its molar absorptivity. Higher values of molar absorptivity correspond to a greater ability to absorb light. Thus, PSs with high molar absorptivities (e.g., strong absorbance) are more useful in PDT applications than PSs with low absorptivities. Given that molar absorptivity is a function of the wavelength of light applied to the chemical species, it is particularly important that the PS has a strong molar absorptivity at the treatment wavelength, ideally in the 600–800 nm range.

In general, it is desired that a clinical PS be a single, pure compound with a known composition that can be easily synthesized, purified, and characterized. These properties enable the PS to be manufactured on a large scale and help to ensure batch-to-batch consistency. Additionally, long-term stability is desired, as it enables for increased shelf-life of the PS. As discussed in more detail below, PSs that are not pure compounds (but rather mixtures) can still be used clinically, depending upon the other properties of the drug.

The possibility of dark toxicity (e.g., toxicity of the drug in the absence of light) is also a concern when indentifying potential PSs. A PS should have very little or, preferably, no dark toxicity and should exhibit cytotoxicity only upon light exposure. This is particularly important given that clinically used PSs typically accumulate in both tumor and normal cells; thus, if the PS exhibited dark toxicity, the normal cells would be adversely affected as the drug was distributed throughout the body.

One of the most important properties of any PS is its $^1O_2$ quantum yield. Quantum yield is a measure of how effectively a chemical species can generate singlet oxygen and is defined as the number of $^1O_2$ molecules generated per photon of light absorbed. The quantum yield of a chemical species is an inherent property of its chemical composition, and the $^1O_2$ quantum yield of PSs can be tuned by changing this chemical composition. While it is sometimes difficult to predict the $^1O_2$ quantum yield a compound will exhibit prior to experimental measurements, a number of chemical moieties have been identified that generally lead to higher $^1O_2$ production [25]. Most notably, PS candidates which incorporate diamagnetic metal ions (i.e., Zn^{2+} and Al^{3+}) and/or halogenated moieties have been found to exhibit higher $^1O_2$ yields than analogous compounds lacking these chemical groups [25–27].

While a number of PSs are currently used to treat various tumor types, none of the PSs in clinical use today possess all six of the criteria outlined above, and

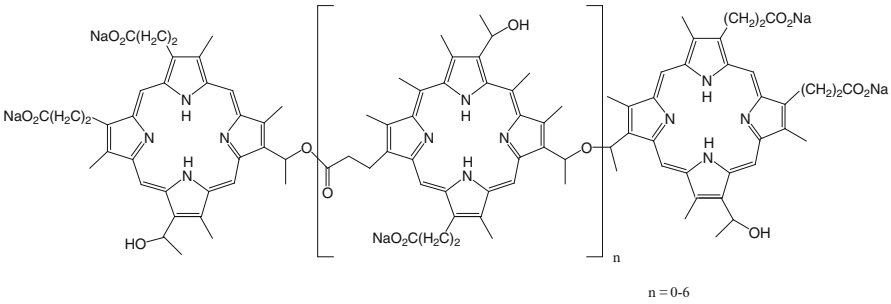

Fig. 22.4 Chemical structure of hematoporphyrin derivative (Photofrin®)

research into new PSs continues in an effort to find a more ideal candidate. Three PSs are widely used for PDT treatment of pre-cancerous and cancerous head and neck diseases: hematoporphyrin derivative (HpD), *m*-tetrahydroxyphenylchlorin (mTHPC), and 5-aminolevulinic acid (5-ALA) [2, 7, 24]. These are discussed in more detail below. A number of other potential agents are emerging as future candidates for clinical use as well.

22.4.2 Hematoporphyrin Derivative (HpD)

HpD was the first PS to be approved, and is the most commonly used PS in PDT treatment. It is used to treat a broad range of cancers; for head and neck disease in particular, HpD has been successfully used in many different tumors, most notably laryngeal and oral cavity tumors. Commercially known as Photofrin®, this PS is a mixture of monomers, dimers, and oligomers derived from hematoporphyrin (Fig. 22.4) and is given intravenously [28]. When HpD is separated into its individual components, the clinical activity is lost [29]; thus, only the mixture is used in clinical PDT treatment. The drug exhibits strong absorbance at 408 and 510 nm, and weak absorbance at 630 nm. Despite the low molar absorptivity in the red spectral region, and subsequent poor singlet oxygen generation, the 630 nm is still commonly used for clinical treatment; long treatment times are needed to make up for the weak photochemical properties at this wavelength [24]. HpD is retained longer by tumor cells than by normal cells; illumination is typically applied 48 h after HpD introduction. At the concentration typically given in the clinic (2.0 mg/kg), a considerable amount of damage to surrounding normal tissue is observed [24]. Recent studies have looked into using lesser amounts of drug (1.2 or 0.8 mg/kg), and found that damage to normal tissue can be reduced at these lower concentrations, yet a significant amount of tumor damage still occurs [30]. One of the main drawbacks with using HpD is that it takes the drug 4–6 weeks to clear the body [24]. Thus, prolonged photosensitivity remains a risk, and patients are encouraged to avoid exposure to direct sunlight and bright indoor lights for several weeks following treatment.

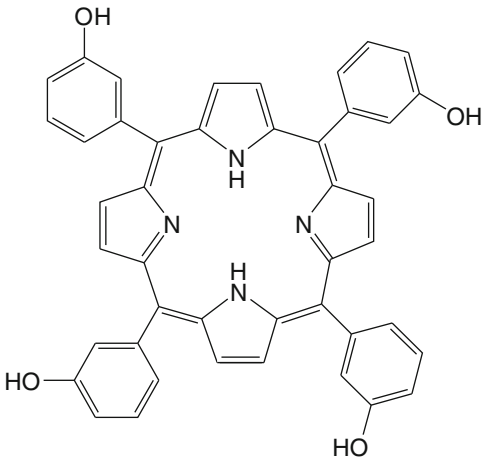

Fig. 22.5 Chemical structure of *m*-tetrahydroxyphenylchlorin (Foscan®)

22.4.3 m-Tetrahydroxyphenylchlorin (mTHPC)

mTHPC, also known as Temoporfin, is a chlorin compound (Fig. 22.5) used in the treatment of head and neck cancer. Sold under the name Foscan®, it is characterized by a high singlet oxygen quantum yield at 652 nm [31], making it a very potent agent. As such, lower concentrations can be used (0.1–0.2 mg/kg are typically given intravenously), and the treatment can be completed in a matter of minutes. However, pain is often reported by the patient during treatment [24]. The distribution and accumulation of mTHPC is slower than HpD: 4 days are needed for the drug to accumulate in the tumor cells and clear the normal tissue. Given the combination of the slow pharmacokinetics and the strong activity of this PS, the patient must execute extreme care to avoid photosensitization in the days between administration of mTHPC and the light treatment, as the PS is known to become activated when exposed to even only dim light. Likewise, the drug takes several weeks to clear the body, so photosensitization is a concern for 2–6 weeks post-treatment [24].

22.4.4 5-Aminolevulinic Acid (5-ALA)

5-ALA is used in the treatment of Barrett's esophagus, actinic keratoses, and head and neck cancer, as well as other tumor types [7, 24]. Commercially available as Levulan®, 5-ALA is considered a prodrug, as it is inactive when initially given to the patient, but reacts biologically to endogenously produce an active drug. 5-ALA is required in the early steps of the naturally occurring heme pathway (Fig. 22.6), and is ultimately converted into Protoporphyrin IX (PPIX), a photoactive compound. The last step of the pathway—the conversion of PPIX to heme—is the rate limiting

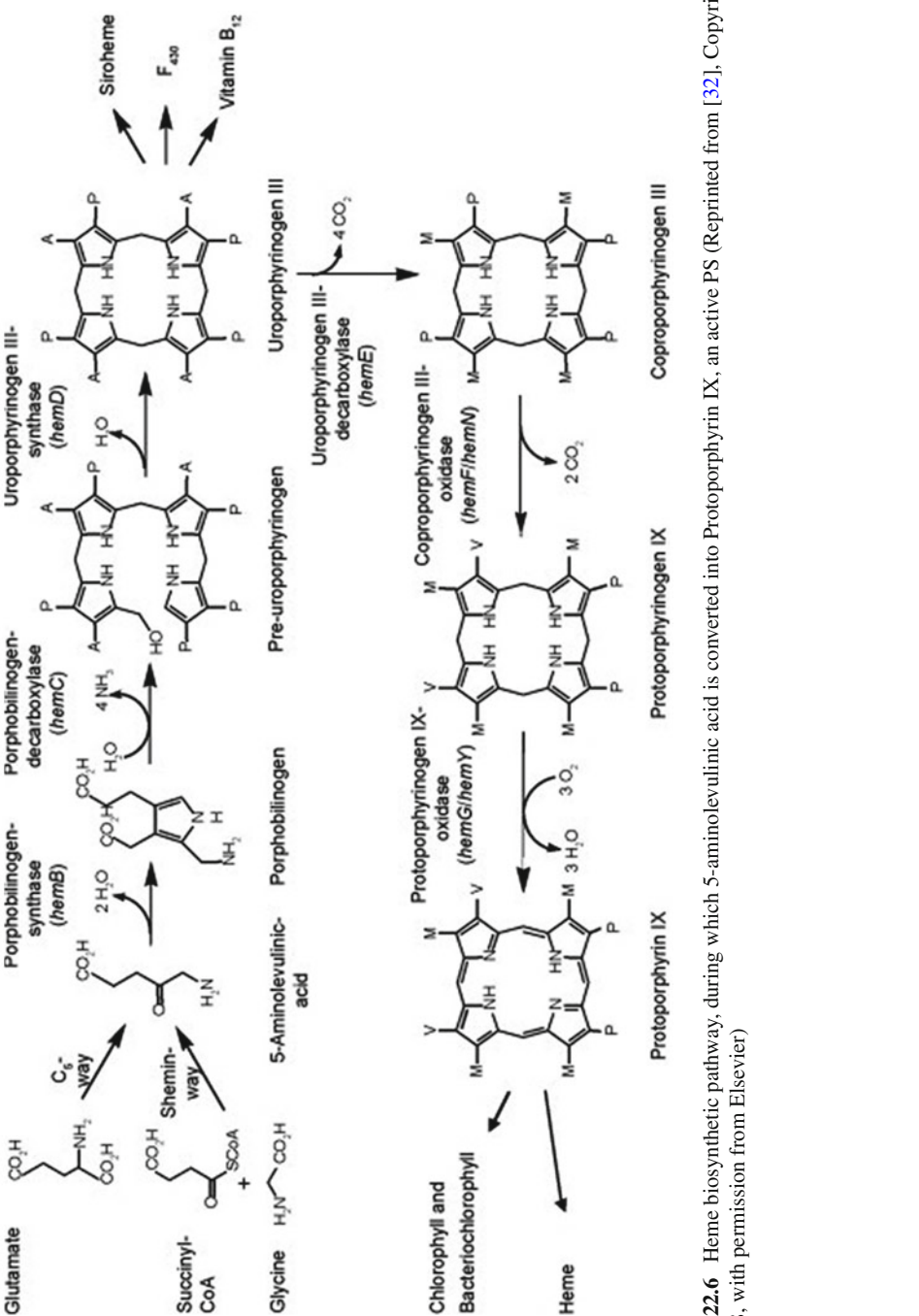

Fig. 22.6 Heme biosynthetic pathway, during which 5-aminolevulinic acid is converted into Protoporphyrin IX, an active PS (Reprinted from [32], Copyright 2008, with permission from Elsevier)

step of this process; therefore, when excess amounts of 5-ALA are given to a patient, the amount of PPIX increases and remains elevated for an extended period of time, allowing it to be utilized as a PS in PDT treatment. Furthermore, the amount of PPIX produced in tumor cells is greater than that produced in surrounding normal tissue, so differential uptake between tumor and normal cells can be achieved with 5-ALA [24].

5-ALA can be introduced orally, topically, intravenously, or via intralesional injection. When applied as a topical solution (as is commonly used in head and neck treatment, particularly for diseases of the oral cavity), the solution is applied for several hours, and light treatment is usually conducted within 18 h of 5-ALA application [24]. 5-ALA can be activated with several different wavelengths, including blue (410 nm), green (510 nm), or red (635 nm) light. Treatment with blue light is most commonly used in the clinic, as higher $^1O_2$ generation is observed at the lower wavelengths, and shorter treatment times can be used. However, using blue light limits treatment to superficial tumors only, due to poor light penetration through tissue. For deeper rooted tumors, red light can be used, but as with HpD, extended treatment times are needed due to poor $^1O_2$ production. In addition to the poor $^1O_2$ generation in the red spectral region, other main drawbacks to the use of 5-ALA include pain during treatment [24] and somewhat poor pharmacokinetic properties, due to the hydrophilic properties of 5-ALA limiting drug penetration through skin and cellular membranes [7, 33].

22.4.5 Emerging Photosensitizers

A key area of future PDT research involves the search for better PSs. This can include both newly developed agents and classes of agents, as well as studies into expanding the uses of currently available agents. In particular, PS-tumor interaction is a key focus of research, as efforts to improve tumor selectivity continue. To this end, some new PSs are being designed to target certain kinds of tumor cells. Three agents showing particular promise are 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-a (HPPH; sold as Photoclor®), sulfonated aluminum phthalocyanine (Photosens®), and 1,3,5,8-tetramethyl-4-ethyl-2-vinyl-klorin-6-carbonic-acetic-7-propion acid sodium-vapor salt (Chlorin e6-PVP, sold as Photolon™). HPPH (Fig. 22.7) has been shown in clinical trials to be effective against esophageal tumors, and it results in minimal sunlight photosensitivity [24, 34, 35]. Photosens® (Fig. 22.8) has been found to be effective for the treatment of early stage and recurrent larynx, pharynx, tongue, and lip lesions, as well as recurrent esophageal tumors [24, 36, 37]. Chlorin e6-PVP (Fig. 22.9) is believed to have potential usefulness in treating superficial and deep head and neck lesions, with less post-treatment photosensitivity than other currently used agents [38].

In an effort to overcome the hydrophilicity limitations of 5-ALA, derivates of 5-ALA have been prepared. One of these, the methylated version of the drug, methyl ester-aminolevulinate (MAL, Fig. 22.10), has been approved for clinical use. MAL,

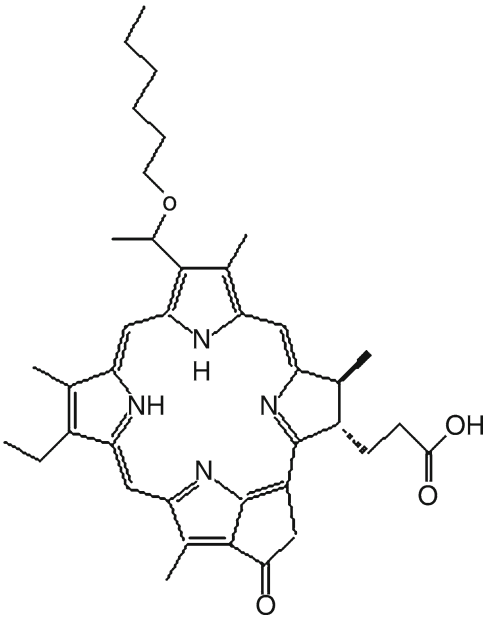

Fig. 22.7 Chemical structure of 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-a (Photoclor®)

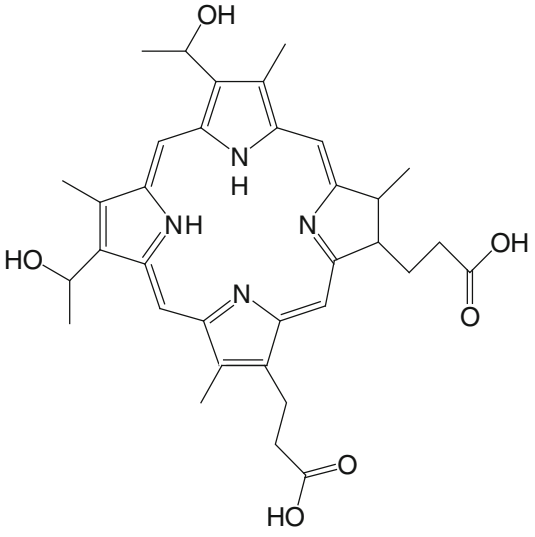

Fig. 22.8 Chemical structure of sulfonated aluminum phthalocyanine (Photosens®)

sold as Metvix®, is used predominately in EU countries and Asia to treat actinic keratoses of the face and scalp, as well as some basal cell carcinomas [39–41]. The terminal methyl group of MAL results in the drug possessing greater lipophilicity than 5-ALA, thus improving tumor uptake. Additionally, the improved lipophilicity

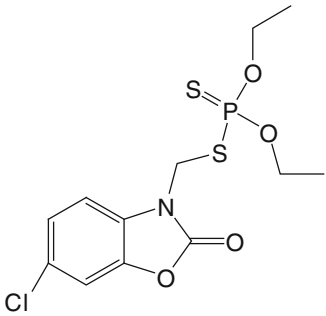

Fig. 22.9 Chemical structure of 1,3,5,8-tetramethyl-4-ethyl-2-vinyl-klorin-6-carbonic-acetic-7-propion acid sodium-vapor salt (Photolon™)

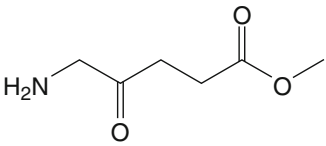

Fig. 22.10 Chemical structure of methyl ester-aminolevulinate (Metvix®)

enables the drug to penetrate the skin further [42–44]. Like 5-ALA, MAL is typically administered as a topical solution, but significantly more PPIX is produced with MAL than can be produced with 5-ALA [7]. The improved pharmacokinetics of MAL further enables a longer activation wavelength to be used (630 nm), and light treatment can be carried out within 3 h after application of MAL [40, 41].

New classes of agents, including porphyrin derivatives, quantum dots, and nanoparticles, are also being studied [45–49]. Alterations in the core chemical structure and attached functional groups of the porphyrin derivatives allow for the development of PSs with potentially increased far-red absorption, enhanced tumor selectivity, and/or increased singlet oxygen quantum yields [49]. The quantum dots and nanoparticles have the potential of possessing tunable optical properties and surface chemistries, which might enable them to improve the sensitization of other PS agents, or to directly interact with molecular oxygen via an energy transfer process [1].

22.5 PDT in Head and Neck Cancer

PDT is most commonly used for treating the following broad classification of head and neck diseases: (1) premalignant and early malignant lesions, (2) secondary or recurrent squamous cell carcinomas, and (3) for cosmetic applications [1]. Each of these areas is discussed in more detail below. In this chapter, we are defining head and neck cancers as those cancers occurring in the mouth, tongue, lips, pharynx, larynx, salivary glands, nasal cavity, neck, and sinuses, as well as related structures in these areas (i.e., skin). Not surprisingly, the predominant histology of head and

neck cancers treated with PDT is squamous cell carcinoma, given its high prevalence in head and neck cancer. However, other head and neck histologies including adenocarcinomas, Kaposi's sarcoma, mucosal melanoma, basal cell carcinomas, and adenoid cystic carcinoma have also been treated with PDT [8]. Here, premalignant and early malignant lesions refer to lesions classified as Tis, T1, or T2, according to the Tumor, Node, Metastases (TNM) Classification System. A Tis staged lesion is one in which tumor cells have not invaded the surrounding tissue; these lesions are also commonly referred to as carcinoma *in situ* (Cis). Secondary/recurrent tumors are typically more advanced and therefore are usually classified as T3 or T4 according to the TNM Classification System (Please see Chap. 6 for a more detailed explanation of the staging system used for classifying head and neck cancers).

22.5.1 Premalignant and Early Malignant Head and Neck Lesions

For early stage head and neck cancers, particularly those of the larynx and oral cavity, PDT offers multiple benefits over traditional cancer therapies, namely: laryngeal preservation, voice conservation, less cosmetic deformities, and salivation preservation. HpD and mTHPC are the most commonly used PSs in PDT treatment of premalignant and early malignant head and neck lesions; however, 5-ALA has also been used.

HpD has been found to be highly effective in the treatment of Cis, T1, and T2 laryngeal, oral cavity, and oropharyngeal premalignant and early stage head and neck tumors [50–52]. A recent study by Schweitzer and Somers looked at 30 patients presenting with Tis, T1, or T2 HNSCC of the oral cavity or oropharynx [53]. Patients were treated with Photofrin®-mediated PDT, and 80% were found to have complete remission at follow-up (ranging from 3 to 144 months). A larger, long-term study by Biel examined 276 patients with early stage HNSCC of the oral cavity and larynx over the course of 17 years (1990–2006). Single-treatment 5-year cure rates for Tis, T1, and T2 oral cancers (n = 113) were 94%; those for Tis, T1, and T2 laryngeal cancers (n = 115) were 91%; and those for superficial T2 and T3 carcinomas (n = 48) were 89.5% [50, 51, 54–56]. An additional 48 patients with superficial T2–T3 oral cavity carcinomas were also treated with Photofrin-mediated PDT, and 89.5% of those patients were disease free after a single treatment. A number of smaller, earlier studies also found excellent results for oral cavity, laryngeal, and pharyngeal tumors [57–66].

Photofrin has also been shown to be effective in treating lip and nasopharyngeal cancers. Zhao et al. reported a 100% cure rate (n = 50) when lip cancer patients were treated with HpD-mediated PDT [67]. Furthermore, when testing 31 patients using combination PDT-cobalt radiation therapy, the same researchers found that HpD-mediated PDT may actually enhance the effects of the radiation treatment [68]. In a study by Kulapaditharom and Boonkitticharoen, 41 patients with premalignant, T1, or T2 lesions of the oral cavity and nasopharynx were treated with HpD-PDT. A complete response rate of greater than 91% was obtained, including a complete response of all T1 and T2 nasopharyngeal tumors [69, 70].

Recent studies have shown mTHPC to be a promising agent for early stage head and neck tumors as well. In a 2007 study of oral cavity and oropharynx tumors, mTHPC-mediated PDT was used to treat 3 Cis lesions, 23 T1 tumors, 15 T2 tumors, and 1 T3 tumor. The trial consisted of 27 patients, some having multiple tumors. Overall, 67% of the tumors were cured, with the Cis and T1 tumors having a very high success rate (85% combined), versus only a 38% combined success rate for the T2 and T3 tumors [71]. In general, most patients in this study were reported to have a good functional outcome, although phototoxicity complications were reported for one patient. A larger follow-up study by Karakullukcu et al. looked at 226 Cis, T1, and T2 lesions in 170 patients and found that 90.7% of the lesions exhibited a response, with 70.8% of them resulting in a complete response [72]. In this study, tumors originating in the tongue and floor of mouth were found to be the most responsive. Earlier studies of mTHPC-treated early stage oral cavity, lip, and oropharyngeal squamous cell carcinomas were also promising, with T1 tumors having a greater response rate than T2 tumors [73–81].

The use of 5-ALA in the treatment of head and neck disease is more restricted than that of HpD or mTHPC, due to its poorer pharmacological properties, as discussed above. Studies involving treatment of oral carcinoma with 5-ALA-mediated PDT have shown somewhat poor results to date [82–84]. However, 5-ALA has been shown to be effective on superficial head and neck lesions such as leukoplakia, acne vulgaris, sebaceous gland hyperplasia, dysplasia, rosacea, and hirsutism [1, 82, 85]. The reported response rates of this PS have varied widely across several studies [52]; these variations are believed to arise, at least in part, from differences in the treatment protocols used [1]. A new skin patch being developed in Germany for 5-ALA application [86–89] may help to improve the inconsistencies among protocols.

A recently reported study has identified a new PS agent that might also be useful in treating early stage HNSCC. Yoshida et al. studied the safety and efficacy of talaporfin sodium (Laserphyrin®, Fig. 22.11, sold in Japan) in 24 patients presenting

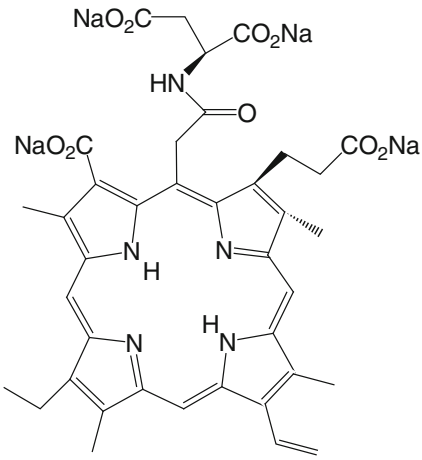

Fig. 22.11 Chemical structure of talaporfin sodium (Laserphyrin®)

with oral, pharyngeal, and laryngeal T1 and T2 cancers [90]. Tumors treated with Laserphyrin® were illuminated at 664 nm using a new low energy ultra mobile semiconductor laser. Two different energy doses were tested: 60–100 and 100–150 J/cm^2. A small number of patients treated at the low dose later exhibited recurrence; however, all patients (n = 16) treated at the higher dose were disease free at follow-up (ranging from 10 to 31 months; 20 month median).

22.5.2 Secondary or Recurrent Head and Neck Squamous Cell Carcinomas

Persistent or recurrent disease is observed in nearly 50% of head and neck cancer patients treated with traditional therapies (surgery, chemotherapy, and radiation) [91–95]. It is believed that residual disease and/or contamination of the surgical field during resection leads to local recurrence in head and neck patients [94]. PDT offers a chance to alleviate some of these problems, particularly the surgical field contamination problem. Others have proposed that PDT could be used to progressively debulk large tumors layer-by-layer [75, 96]. Importantly, PDT has also been shown to be an effective palliative treatment in cases where other treatment options have not been successful [1]. As with the treatment of early stage head and neck lesions, HpD and mTHPC are the two main PSs used for PDT treatment of advanced stage head and neck disease; 5-ALA has also been used sparingly.

Initial studies of PDT in the treatment of advanced HNSCC were conducted by Biel, who used Photofrin-PDT as an intra-operative adjuvant treatment method in 18 patients with recurrent HNSCC [50, 97, 98]. All patients had originally undergone surgical resection, chemotherapy, and radiotherapy. In post-operative follow-up after the PDT treatment (ranging 133–164 months), only six of the patients (33.3%) had developed recurrent or metastatic disease, and only two of these cases occurred within the field of PDT treatment. Biel also looked at another group of 17 patients with advanced laryngeal (n = 11) and oral cavity (n = 6) tumors [50]. No recurrences were observed in the post-operative follow-up (16–69 months) of the laryngeal tumor patients; only one recurrence was observed in follow-up (12–58 months) of the oral cavity tumor patients, and this tumor was successfully removed via surgical resection.

More recent studies reported in the literature have favored the use of mTHPC for the treatment of secondary or recurrent squamous cell carcinomas. A 2004 multicenter study by D'Cruz et al. used mTHPC-mediated PDT to treat 128 patients exhibiting advanced head and neck cancers [99]. Previous conventional therapies had failed with the patients in this study; however, upon treatment with mTHPC-PDT, 38% of patients achieved a tumor response, with 16% of them achieving a complete response. Additionally, a significant quality of life benefit was reported for 53% of the patients. Patients with tumors that were 10 mm or less in depth and/or patients with fully illuminated tumors exhibited the greatest response of any

patient subset in the study, and no major toxicities were reported. A separate study found mTHPC-mediated PDT to be more cost effective than four cycles of palliative chemotherapy [1, 100], further highlighting the potential benefits of using PDT.

Two more recently reported studies utilizing mTHPC have shown similar results to the earlier studies. In Germany, Lorenz and Maier [101] treated 35 patients presenting with recurrent squamous cell carcinoma or secondary head and neck tumors with mTHPC-mediated PDT. Previous treatment had been unsuccessful for these patients. With PDT treatment, 60% (n = 21) of the patients achieved local control, 28.5% (n = 10) achieved partial remission, and 11.5% (n = 4) had no response. No serious complications were reported. The median survival duration post-treatment was 356 days, and the median duration of recurrence-free survival was 181 days for patients exhibiting a complete remission. A 2010 multicenter study conducted in the Netherlands by Tan et al. [102] used mTHPC-PDT to treat 39 patients with recurring HNSCC tumors. Eight patients were deemed untreatable, but 54% of the remaining patients were found to exhibit a response. Those responding to treatment had much greater median survival rates than nonresponders (37 versus 7.4 months), and seven patients were still free of disease at a median 4.8 years after treatment. Again no major toxicities were observed.

Limited studies of advanced stage head and neck tumors have also been conducted using 5-ALA [82–84, 103]. Tumor types treated included oral cavity, laryngeal, and hypopharyngeal tumors. While some success was achieved using 5-ALA, the results were not as favorable as those reported for similar studies using HpD and mTHPC.

A technique called interstitial photodynamic therapy (IPDT) has also been employed in the treatment of large tumors. In this case, thin optical light diffusers are placed into the tumor mass in order to deliver light to deeper areas of the tumor [1]. It is believed that IPDT improves photo-oxidation and distribution within the tumor bed, thereby enhancing the treatment effectiveness. This technique is commonly used as a last resort, however, as long-term complications have been commonly reported. In Phase I/II study results reported in 2004, Lou et al. used mTHPC-mediated IPDT to treat 45 patients with persistent or recurrent head and neck cancer [104]. These patients were unsuitable for further conventional therapy treatments. The IPDT treatment resulted in a complete response for 9 (20%) of the patients, with 5 of the patients still being alive and disease free at follow-up (10–60 months post-treatment). An additional 24 patients (53%) obtained symptomatic relief. Among the 33 patients who exhibited a response, the median survival duration was 16 months; those not responding to the treatment had a median survival time of only 2 months. Carotid blowout was reported for one patient.

In a more recent study, mTHPC-mediated IPDT was used to treat 20 patients with recurrent nonmetastatic base of tongue cancers [105]. These patients all underwent previous radiation therapy and were not candidates for, or chose to refuse, salvage surgery or reirradiation. No short-term complications were reported following PDT treatment, and nine patients (45%) had a complete response at 6 months. Four patients were disease free at longer follow-up periods (46–80 months). Long-term complications were observed in some patients, however, as six patients suffered from pharyngocutaneous fistula, one had serious bleeding, and two exhibited

cutaneous metastasis. In an effort to reduce some of these complications, both magnetic resonance-guided IDPT [1, 106, 107] and ultrasound-guided IPDT [108] are currently being studied, in an attempt to deliver the light more accurately, safely, and uniformly.

The studies described above highlight how PDT may be used as an adjuvant intra-operative treatment modality and, in some cases, may be used to improve cure rates of recurrent head and neck tumors. Larger tumor-free margins of resection can be achieved using PDT, thereby preserving a greater amount of the surrounding normal structures [50]. It is noted, however, that these early studies also suggest that the location of the tumor may play a large role in determining the potential efficacy of PDT treatment in cases of advanced disease. For example, laryngeal carcinomas are a potentially good target, as PDT can preserve voice capability, and partial/total laryngectomies may be avoided through the use of PDT. Furthermore, unlike conventional laser or surgical excision or vocal cord stripping, PDT does not result in glottic scarring, and the side effects of PDT treatment in laryngeal cancers is typically much less than that observed with traditional radiotherapy and chemotherapy techniques [50]. In contrast, oropharyngeal and nasopharyngeal tumors are often difficult to treat with PDT due to difficulty in light delivery, resulting from variations in the geometry of the nasopharyngeal cavity among different patients [10, 109]. This commonly results in an inhomogeneous illumination field, and light overexposure is a problem in these tumors. To overcome this issue, new light delivery applicators are being designed to more accurately deliver light to the targeted treatment area [110, 111].

22.5.3 Aesthetic and Cosmetic Applications

One of the benefits of utilizing PDT in the treatment of head and neck cancers is that, compared to other conventional treatment modalities, it can reduce cosmetic and aesthetic morbidities [112]. In addition to treating tumors, the use of PDT for primarily aesthetic and cosmetic applications relating to head and neck disease has increased in recent years. The FDA now recognizes 5-ALA for a number of off-label uses, including photorejuvenation and the treatment of sebaceous gland hyperplasia, hirsutism, and rosacea [1, 113–115]. 5-ALA-mediated PDT has also been used to treat acne vulgaris, actinic damage, Bowen's disease, and rhinophyma [1, 116–118]. Additionally, abnormal pigmented lesions—including ephelides (freckles), lentigines, and keratoses—can be treated with 5-ALA-PDT utilizing a 532 nm light source [1].

As mentioned above in Sect. 22.5.1, protocols used in the deployment of 5-ALA sometimes vary considerably among clinicians; thus, a variety of success rates have been reported with this PS. However, 5-ALA-PDT is still widely considered to be an effective therapeutic technique for the treatment of these various head and neck related skin conditions. This treatment is not without side effects, however, as pain is often reported both during and after treatment, and both swelling and erythema

are sometimes observed within 24 h of treatment [1]. These effects are often greater when clinicians employ methods to try to increase PDT efficiency (i.e., longer incubation time of 5-ALA, use of higher power energy sources, etc.) [1, 119]. However, a study has found that these side effects may be lessened by using a less aggressive treatment approach. Clinicians treating acne with 5-ALA-PDT over the course of multiple treatment sessions utilizing a shorter (less than 1 h) 5-ALA incubation time observed a decrease in multiple side effects (crusting, dyspigmentation, and edema) and an increased therapeutic response [120].

22.6 Conclusions and Future Directions

PDT provides numerous benefits for treating head and neck cancers that cannot be found with other currently used clinical modalities. Among these benefits are low systemic toxicity, selective tumor destruction, no lifetime dose limit, and the ability to be used in combination with other treatment modalities. Patients suffering from head and neck cancer often exhibit hindrance of functional capabilities due to a loss of excessive tissue [50]; thus, being minimally invasive and tissue sparing, PDT can serve as a particularly important technique in the treatment of head and neck cancers. Moreover, unlike conventional chemotherapies, developed resistance to PDT has not been reported [1, 121]. PDT treatment is versatile enough that it can be used for both premalignant and malignant tumors (including early and later stage tumors), as well as for cosmetic applications. Furthermore, the treatment can be easily performed in a variety of clinical settings, and patients have far fewer side effects than observed with other treatment modalities.

Despite these numerous benefits, PDT is still a vastly underutilized therapeutic technique in the treatment of cancer, particularly in head and neck cancers. Bredell et al. suggest that PDT is primarily limited by a fundamental lack of clinical knowledge and a lack of established treatment protocols [1]. Increased clinical trials, particularly multicenter trials, are needed to gain a better understanding of the breadth to which PDT can be used to treat various diseases, and to better identify patients who will likely respond to PDT treatment. Furthermore, members of the medical community in general still consider PDT to be a developing technology [1], making clinicians less comfortable in choosing it as a treatment option. Moreover, insurance companies will typically cover treatment for premalignant lesions and malignant tumors, but they often provide far less coverage, if any, for general dermatology procedures in which PDT might also be used [122, 123]. As such, clinicians may be less likely to invest in the technology needed to perform the technique if they do not feel it will be used to its full potential within their clinic.

Even though these current limitations may be challenging to overcome, PDT holds tremendous future promise, and further work is being pursued to improve the efficacy of the treatment. Given the relatively recent success in developing

PSs with improved wavelengths and molar absorptivities, it is believed that PDT use will continue to increase in the future. As mentioned above in Sect. 22.4.5, there is a strong research focus on developing new and improved PSs. These next-generation PSs will be able to treat deeper rooted tumors and larger tumor volumes, thus increasing the patient population who might benefit from this technique. Advancements continue to be made in light source options as well (such as improved laser technology and LEDs with greater tissue penetration), and researchers are also making strides towards better understanding the mechanisms by which PDT damages tumors [45]. Furthermore, researchers are looking into the possibility of using PDT for treating metastatic tumors, and possibly using PDT to prevent metastasis from occurring in the first place [124–126]. It is hoped that clinical efforts will be able to keep pace with the research advancements, and through a combination of increased clinical trials and continued basic research efforts, PDT will one day reach its long-held potential of being a widely utilized treatment technique, particularly in the treatment of head and neck cancers.

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Chapter 23
The Changing Face of Maxillofacial Prosthodontics

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Contents

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Abstract An overview of oral and extra-oral (facial) maxillofacial prosthodontic treatment options will be reviewed. Historical, current, and future perspectives will be presented in an attempt to provide a comprehensive understanding as to the considerations and thought processes that guide the clinician providing these rehabilitative services. In so doing, it is hoped that those in need of such treatment can gain a better understanding of and appreciation for the complexities associated with this type of management. While the provision of health care, in general terms, is a rather complex web, those in need of oro/facial rehabilitation represent a unique subset of significant challenges. These challenges are not limited to the provision of care alone, but rather their complexity is magnified exponentially by many unknowns such as disease control/progression, coordination of care amongst those providers managing the disease process being in concert with those providing rehabilitation services, psychosocial issues, family issues, insurance coverage issues or lack thereof, to name a few. Maxillofacial Prosthodontists, providers of such rehabilitation services, are a dedicated group of individuals whose focus, in simple terms, is to attempt to make their patients "whole again." "Whole again" in the context of replacement by means of prostheses fabricated for lost/compromised oro/facial anatomy.

The focus of this chapter will be limited to patients in need of such services resulting from a diagnosis of malignancy in the region of the head and neck. This patient group, those having a diagnosis of head and neck cancer or benign disease, represents a subset of those in need of such rehabilitation services. Other individuals needing such rehabilitation services stem from traumatic injury or congenital anomalies of the head and neck region.

These treatment interventions focus on anatomical sites that become compromised and are subdivided into intra-oral and extra-oral prosthodontic management. Amongst the intra-oral treatments, further subdivision of maxillary (upper jaw) with or without soft palate compromise, and mandibular (lower jaw). For extra-oral treatments, loss of nasal, auricular, ocular, orbital, and multi-site compromise results in the need to replace lost facial anatomy.

Most individuals in need of these types of rehabilitation services and as well as most providers of management of head and neck cancer, generally speaking, have limited knowledge of what rehabilitation options there are, what can be gained by them, and the complexities associated with provision of them. It is the expectation that this chapter will assist in closing that knowledge gap and will improve the interface between the provider of such services, the referring doctors and most importantly, the patients in need of such services.

Keywords Squamous cell carcinoma • Adenoid cystic carcinoma • Osteogenic sarcoma • Chondrosarcoma • Maxillofacical prosthesis • Surgical, interim, and long range obturator • Cicatrical line • Palatal augmentation prosthesis • Mandibular resection prosthesis • Osseointegrated implant • Craniofacial implant • Free flap • Maxillectomy • Mandibulectomy • Orbital exenteration • Orbital enucleation • Occular prosthesis • Orbital prosthesis • Rhinectomy • Nasal prosthesis auriculectomy • Auricular prosthesis • Hyperbaric oxygen • Extraoral/intraoral fixed and removable implant prostheses

23.1 Introduction

How does one make understandable the unimaginable? Anyone with a diagnosis of head and neck cancer sitting across from a Maxillofaical Prosthodontist prior to their pursuing cancer treatment being told that a portion of their face and/or oral cavity, of necessity, to manage malignant disease soon will be made among the missing. The unimaginable suddenly comes to the fore for such a patient and the need for their management/rehabilitation begins a process that is difficult for anyone to comprehend. Of the more than 13,000 diseases that can be medically treated many result in a reversible change back to what is characterized as "normal" [1]. However, in some circumstances permanent disability whether it results from brain damage, chronic irreversible disorders, or loss of anatomy results in a permanent, devastating change deviating from a return to "normal." These irreversible changes are difficult to understand for those not so afflicted. It is only those facing such a situation who can experience how daunting, frightening, and emotionally debilitating such an intrusion into what thus far was a normal existence which has now become irreversibly not so. Now, the focus going forward necessitates adaptation to what comparatively very few encounter during their lifetime. The unimaginable suddenly becomes a reality. That reality triggers a range of emotional upheaval that is highly variable from one patient to the next facing such situations. Elizabeth Kubler Ross identified such emotional upheavals in her book entitled "*On Death and Dying*" [2]. Those stages of grief evoke a cascade of emotions for any individual about to face their maker and that range of emotions is paralleled with the reaction patients have when facing such a daunting situation as a cancer diagnosis that will result in a physical change in appearance and/or functional compromise in the region of the head and neck.

For the provider tasked with making understandable the unimaginable, there also is an emotional toll for him/her to be paid. Even for the experienced provider, it never is easy whether it is their first case, or the hundreds that follow, to inform the patient of what is likely to follow and how it will be managed. Nonetheless, that pre-operative conversation that takes place between provider of maxillofacial prosthetic rehabilitation services and the patient in need of such management sets the stage for the drama about to unfold. In most circumstances this journey involving the provider, the patient and his/her family is so vastly different from anything else

anyone encounters in provision of health care that making it understandable is more challenging, than the provision of care itself.

This chapter will attempt to describe the various treatment procedures commonly available to manage anatomical compromises that emanate from treatment of malignancies in the region of the head and neck. Malignancies in this anatomical region that are deemed treatable with the intent of cure, generally speaking, have historically been managed first by surgically eradicating the bulk of the tumor that is then followed by adjunctive therapy that commonly consists of post-operative radiotherapy. More recently, post-operative radiotherapy has been combined at the same time (concomitantly) with administration of chemotherapy. In some circumstances, chemotherapy administered either before or after completion of radiotherapy (adjuvant chemotherapy) has been added as an alternative treatment protocol to concomitant management. For some tumors in the region of the head and neck, some treatment teams attempt to treat these malignancies with radiation and chemotherapy alone leaving failed attempts to cure them then being managed if deemed treatable by "surgical salvage." The majority of malignancies in the region of the head and neck are squamous cell carcinomas thought in most instances, but not always, caused by a long history of cigarette smoking and/or alcohol abuse. There is an array of other benign and malignant diseases that impact the head and neck region whose etiologies are not attributed to specific self induced insulting agents. More recently, the Human Papilloma Virus has been implicated as another etiological agent responsible for patients being diagnosed with head and neck cancer. Head and neck cancer treatment, in its current form is generally tailored to address the specific cell type of the disease based on documented case series outcome assessment reports, multicenter clinical trials assessing various treatment protocols reported in the literature that describe outcome, success rates, complications of a variety of treatment protocols provided, and whole array of other factors.

The maxillofacial prosthodontic treatment options for anatomical compromise of the partially edentulous or edentulous maxilla (upper jaw) with or without soft palate involvement, partially edentulous or edentulous mandible, ear, eye, nose and facial anatomy compromise that extends beyond one anatomical site will be reviewed. Since no two patient treatments are identical, a broad overview in an attempt to make understandable what these treatments are, their goals, objectives, limitations, and challenges will be described.

23.2 Maxillofacial Prosthodontic Rehabilitation of the Maxilla

One of the most common interventions tasked to the Maxillofacial Prosthodontist is fabrication of an obturator. The term obturator, simply defined, is the provision by artificial means of a separation or seal between two spaces. An example of obturation is placing a cork in the opening of a wine bottle thereby making its contents unable to leave the confines of its container. For a patient in need of tumor ablation surgery

that involves the upper jaw, the creation of communication between the oral cavity, maxillary sinus and/or the nasal cavity results in an anatomical compromise that can be remedied by the provision of an obturator. The goals of obturation are to provide a patient, by artificial means, with a removable prosthesis, a separation between the oral cavity from that of the maxillary sinus and/or nasal cavity. In so doing the restoration of important oral functions related to speech, swallowing, and mastication is facilitated. Typically, obturators are classified as surgical, interim, and long range.

The anatomical compromises of the maxilla resulting from tumor ablation surgery, regardless of the primary cell type, vary and as a result a number of other considerations needing be factored in as they relate to the design and fabrication of an obturator. Various classification systems have been published to describe these permutations of anatomical compromise of the maxilla [3–6]. The surgical management addresses what portion of the anatomy of the maxilla (upper jaw) that will need to be lost to rid the patient of the malignancy. The extent of the anticipated loss is dependent on the location of the tumor and its relationship to the upper jaw and hard and soft palate. Given that the anatomy of the upper jaw is comprised of a right and left maxilla, removal of the left or right side is described as a left or right subtotal or total maxillectomy.

When both maxillae are removed surgically it is defined as a bilateral total maxillectomy i.e., removal of the entire upper jaw and in some circumstances the entire soft palate as well. This latter description (bilateral total maxillectomy) is also not described in the classification systems referenced above. Management of bilateral total maxillectomy by conventional removable obturator treatment is a daunting challenge and may in fact be the least manageable situation as regards restoring meaningful function.

Involvement of the soft palate portends more complex management as regards effective obturation in that it adds a caveat to the classification systems describing these anatomical compromises. The classification systems referenced earlier limit their description to the anatomical loss associated with the upper jaw. Soft plate compromise necessitates attempting to restore its function to affect normalization of speech and swallowing above and beyond obturation of a maxillectomy. A patient having a maxillectomy requires obturation of a static, defined anatomical compromise. Soft palate compromise requires management of a dynamic function rather than a static closure of a defined space. The complexity associated with prosthodontic management of the soft palate compromise is in a category of its own and likely would benefit by having a separate classification system for the various permutations of soft palate compromise and their management.

Tumor extension to and through the floor of the orbit could result in loss of support for the eye or loss of the eye and surrounding contents of the orbit. If the floor of the orbit is part of tumor resection, the likely result will be diploplia (double vision) that in most circumstances remedied by surgical management to reconstruct the needed support to position the affected eye in proper relationship to the unaffected side. This type of surgical intervention is usually accomplished with either soft tissue (facia lata sling), bone grafting the floor of the orbit or use of alloplastic titanium mesh. Fortunately, this daunting anatomical compromise is not common.

When the eye also needs to be sacrificed, provision of both extra-oral and intra-oral rehabilitation is necessitated. The method for retaining the orbital prosthesis in relationship to the maxillary obturator can be created a number of different ways with the two prostheses being separate from each other or interrelated.

Another important consideration regarding what anatomy is involved as part of the maxillectomy, is whether or not the pterygoid muscles/plates that are directly behind the posterior wall (back) of the maxillary sinus are a planned part of the resection. Loss of this anatomy does not add a significant additional challenge to fitting the obturator prosthesis. However, the impact this anatomical compromise often creates is a limitation of the patient's ability to adequately open his/her mouth given that the pterygoid muscles are a major player in jaw movement. The resection of these muscles, surgical scarring alters the opening function of the lower jaw. With that said, a limitation of oral opening can be further compromised by fibrotic tissue changes impacted by radiotherapy. This compromise can create a significant management issue as it relates to the patient's ability to place and remove the oturator prosthesis with their having limited oral access due to limitations of their ability to open their mouths.

23.2.1 Surgical Obturators for Dentate Patients

The magical thing about surgical obturators is that they are fabricated prior to surgical excision of the tumor and made to fit the yet to be determined anatomical compromise resulting from the tumor ablation surgery. For this to be done, it is essential the patient is seen by the Maxillofacial Prosthodontist before the planned surgical date. In so doing pre-operative records, a comprehensive oral/dental exam, and radiographs can be obtained. Preferably, lead-time needed for the prosthesis to be fabricated and made available for the surgery date should be considered in developing the treatment plan, sequencing/scheduling. In order for the prosthesis to satisfy the yet to be determined anatomical compromise, it is essential that a good level of communication between the head and neck surgeon and maxillofacial prosthodontist exist after pre-operative records are obtained. The medically prescribed surgical obturator prosthesis must be designed and fabricated based on the surgeon's input as to what he/she anticipates will be the extent of the tumor resection including what teeth (if any) will remain, whether the soft palate will be involved and, if so, to what extent. This prescription for fabrication of the obturator is based on clinical examination and radiographic assessment of what the anticipated margins of the surgical resection will be needed to remove the bulk of the disease. Input from the maxillofacial prosthodontist as to what offers the best abutment support for the prosthesis design is a key component for the planned surgical excision.

Most important, is a decision about remaining abutment support in that the anterior vertical margin of resection should always be planned such that the tooth immediately adjacent to the surgical site should have its periodontal/bone

support uncompromised by the tumor ablation surgery. To accomplish this desired outcome, it is recommended that the tooth immediately adjacent to that which will remain should be extracted and the vertical cut associated with the tumor removal be made vertically through the center of this tooth socket. As well, the tooth immediately adjacent to the anterior aspect of the surgical site should not be a lateral incisor in that a lateral incisor is the smallest, shortest rooted tooth in the upper jaw that does not offer a good abutment support for the obturator. Anchorage of the obturator to this tooth (the lateral incisor) to support all of what is surgically removed, generally speaking, portends compromise and the possible loss of the lateral incisor. The need for this change, especially after the patient undergoes postoperative radiotherapy creates a dilemma for potential of compromised healing should the tooth need be extracted along with the attendant need to modify the prosthesis by adding this tooth to the prosthesis and placement of a new retentive clasp on the tooth now adjacent to the extraction site in most circumstances that being the central incisor.

Other important considerations prior to surgical intervention and obturator fabrication are the assessment of the condition of the teeth, especially those that will be tasked to retain the oburator prosthesis. The health of the dentition, status of existing restorations, periodontal supporting structures, carious or pulpal involvement of the dentition all need to be carefully assessed and managed pre-operatively. The occlusal relationship (how the upper and lower teeth interface) needs to be evaluated prior to recording impressions so that it can be ascertained that enough clearance for retention clasp placement on the appropriate abutment teeth can be accommodated and if not, appropriate modifications made, such that those modifications can be facilitated prior to recording impressions.

Another key consideration related to surgical obturator design and fabrication in this author's opinion is for the surgical obturator design/fabrication to incorporate an additional key psychological management component. If a patient presents preoperatively with an intact maxillary dentition (a full or partial complement of natural upper jaw teeth) and the planned surgical intervention will extend to the canine tooth and/or involve anterior teeth (central or later incisors), the surgical obturator (which in most circumstances is, in part, defined by having no tooth replacement) is designed to provide for such. It is hard to make understandable many issues related to Maxillofacial Prosthodontic rehabilitation. In this circumstance, simply put, making people faced with significant anatomical loss/functional compromise at the time of tumor resection "whole again" by providing a full complement of tooth replacement (or at least a full smile component of replacement) by anecdotal patient report has had a significant psychologically favorable impact on their recovery. When compared to simply covering the defect at the conclusion of surgery with a clear plastic clasp retained prosthesis the patient would otherwise be left with a dark hole. However, by camouflaging the event does seem to offer some solace (Figs. 23.1 and 23.2). In this day and age, scientific scrutiny is generally the "evidence" needed to support assertions such as this. Anecdotal experience over many years seems to offer justification enough for this assertion.

Fig. 23.1 Surgical obturator for dentate patient. Clear acrylic palatal coverage to support the medicated dressing placed into the surgical site with the prosthesis being retained on the remaining teeth with stainless steel wire clasps

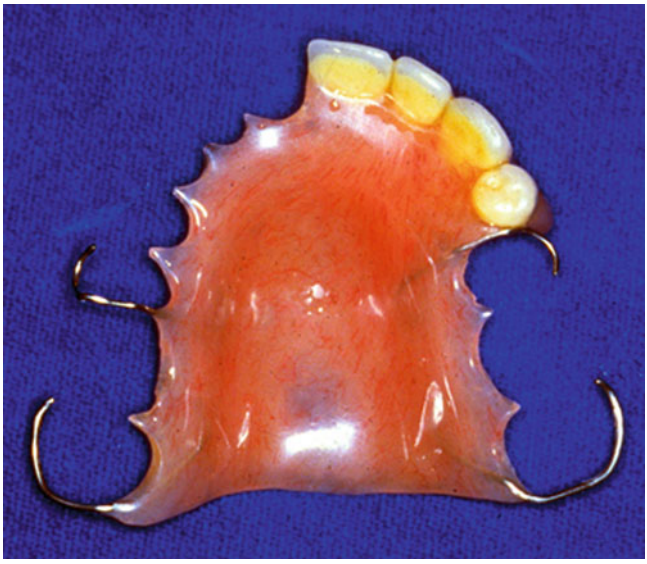

Fig. 23.2 Interim obturator providing for tooth replacement for a maxillectomy involving the left anterior segment of the maxilla

Patients having been diagnosed with a malignancy of the para-nasal sinuses with spread that involves the maxillary teeth, surrounding bone, the hard and/or soft palate or tumors emanating from the hard palate or upper jaw extending into the maxillary sinus and/or nasal cavity managed by surgical excision are in need of obturation. Surgical removal of the tumor leaves the patient with a direct communication between the oral cavity and the maxillary sinus and/or nasal cavity that are anatomically positioned directly superior to the maxillary teeth, jaw and hard palate. Surgical obturators serve a number of functions. The surgical obturator's primary function is to serve as a support for the medicated pressure dressing placed in the surgical site at the conclusion of the tumor ablation procedure. If the clasp retention is not adequate to retain the prosthesis and stabilize the packing in the wound an additional retentive element is added. An orthopedic bone screw can further secure/retain the prosthesis by placing directly through the prosthesis into the substance of the residual hard palate. It is the very last component of tumor ablation surgery attended to prior to extubating the patient followed by his/her discharge from the operating room to the recovery room. Without adequate obturation provided at the time of surgical excision patients are left with an inability to effectively speak, swallow, and chew. In most circumstances, a surgical obturator is the ticket for discharge from an in patient hospital stay in that most hospitals/providers will not discharge a patient from an in patient hospital stay following maxillectomy unless they are able to demonstrate an ability to accommodate nutritional intake by mouth. As well, without obturation, a patient will have a significant challenge communicating with family, nursing staff, physicians, and others. Further, the obturator limits egress into the wound and the dressing placed and thereby reduces the potential for post-operative infection. Therefore, the surgical obturator prosthesis serves many key functions not the least of which is a significant cost savings by obviating a long in patient hospital stay.

The surgical obturator prosthesis is generally left in place for the early post-operative course, approximately 5–10 days, so as to allow the surgical site to heal undisturbed. Once this quiescent period of the undisturbed wound passes, the surgical team removes the obturator, the orthopedic bone screw, if used, the medicated pressure packing dressing, lavages the wound and sends the patient to the Maxillofacial Prosthodontist to make adjustments to the prosthesis. This postoperative prosthesis modification is by design so it can be better adapted to the now defined borders of the healing surgical site. This addition adjustment to the prosthesis is provided by using a resilient reline material (a plasticized version of methylmethacrylate, acrylic). The material is applied to the surgical obturator with the goal to adapt the prosthesis to the borders of the surgical site. Once done the prosthesis should provide better fit of it to the patient and hence assists in normalizing speech and swallowing. Since the maxillectomy site is in a state of post-operative healing/maturation the need for ongoing monitoring, adjustment by reduction of the prosthesis's contour to address pressure irritation or addition of it to provide a better seal is ongoing. Also, this is the time when the patient is instructed in the placement, removal, care, and cleansing of the wound and the prosthesis. Oft times, especially for patients with no prior experience in wearing/using a removable prosthesis, a challenge is presented to the patient

to learn how to master this new skill. Much like learning to tie one's shoe laces, the placement and removal of an obturator prosthesis can be somewhat daunting for the patient at first, especially for those with no prior experience/history of wearing a removable prosthesis. Family members, home health aides, are useful adjuncts who should be present for this appointment so the patient is provided with a support mechanism/back up to rely upon going forward for any assistance needed during this accommodation interval.

A good line of communication with the patient's general dentist is also an important adjunctive interface, especially if the patient is not geographically proximate to the treatment center/maxillofacial prosthodontist's office. Most general dentists and for that matter surgical nursing staff are neither familiar nor comfortable dealing with issues related to obturator therapy. However, the patient's general dentist on occasion, in some circumstances, can be called upon to triage, provide an initial assessment of patient concerns, and offer relatively simple management typically needed such as adjusting pressure/sore spot areas and/or retention of clasps. This type of assistance is very helpful in that patients might avoid a long trip to the medical center that is especially helpful during the early post-operative period.

23.2.2 Surgical Obturators for Edentulous Patients

The rehabilitation challenge for edentulous patients (those with no remaining natural teeth) in need of a maxillectomy is to stabilize and retain an edentulous surgical obturator on the remaining upper jaw following a maxillectomy. Most edentulous patients are able to successfully wear and function with a maxillary complete denture based on an intact completely edentulous maxilla. This ability varies on the patients' residual anatomy of the upper jaw and the ability of the prosthesis to create a seal between it and the tissue base on which it rests. Patients having a long history of successfully wearing removable complete denture prostheses have an advantage as regards their adapting to wearing an edentulous obturator. Patients who are having all their remaining teeth removed as part of the tumor ablation surgery, especially those who have never worn a removable prosthesis of any kind are significantly more challenged in accommodating to this newfound anatomical compromise and its associated prosthetic rehabilitation management.

When a communication is created between the mouth and the overlying sinus and/or nasal cavity as a result of tumor ablation surgery, the ability to create a seal ("suction") between the prosthesis and the remaining tissue bed is no longer possible. With that said, unlike dentate patients the only means of obtaining support, stability, and retention of the edentulous obturator prosthesis at the conclusion of tumor ablation surgery is to provide a mechanism for anchorage of the prosthesis to the residual maxillary anatomy. The commonly employed method is to use an orthopedic bone screw(s) placed through the surgical obturator and directly into the residual hard palate to provide the anchorage needed for the immediate postoperative course. The screw anchored prosthesis is secured in place after first managing

the maxillectomy site by placement of a medicated pressure dressing. In most circumstances, the surgical obturator employed for an edentulous patient is a clear acrylic cover rather than using the patient's existing maxillary denture prosthesis. The rationale for this type of management that differs from that previously described for the dentate or partially dentate maxillectomy patient is to not create load on the underlying supporting tissues or wound during the immediate post operative healing phase. Once the initial healing has occurred, the surgical obturator and packing are removed; the wound rinsed and cleaned (lavaged) and the patient's existing complete denture (if deemed serviceable) can be retrofitted to the surgical site with resilient reline material. In so doing, it can be adapted it to the contours of the surgical site so it can serve as an interim edentulous obturator prosthesis. As previously noted for dentate patients, the surgical site is a healing wound and attendant tissue changes will necessitate ongoing monitoring and adjustments to keep the prosthesis properly related to the changing topography.

The ability to create adequate retention in the early post-operative healing phase is challenging given the wound has yet to complete its maturation process. One of the key elements in providing retention for an edentulous obturator is to be able to engage the developing scar band (cicatrical line) on the inner aspect of the cheek (the lateral aspect of the tumor resection). This scar band forms as a result of the incision line that defines the lateral border of the tumor resection. Many maxillectomy procedures currently are approached entirely via an intra-oral approach rather than using a Weber-Ferguson full thickness flap excision approach [7]. In either case, the surgeon oft times places either a spit thickness skin or synthetic skin (Alloderm, LifeCell Corporation, Branchburg NJ) graft on the inner aspect of the cheek wound above the incision line in the cheek. This skin graft/mucosal junction, (cicatrical line) scar band is an essential anatomical landmark to engage above with the prosthesis such that downward displacement of it can be offset. In so doing, an adequate seal between the prosthesis and the lateral tissue borders can be created. Filling the cavity of the surgical site entirely can be more of a hindrance rather than help, especially in regard to the medial aspect of the surgical site in the region of the nasal cavity, where the lining tissues are richly vascularized and highly innervated. Pressure on these tissues can ofttimes result in discomfort and/or bleeding. As well, if the tumor resection did not include the inferior turbinate of the nasal cavity the prosthodontist is more limited/challenged in his/her ability to adequately fit a obturator prosthesis to this impediment. With the prosthesis extended over and above the anterior aspect of the soft palate and laterally above the scar band (once established) and in some circumstances in the region of the now absent anterior nasal spine (the region just behind the nostril), an edentulous obturator ofttimes can be adequately retained within the surgical site. This interface of the prosthesis fitted to the surgical site along with the prosthesis related to residual edentulous maxillary anatomy of the non-operated portion of the remaining maxilla usually with the adjunctive use/placement of conventional denture adhesive provides a reasonable facilitation of retention of the prosthesis. In so doing, the interim edentulous obturator prosthesis can provide adequate support, stability, and retention offering reasonable restoration of function as it relates to speech, mastication, and swallowing.

In rare circumstances, patients who are unable to negotiate wearing an edentulous obturator with the above noted modifications are sometimes managed by fabrication of a unilateral obturator first described by Parel [8]. With this approach, obturation is the only goal of treatment and not provision of a capacity to chew. This type of prosthesis can facilitate assistance with speech and swallowing. It is, by design, fitted exclusively to the surgical site with no planned coverage over the residual hard palate or maxillary ridge. It is fit to the recesses (undercuts) in the maxillectomy essentially filling what was the maxillary sinus with a hollow bulb resilient extension with a clear acrylic base at its inferior (oral) surface.

23.2.3 Prosthodontic Management for Patients Treated with Dentate and Edentulous Obturators Having Soft Palate Compromise

When tumor ablation surgery extends onto the soft palate or necessitates removal of half or the entire soft palate another level of complexity for rehabilitation management occurs. The soft palate is a key component of the anatomy whose function is a major player for facilitation of speech and swallowing. It is comprised of left and right two paired muscle groups (tensor and levator veli palatini) that meet in the midline of the soft palate. Once this neuromuscular configuration is disturbed by surgical intervention it sets forth a cascade of functional disability that significantly impairs speech and swallowing.

For dentate patients, it is possible to design a surgical obturator prosthesis in such a way that the soft palate compromise can be initially obturated [9]. The method generally pursued is to plan for an overextended resilient cover for the anticipated margin/extent of the soft palate resection. In so doing, the surgeon can easily adjust this resilient extension in the operating room to tailor the prosthesis to this anatomically compromised area so it will be appropriately covered by the prosthesis. It is important to note that soft palate surgical compromise also creates what is referred to as “soft palate surgical shock” that makes its function compromised for approximately 7–10 days post op before the muscle function “wakes up” again. This development of this phenomenon necessitates careful monitoring as the need for revision of the contours of the prosthesis to accommodate to this change is critical for facilitation of the ongoing comfort and function offered by the prosthesis.

Edentulous patients undergoing maxillectomy that involves the soft palate largely are better served by not extending onto the anticipated area of the soft palate compromise in that they are better managed with either a naso-gastric or PEG tube (feeding tube placed directly through the abdominal wall into the stomach) to provide for appropriate alimentation/nutritional needs for the immediate post operative course or beyond.

When half of the soft palate is removed in an anterior/posterior dimension, in effect one half of the soft palate muscle group contribution is sacrificed and the

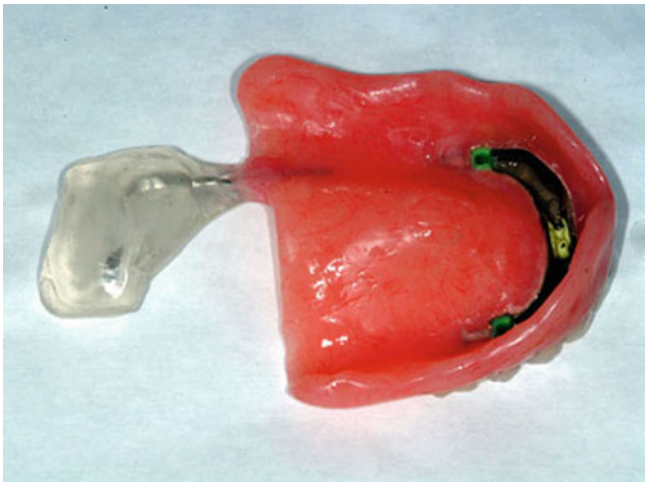

Fig. 23.3 A nasopharyngeal edentulous implant retained obturator designed to address compromise of the soft palate. Note the "hockey stick" configuration of the clear acrylic extension that is related to the remaining soft palate

remaining muscle function/contraction tends to move away from (laterally) and forward (anteriorly) in relationship to the area of tumor resection. When this type of deficit presents, the prosthesis needs to be designed with a "hockey stick" configuration so that contact of the prosthesis with the movement of the residual soft palate is maintained thereby facilitating swallowing and speech (Fig. 23.3). In some respects, loss of the entire soft palate is more manageable with a prosthesis design that can more easily restore normalized speech and swallowing. This type of obturation has been shown to be effectively provided for patients with unrepaired cleft palates where obturation of the nasopharyngeal port i.e., the area the needs to be sealed/closed between the mouth and nose to create aspects of normal speech and facilitate swallowing.

Surgical reconstruction has been attempted as an alternative to obturation of maxillectomies with soft palate involvement with mixed results. Usually, a radial forearm soft tissue free flap is used to create soft tissue volume in the region of a soft palate anatomical compromise [10]. However, simply transferring soft tissue alone does not provide for a restoration of normal neuromuscular function offered by an intact/functioning soft palate. With that said, it is the incredible will for a patient so compromised to strive for optimal function that offers the potential to approach "normal" function. Not infrequently, a dysfunctional free flap transfer used to reconstruct the soft palate offers more of a hindrance than help in prosthodontically restoring nasopharyngeal competency. A dysfunctional soft tissue free flap transfer creates even greater challenges to find and create a solution with a prosthesis that needs to thread its way past the soft tissue flap and provide for the needed obturation.

23.2.4 Interim Obturators for Dentate and Edentulous Patients

Classically described, an interim obturator is a prosthesis fabricated following maxillary tumor ablation surgery has occurred and subsequently healed. For those patient's treated with a clear surgical obturator its interim replacement serves several functions not offered by the initial surgical obturator. As previously noted and in most circumstances, surgical obturation is largely devoted to serve as a temporary artificial separation between the oral cavity and the maxillary sinus and/or nasal cavity. In large measure, its intended purpose is to serve as a support for the surgical dressing and therefore offers little beyond that function. Once healing of the tumor ablation site is more complete and the patient is recovered from the surgical intervention the need for more effective rehabilitation is desirable and often sought by the patient. The interim obturator offers a solution to satisfy that need. Simply put, the interim obturator offers anatomical replacement of the oral structures lost by the surgical resection. While functional improvement even with prosthodontic replacement of lost oral structures does not provide a significant rehabilitation of these lost structures, it does offer assistance with improvement of speech and swallowing, given that more normalized anatomical contours are provided by this type of prosthesis when compared to the surgical obturator. Some clinicians choose to fabricate the interim obturator in such a way that the extension into the now healed surgical site simulates the design/contour of the long-range prosthesis. Oft times however ongoing changes of the anatomical contour of the surgical site or tissue changes related to the impact of post operative radiotherapy necessitate revisions/refitting of the obturator portion of the prosthesis.

For edentulous patients as previously stated conversion of a existing maxillary complete denture prosthesis if it is determined that it is adequately related to the remnant upper jaw into an interim obturator. One rationale for this is the existing prosthesis is familiar to the patient and transitioning what is known into something that is new and different reduces the "speed bump" of change the patient needs to accommodate. Alternatively, an entirely new prosthesis can be fabricated at this juncture but likely will need to be revised/replaced after all tumor management therapy is completed and tissue response to same is resolved.

23.2.5 Long Range Obturators for Dentate and Edentulous Patients

The design, fabrication, materials used, and timing for provision of a long range obturator prosthesis is largely indicated, first and foremost, by arrival at the milestone of the patient having a quiescent period of tumor free experience. There are no specific guidelines or a crystal ball readily available to assist the clinician as to when the right moment arises to pursue this treatment intervention. Generally it takes place no sooner than 3 months post completion of cancer management. Commonly at this juncture, a post treatment scan is obtained and that combined with clinical assessment verifying the patient has no evidence of disease is usually the green light

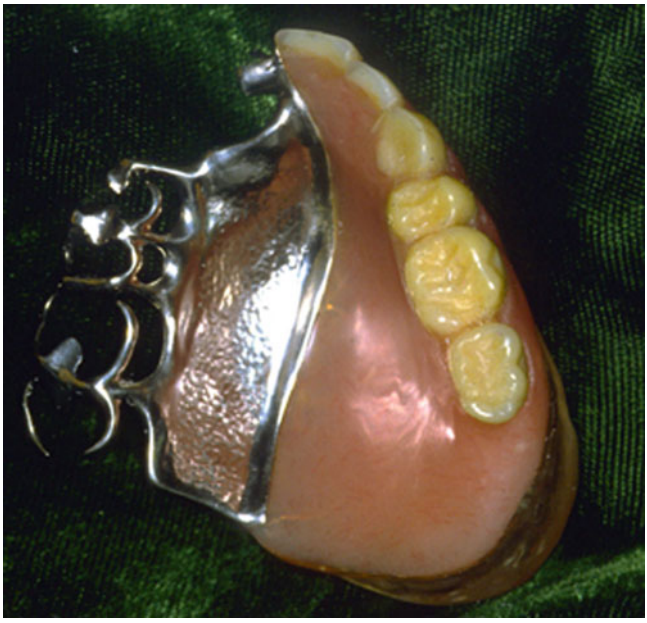

Fig. 23.4 A cast framework obturator designed to provide anatomical replacement for the resected left maxilla

to proceed with long-range rehabilitation. Some patients elect not to do so with their having adapted to function with their interim obturator treatment and are adverse to further change. In fact, for some patients despite the best efforts of the treating provider the interim obturator "comfortable bed room slipper" is better appreciated by them than that of the long range cast framework obturator ("the new shoe"). In and of itself, the long-range obturator requires yet another adaptation on the part of the patient. After enduring a litany of adaptations since the initial insult of anatomical compromise necessitated by the tumor ablation surgery this last rung in the ladder of change can be onerous for some. Nonetheless, the "gold standard" of rehabilitation for dentate patients having a maxillectomy to date continues to be the cast framework long-range obturator (Fig. 23.4).

Much like conventional removable partial denture design for partially dentate patients in need of tooth replacement there are an array of philosophical approaches to framework design. Cast clasp placement, distribution of load considerations, minor and major connector designs are all technological issues that the clinician attempts to factor into the design of a cast framework obturator prosthesis [4, 10]. The number, health, distribution of these potential natural tooth/or implant abutment supports dictate, in large measure, the design for the support, stability and retention of the prosthesis. The amount of residual hard palate impacts the stability of the prosthesis. For those patients whose tumor resection extends beyond the midline of the affected side, results in a less stable base results on which the prosthesis can rest. Conversely, the smaller the size of the defect the more difficult it is to seal

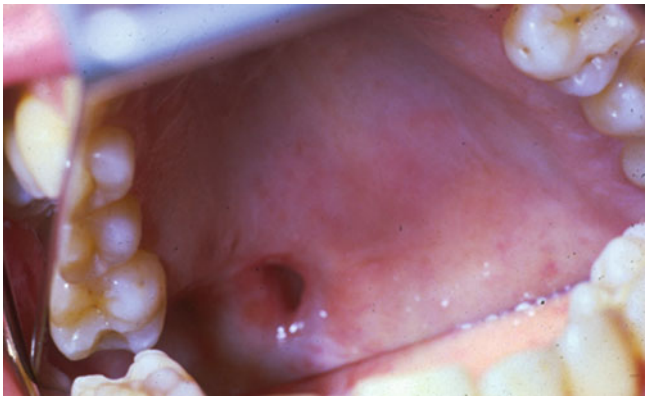

Fig. 23.5 A small oro/antral communication at the hard/soft palate junction represents a significant challenge for obturation. The posterior aspect of the defect is in a region of moveable tissue hence making a static structure providing an adequate and predictable seal more difficult than compared to fitting a prosthesis such as that in Fig. 23.4 to a static healed surgical site

the oral cavity from the sinus or nasal cavity (Fig. 23.5). Moreover, surgical compromise extending onto the soft palate or including the soft palate offers significantly greater challenges in restoring oral function as it relates to speech and swallowing. Radiation effects in the region of the hypopharynx can negatively impact swallowing. The obturator prosthesis does not resolve this issue.

23.2.6 Palatal Augmentation Prostheses

For individuals experiencing compromise of the oral tongue following tumor ablation surgery such as partial or total glossectomy, oral function as it relates to speech, swallowing and mastication is negatively impacted. The oral tongue is the "quarterback" of the oral cavity and once its substance, innervation, and range of motion are altered significant challenges in oral function ensue. One method in attempting to improve oral function following compromise of the tongue is to fabricate a prosthesis that alters the contour of the hard palate such that the remnant or reconstructed tongue can approximate this contour and hence facilitate improved function. In effect, the contour of the palatal augmentation prosthesis is designed by the patient functionally generating the prosthesis's contour using specialized impression techniques. The augmented contour can afford the patient the ability to better approximate their residual or reconstructed tongue to it thereby making swallowing and shaping of the air stream to facilitate more intelligible speech possible. While the net gain with the use of a palatal augmentation prosthesis oft times is limited, even a small improvement can have a large impact on the patient's ability to work toward a more normalized existence.

Coordination of this type of rehabilitation effort requires collaborating with a well-trained speech pathologist to assess and monitor speech changes and thus provide a regime of exercises to develop improved tongue function. The assessment/input

from such a trained individual is invaluable in offering guidance to the maxillofacial prosthodontist in regard to their suggesting changes that can be made to the topography and contour of the palatal augmentation prosthesis so improved function can be accomplished.

In those instances where the base of the tongue, epiglottis, or radiation fibrosis of the hypopharyngeal muscles and lining tissues presents in addition to compromise of the oral tongue, improvement with the use of palatal augmentation prosthesis in this constellation of anatomical compromise is much more guarded. The goal is to prevent egress of food, liquids or foreign objects (aspiration) into the lungs that could lead to infection, pneumonia, etc. Patients with significant anatomical compromise and loss of function are highly motivated to seek return to normal function. In this situation the driving force is to eliminate the need for a PEG tube as a sole source for nutritional support. Since the overwhelming majority of the population has not been confronted with this dilemma making resonate how powerfully motivating being in this situation is and how hard these patients work to gain functional improvement simply cannot be described or made to resonate with those not so afflicted.

23.3 Surgical Reconstruction of Maxillectomies and Its Interface with Maxillofacial Prosthodontic Rehabilitation

The development of autogenous reconstruction (free flap micro-vascular tissue transfer) procedures has evolved over that last few decades [11]. The free flap tissue transfer has created a whole new arena as it relates to Maxillofacial Prosthodontic treatment services. The most common combined hard and soft tissue donor sites are the fibula, iliac crest, and scapula. With tissue transfer reconstruction combined with the use of osseointegrated implants, three dimensional imaging, modeling, and planning techniques to assist in designing/planning/fabrication of prosthodontic rehabilitation continues to evolve and is being molded and shaped as the "new age" approach for making patients "whole again" evolves. The principle objective for this approach is to eliminate a sinus/antral communication and therefore eliminate the need for removable prosthodontic rehabilitation to close the surgical resection site with a removable obturator prosthesis. The challenges associated with these surgical reconstruction procedures are many, not the least of which are a significantly extended surgical intervention, longer in house recovery time largely necessitated by the post operative management of donor rather than recipient site, the need for further revision of the tissue transfer, the challenge in getting support and provision of replacement of the lost dentition as part of the comprehensive rehabilitation management.

A number of publications in the surgical literature indicate that patients having undergone surgical reconstruction as arriving at the cross roads of being described as being "rehabilitated" in that they are able to "speak, swallow, and ingest a soft mushy diet [12]. Unfortunately, many of these patients' perceptions do not parallel that assessment and seek comprehensive oral rehabilitation in their quest to be made "whole again". In an attempt to make this resonate and be understandable, patients who are surgically reconstructed are relegated to eating porridge, yogurt, cottage

cheese, mashed potatoes, scrambled eggs, blenderized food etc. as their mainstay diet. In some circumstances albeit reconstructed they may continue to be reliant on a PEG (Pan Epigastric Gastrotomy) tube for direct delivery of their nutritional needs directly into their stomach. Normal individuals not so afflicted nor confronted in participating in those methods of nutritional support simply cannot understand how emotionally debilitating being left in that situation can be. Maxillofacial Prosthodontists' treatment goals are to move beyond leaving patients in such a compromised state so they can be comprehensively rehabilitated and not only surgically reconstructed. There is an enormous difference between the two i.e., reconstruction vs. rehabilitation, and developing an understanding of the differences between them is the crux or cornerstone that needs to be assimilated so that those in need of being made "whole again" can indeed become so. The essential ingredient missing for this infetesimally small segment of the patient population in need of oro/facial rehabilitation services is the lack of understanding and support for this type of comprehensive rehabilitation treatment. The sad reality of this situation is that if every patient in need of such services were fully supported (regardless of type of health insurance coverage they have) to have maxillofacial rehabilitation services provided, it would represent a microdot in the bottom line of all health care cost expenditures. Despite that reality, each patient's rehabilitation needs represents a battle royal with heath care carriers be they state, federal, private, HMO, PPO, Military or any other type of coverage. In sum and substance, the efforts put forth to obtain support for the provision of maxillofacial prosthodontic rehabilitation care for patients that are surgically reconstructed represents a significantly greater and more formidable challenge than the provision of such care itself. This reality represents yet another theme that is difficult to make resonate, but nonetheless is a sad reality associated with addressing this need.

As regards reconstruction procedures for the maxilla, various algorithms have been described [13–15]. Generally speaking, primary reconstruction i.e., free tissue transfer at the time of tumor resection, in some centers provision of primary implant placement into the bone stock of the tissue transfer and more recently immediate loading of implants placed in these grafts are considered the treatments of choice. Patients who are years after having tumor ablation surgery can be considered as candidates for surgical reconstruction. However, such reconstruction efforts have indeterminate risks associated with compromised healing, especially for those who received adjunctive pre- or post-operative radiotherapy. Often, the use of adjunctive Hyperbaric Oxygen Treatment is recommended to assist in maximizing the healing potential for those patients compromised in the region of the original tumor resection. The surgically compromised sites negatively impacted by surgical scarring and radiation induced reduced circulatory capacity (peripheral endarteritis) all of which contributes in circulatory compromise and potentially impaired healing. It is the recipient site (area of original tumor resection) that is more a concern than the tissue being transferred and immediately vascularized by facilitation of micro-vascular "hook up" to local blood supply. Further, the type of free flap, be it both bone and soft tissue or soft tissue alone impacts the potential for rehabilitation. Simply put, a soft tissue free flap closure alone either for dentate or edentulous patients makes it extremely challenging if not impossible to offer meaningful complete oral

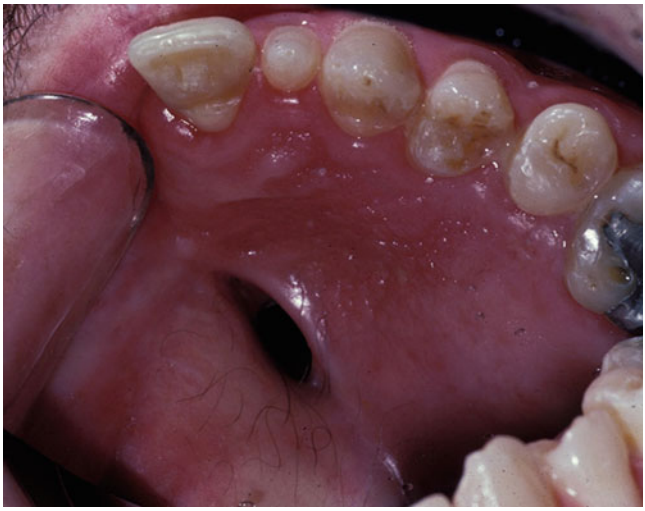

Fig. 23.6 Image of an iatrogenically induced failed surgical flap reconstruction. Pressure from the obturator prosthesis resting on the juncture between the soft tissue free flap at the suture line to the residual hard palate mucosa was the causal agent for this compromise resulting in the creation of a neo oral/antal communication after surgical closure

rehabilitation. The reason for making this assertion is that a soft tissue closure of a maxillectomy does indeed provide a separation between the mouth and sinus and/or nasal cavity but also offers an unstable base onto which a prosthesis can be placed. If done so, the loading of such a prosthesis on the soft tissue flap reconstruction puts the interface between the flap and the tissue to which it is interfaced at risk for breakdown and possibly recreating a communication between the oral cavity and the maxillary sinus and/or nasal cavity (Fig. 23.6). Needless to say, to have a patient subjected to significant surgical intervention/potential donor site morbidity and ultimately experience an iatrogenically created neo-oral/antral communication is not good patient management.

For patients with remaining dentition on the unaffected upper jaw following maxillectomy, the goal for free flap reconstruction is to create a new intact upper jaw (neo-maxilla) into which osseointegrated implants can be placed in appropriate positions in this newly reconstructed upper jaw such that these implants can ultimately support the replacement of missing dentition. The soft tissue pedicle of the free flap used for the coverage over the bone graft on the oral side needs to be debulked at the time of implant placement surgery and/or at the time of uncovering the implants if they are placed as a delayed approach. The goal is to create a peri-abutment soft tissue/implant interface that can be maintained. Typically, this interface is difficult to create and as a result despite offering successful rehabilitation, soft tissue management can be an ongoing challenge. In some circumstances a split thickness skin graft is provided in the peri-implant sites in an attempt to create wallpaper like attachment of the graft in the region of the implants so maintenance and soft

tissue health can be optimized which is a critical component for the long-term survival of rehabilitation efforts. Free flap reconstruction efforts rarely create an adequate gingivo/buccal sulcus and especially when the reconstruction's anterior extent is in the region of the "esthetic zone" i.e., in the maxillary canine to canine region esthetic challenges are substantial and difficult to manage.

23.3.1 Rehabilitation of Bilateral Total Maxillectomy

For those patients undergoing removal of the entire upper jaw, a stand-alone category of complex rehabilitation need arises (Fig. 23.7). In the past such patients were left with a surgical compromise that left them with no anatomy from the top of their tongue to the underside of their eyeballs. Monumental efforts were expended by Maxillofacial Prosthodontists to create removable prostheses that could offer some attempt at rehabilitation of these enormous surgical deficits (Fig. 23.8a, b, c, d). As previously stated, nutritional intake orally is severely curtailed leaving such patients with significant compromise. Oral intake is not limited to obtaining nutritional support but also represents a key component to socialization. Patients without rehabilitation of bilateral total maxillectomies clearly are relegated to a severely curtailed capacity as regards their interacting with friends, family; co-workers. They essentially are relegated to becoming recluses and as a result are frequently dealing with severe depression. To be "reconstructed" in this circumstance offers some positive outcome but as previously stated the difference between being reconstructed and rehabilitated is enormous. The technologies and procedures associated with providing a

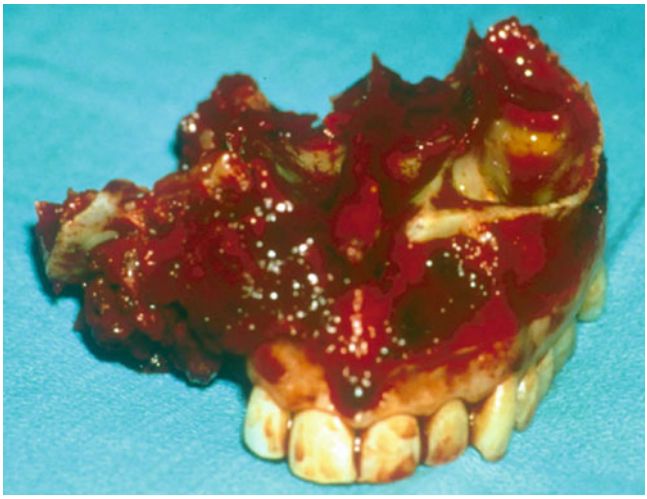

Fig. 23.7 A surgical specimen of an incremental bilateral total maxillecomy. The right posterior maxilla was removed previously and subsequent recurrance necessitated removal of the entire maxilla

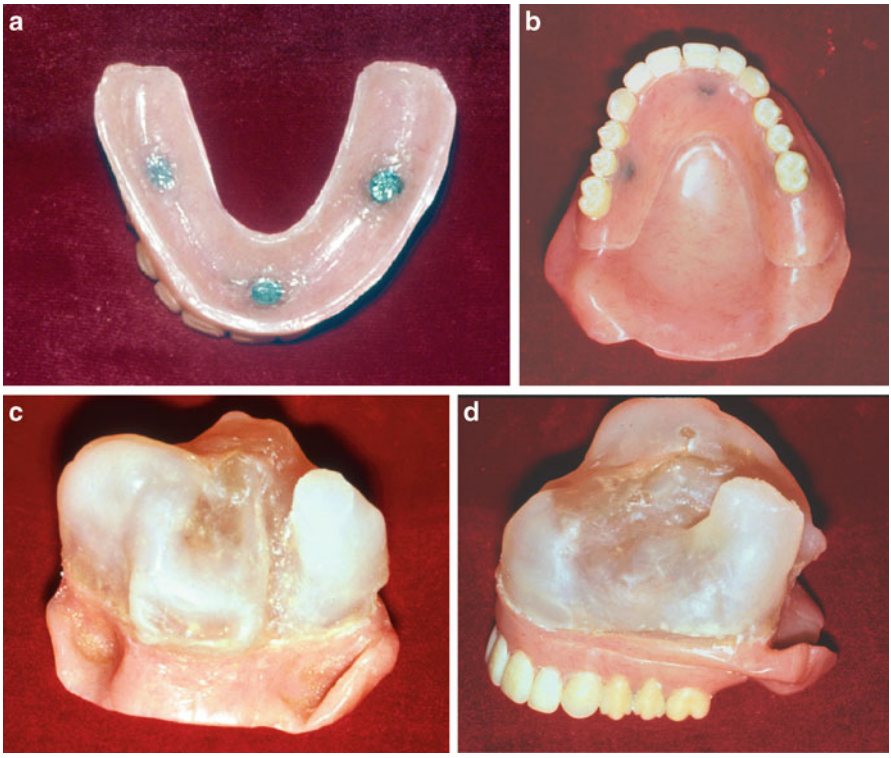

Fig. 23.8 (**a**) The interface of the dental component of a two piece bilateral total maxillectomy obturator. The *gray circles* are cobal samarium magnets that provide retention of the dental component to the hollow bulb bilateral total maxillectomy tissue borne obturator (*upper left*), (**b**) intaglio surface view of the two-piece obturator assembled with magnet retention connecting the two pieces (*upper right*), (**c**) posterior view of the obturator demonstrating the silicone veneered tissue interfaces that extend into undercuts to assist in prosthesis retention (*lower left*), (**d**) lateral view demonstrating the vertical height of the prosthesis from the biting surface to the superior extent of that which rests in the surgical site. The two piece design facilitates ease of placement for the patient having limited oral opening (*lower right*)

meaningful rehabilitation for this patient cohort is, simply put, indescribable. The ability to take a patient from such a hugely compromised state and make it such that speech, swallowing, and mastication can be fully restored is a monumental step forward for patients in need of such management (Fig. 23.9).

Expanding on this effort can only be surpassed by those individuals not only with loss of their entire upper jaw but their soft palate as well. It is possible to rehabilitate such individuals to near normal function with implant based free flap maxillofacial prosthetic rehabilitation. With that said, attempts to surgically reconstruct the entire soft palate is virtually impossible. However, a prosthesis that is designed to replicate the soft palate's function can be readily accomplished and provide for near normal function assuming the remaining muscle groups in the posterior and lateral walls of the nasopharynx are functionally intact.

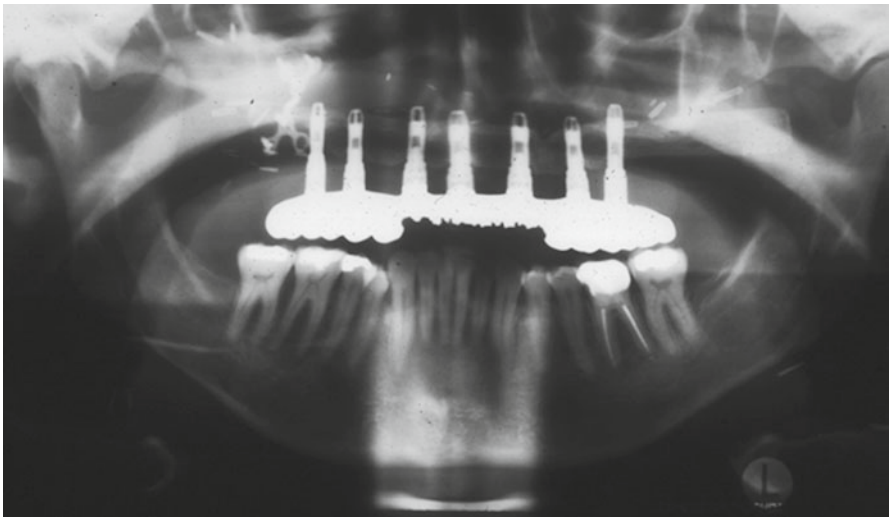

Fig. 23.9 Panoramic radiograph of a fibula free flap reconstruction of a bilateral total maxillectomy that was subsequently implanted with seven osseointegrated implants and rehabilitated with a screw retained fixed implant supported prosthesis. This management was provided to replace that noted in Fig. 23.7. The difference between this type of rehabilitation compared to that in Fig. 23.8 is incomparable with the latter offering the patient near normal function as regards speech, swallowing and masticatory function

23.3.2 Issues of Prosthodontic Rehabilitation vs. Surgical Reconstruction of the Maxilla

To date, choosing between prosthodontic vs. surgical reconstruction is measured by obturators being the "gold standard" against which all other efforts of maxillectomy rehabilitation are measured [16]. While all efforts to rehabilitate a patient who has is permanently compromised only then is it understood that change is a difficult path to follow in efforts to restore what one defines as "normal". At that point of no return, the interface between the patient and the provider attempting to put back what has been taken away takes on a whole new dimension. The reality for the patient is that this permanent change now has to be accommodated. The thought processes associated with dealing with this functional and anatomical compromise are all over the map as noted earlier with reference to Elizabeth Kubler Ross's documented attestations associated with human behavior [2].

Currently, there are no clear decision trees that are known to exist for planning resection/reconstruction/rehabilitation for patients needing maxillary tumor ablation surgery. The variables associated with how these decisions are made are highly complex and vary from patient to patient due to a myriad of patient factors, anatomical challenges, psychosocial issues, insurance coverage issues, medical co-morbidities to name a few. Even when successfully reconstructed/rehabilitated the length of service, potential for recurrence/new primary disease are ongoing question marks

going forward. Careful follow-up surveillance is an essential and critical aspect of patient management from an overall health as well as the status of the prosthodontic rehabilitation's need for service, repair, and modification.

Compromise the maxilla's anatomy and surrounding structures also imparts a loss of sensory input due to neurological input compromised by the tumor ablation surgery. The impact on the tissues in the field of radiation treatment continues to be affected long after this adjunctive treatment is completed. Trismus (restricted lower jaw opening/movement) due to radiation fibrosis of the muscles of mastication can be a rather daunting challenging problem that may need active management with various exercises, stacked tongue blades, and tools designed to manage this condition such as a Thera Byte, or Dynasplint [17, 18]. If a fixed implant based prosthesis is used to provide oral rehabilitation following surgical reconstruction of a maxillectomy the need for access to the screws retaining the prosthesis is inherent so modifications, revisions, repairs of it can be facilitated. Ongoing progressive trismus can challenge the clinician's ability to provide this type of management if the trismus results in limited or the inability to access the release of the fixation screws to address these needs.

In most circumstances the adaptation to any rehabilitation effort is in need of a period of accommodation as it relates to speech, swallowing, and mastication. Implant based prostheses on a reconstructed maxilla usually, by anecdotal patient report, takes upwards of a year before it is felt to be a part of the individual so treated.

23.4 Maxillofacial Prosthodontic Rehabilitation of the Mandible

Tumor management associated with the lower jaw can be limited to the jaw itself or may also involve adjacent structures such as the oral tongue, tonsillar pillar, and/or buccal mucosa. When the mandible alone is compromised by malignancy in cases where the tumor's location is the gingival or overlying alveolar mucosa, the surgical management can be addressed by what is referred to a partial mandibulotomy i.e., either a vertical or horizontal removal of the jaw structure associated with removal of the malignant neoplasm.

However, malignancy that involves structures adjacent to the mandible, most commonly the lateral border of the tongue, creates a significantly more challenging management as regards rehabilitation. It has been said the tongue is the "quarterback" of the oral cavity and its range of motion and functional relationship to the natural dentition or contours of a prosthesis is critical for any potential oral rehabilitation to be effective regardless of the approach taken. Malignancies of the floor of the mouth, lateral border of the tongue, tonsillar pillar can extend to the periosteum on the tongue (lingual side) of the lower jaw and this finding typically necessitates including a portion of the lower jaw in the management of the tumor resection with the intent of obtaining a clear margin of resection. Typically, patients with the need for the mandible to be included in the surgical resection undergo what is referred

to as a composite resection of the mandible that results in a discontinuity defect. A discontinuity defect that is not reconstructed leaves the patient with only one functioning temporomandibular joint (TMJ). Given the normal intact lower jaw is the only bone in the body that has a left and right joint connected to the same bone, leaving the patient with only one functioning joint creates a compromise that offers significant challenges in attempting to restore a functional masticatory system. A discontinuity defect of the mandible as a result of having a composite mandibular resection causes the remaining lower jaw to deviate to the site of the surgery and rotate away from the opposing maxillary dentition. The chin point in relationship to the nasal tip is not aligned in that the chin drifts beyond its normal midline relationship to the middle of the face to the affected/operative side. This deviation is impacted further in a negative sense with the addition of post-operative radiotherapy that creates "radiation fibrosis" of the tumor bed. This tissue change makes the range of motion of the mandible more limited and causes further deviation/distortion of its relationship to the norm.

23.4.1 Treatment of the Dentate Mandible

For patients undergoing a composite resection of the mandible (a removal of the body of the mandible) i.e., a creation of a discontinuity defect resulting in the patient being left with only one functioning (the unaffected side) temporomandibular joint. With this type of surgical management a significant challenge for rehabilitation and maintenance of the relationship between the remaining mandibular (lower jaw) dentition (teeth) and the opposing jaw dentition presents. In most circumstances today the lower jaw needing this management is more commonly managed with surgical reconstruction and thereby restoring its continuity and allowing the patient to achieve near normal function. However, not every patient in need of such management receives such a reconstruction and not every reconstructed jaw following tumor ablation surgery results in adequate restoration of the relationship between the upper and lower teeth being related in an acceptable manner that affords normalized function. Further, the location of the tumor involving the lower jaw creates an array of possible anatomical compromises. The garden-variety composite resection of the mandible usually involves removal of the posterior body of the mandible. Typically, the temporomandibular joint on the affected side is left in place with the posterior cut for a composite resection at the neck of the condyle. This approach is taken if the joint is not considered compromised by the tumor largely to minimize the cosmetic deformity that would be exacerbated by the removal of the condyle. If removed, it creates a more noticeable depression on the side of the face having had the composite resection by creating a notable depression just anterior to the ear. This anatomical compromise is dictated by the need to obtain surgical access and provide for a clear margin for tumors involving the floor of the mouth, lateral border of the tongue, base of tongue and/or tonsillar pillar.

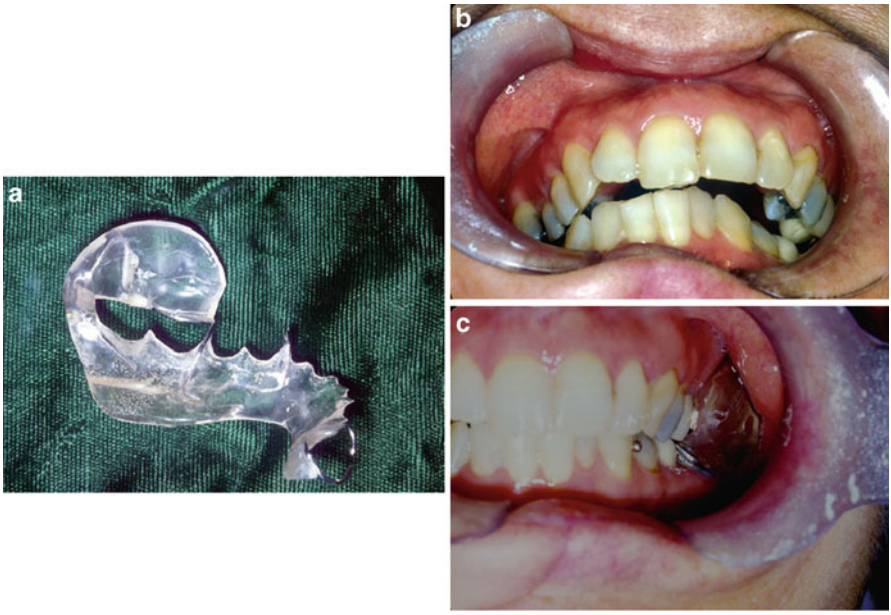

Fig. 23.10 (**a**) An example of a mandibular guide flange prosthesis (*lower left*), (**b**) the occlusal relationship of a patient with a right composite mandibular resection demonstrating deviation of the mandible to the affected right side and rotation away from the maxillary teeth (*upper right*), (**c**) the same patient demonstrating normalized occlusal contact as a result of placement of the prosthesis depicted in (**a**) (*lower right*)

A discontinuity lateral/posterior deficit of the mandible for patients with otherwise existing natural dentition can be managed with a variety of prostheses either at the time of surgery or post operatively. The best management is at the time of tumor resection by placing the patient into inter-maxillary fixation so the relationship of the contacts of the upper and lower remaining teeth can be stabilized during the initial healing period. Arch bars or labio-lingual splints can be used to facilitate the inter-maxillary fixation. Once initial healing has taken place the wiring of the upper jaw to the remaining lower jaw can be undone and the patient can be instructed in the placement of orthodontic rubber bands on the arch bars to assist in training the remaining lower jaw, unaffected side TMJ, and remaining muscles of mastication to now learn to function as a unilateral joint system so as to create a path of residual mandible opening and closing that allows for inter-arch i.e., maxillary/residual mandible remaining tooth contact and to learn to chew. Not uncommonly, such patients experience scar contracture and/or post operative radiation fibrosis that can negatively impact their ability to achieve a functional occlusal contact between their upper jaw and remaining lower jaw. In those circumstances either a mandibular or maxillary guide flange prosthesis can be fabricated such that the prosthesis can be used as a training device to guide the residual mandible to its intended functional position (Figs. 23.10a–c and 23.11a–d). For those patients where either of the above

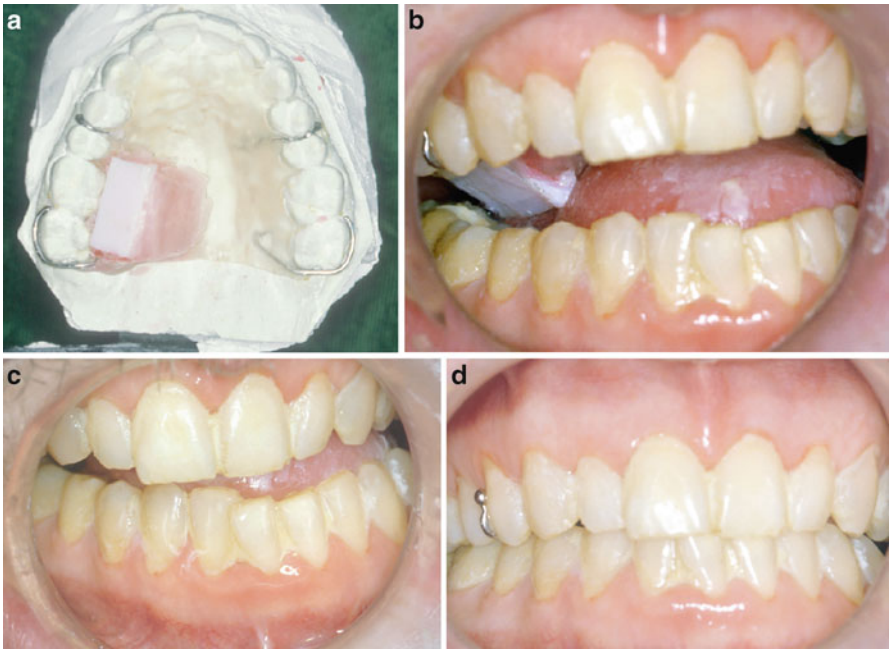

Fig. 23.11 (**a**) Occlusal view of a maxillary guide flange in progress. The white plastic ramp is embedding on a wax platform to create its best position/angulation to allow for the patient's lower jaw having experienced a left composite mandibular resection to contact, guide and slide the remaining mandibular teeth into normalized contact (*upper left*), (**b**) an intra-oral view of the developing prosthesis being assessed clinically (*upper right*), (**c**) the occlusal relationship the patient can achieve with out the prosthesis (*lower left*), (**d**) the occlusal relationship able to obtained with the completed maxillary guide flange prosthesis in place (*lower right*)

noted interventions are not provided and significant scar contracture and radiation fibrosis contributes to significant deviation from the normal upper/lower jaw dentition interface. Management for that presentation is a prosthesis can be designed for the upper jaw that can offer a platform to which the lower teeth can contact and perhaps offer some semblance of masticatory function.

While attempts to keep the mandible intact for cancerous lesions limited to the gingival tissues around natural teeth, lichen planus reverting to squamous cell carcinoma of oral mucosa, or odontogenic keratocysts can sometimes be managed more conservatively. These surgical approaches usually are via a marginal mandibulotomy either by a vertical removal of the lingual plate of the lower jaw or a horizontal resection approach above the mandibular neurovascular bundle. When this type of anatomical compromise is created, conservative prosthodontic management is severely challenged. Simply put, an adequate base onto which a prosthesis needs to rest is needed for it to be tolerated, accepted by the patient, and offer some functional capability as regards improvement.

In the current era of rehabilitation efforts, the introduction and use of osseointegrated implants has made a dramatic impact on being able to provide meaningful

rehabilitation of form and function. However, it should be stated rather emphatically that simply replacing missing teeth does not in and of itself fix all that is compromised. Surgical removal of tumors of the lower jaw can impact adjacent tissues such as the tongue, floor of the mouth, cheek, sulcus and so on. Tongue tethering typically resulting from using local tissues following resection to obtain wound closure offers more of an impediment to restoring oral function than anything a replacement of missing dentition regardless of approach can accomplish. Import of soft tissue via a radial forearm vascularized free flap has been shown to modulate the concern regarding tongue tethering. As well, loss of innervation, and/or oral competency is not simply resolved by replacing missing/lost teeth. Nonetheless, and as previously stated, patients in such situations, generally speaking are highly motivated and functionally adaptive such that otherwise perceived insurmountable functional challenges are often overcome to make what otherwise would be considered impossible… possible. It is the incredible will of patients to accommodate to these challenging anatomical compromises be modulated more than the provision of a prosthesis.

Malignancies involving the anterior floor of the mouth and/or anterior mandible create an entirely different category of rehabilitation need. In the past, considerable efforts were expended to deal with an anterior discontinuity defect of the mandible. The midline of the lower jaw (anterior arch of the lower jaw) represents an area that is particularly challenging. The movement of the lower jaw and associated musculature creates a significant load effect on this U shaped bone. Failed attempts to rehabilitate an anterior discontinuity defect of the mandible leaves such patients with “Andy Gump” deformities resulting in their not being able to speak, swallow, or chew. Given the mandible is the “curtain rod” for the structures in the neck such as the larynx, esophagus, and tongue, the lack of an intact mandible necessitates provision of a permanent tracheostomy to maintain an air way and a feeding tube either naso-gastric or more commonly today a PEG tube to provide ongoing nutritional support. Leaving a patient in such a state is an extremely physically and emotionally debilitating situation.

With the introduction of the micro-vascular free flap surgical reconstruction [19] secured in place with titanium screws and plating [20] procedures, a remedy for this devastating situation can now be employed to effectively and predictably restore form and function. Heretofore, despite well intended attempts to use a array of alloplastic materials such as, Kirschner wires, surgical grade stainless steel screw fixated straps, surgical grade chrome cobalt cast cribs to support membrane based alloplastic bone grafts either block or particulate, block grafts, cadaver bone, etc., that in most circumstances did not offer long range meaningful rehabilitation. Rather, these efforts, ofttimes, created more problems then they solved.

23.4.2 Treatment of the Edentulous Mandible

A patient missing all lower jaw teeth facing a tumor ablation surgery that will leave him/her with a discontinuity defect presents a huge challenge as regards oral rehabilitation.

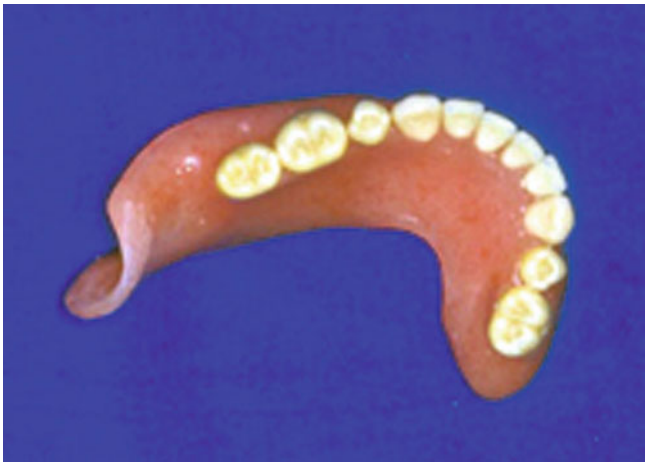

Fig. 23.12 Example of a edentulous mandibular resection prosthesis fitted to the remaining lower jaw following a right composite resection of the mandible

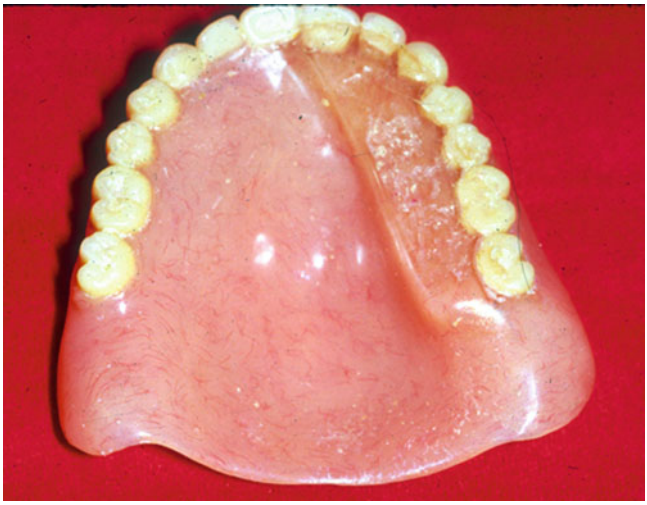

Fig. 23.13 A maxillary complete denture fabricated for a patient with a mandibular composite resection. The clear plastic platform on the right side of the figure provides the patient with a place to achieve occlusal contact regardless of the multiple deviated jaw positions/path of closure the edentulous mandible based on only one temporomandibular joint can provide

A discontinuity defect of the mandible is the condition that leaves the patient with a residual lower jaw that has only one remaining functioning temporomandibular joint. It is well known that restoring effective function of a patient's intact lower jaw with a mandibular complete denture prosthesis opposing a maxillary complete denture

facilitates a restoration of function that represents approximately 18% of functional capability when compared to a patient with intact natural teeth in both jaws that are properly occluding [21]. If an edentulous patient has a discontinuity defect of the mandible, successful function with a mandibular resection denture (essentially a part of a complete denture) affords functional return that is considerably less than that offered with conventional denture therapy. Unlike for dentate patients, an edentulous patient cannot be rehabilitated with guide flange prosthesis in that edentulous prostheses would be destabilized by attempting to redirect the residual mandible into a normalized path of closure. Instead a modification of the maxillary complete denture is made by widening the occlusal table on the unaffected posterior sextant to allow for the patient lower jaw when closing to come into contact wherever and whatever path of closure is possible (Figs. 23.12 and 23.13) Curtis classified an edentulous patient undergoing a loss of continuity of the mandible following a composite resection of the mandible as being "the forgotten patient" [22].

As noted for the dentate patients, a reconstruction of a discontinuity defect of an edentulous mandible is currently a likely consequence of management in most major medical/head and neck cancer treatment centers. But as previously stated for surgically reconstructed maxillae, simply restoring the anatomy does not provide for comprehensive rehabilitation. As well, the cast framework obturator is considered the "gold standard" against which other forms of rehabilitation are measured. For patients with discontinuity defects of the mandible treated with edentulous mandibular resection prostheses, i.e. denture prostheses fit to the remaining portion of the unresected jaw that is not the case. Despite some patients so treated are able to return to some semblance of function, clearly left with such an anatomical compromise does not allow them to approach what one would consider as "normal function". This concept seems to be not well appreciated especially for health insurance carriers. As previously noted, limitation of tongue range of motion and innervation usually is part of this constellation related to rehabilitation challenge. In that regard, speech, maintaining stability of the mandibular prosthesis, ability to chew, and swallow are all balls that need to be kept in the air to affect any hope of reasonable oral function.

Restoration of oral function necessitated by anatomical compromise resulting from surgical management to eradicate oral cancer in the opinion of this author should be considered as a stand-alone category of care need. Moreover, to not afford such individuals with appropriate and comprehensive oral rehabilitation facilitates increased health care costs as regards management of these patients' disabilities with their needing significant ancillary treatment. Much of this management can be avoided by supporting what is needed in the first place…. comprehensive oral rehabilitation. It is unfathomable why this concept can't be grasped. As previously noted with the maxillectomy patient who is not rehabilitated, patients with mandibular compromise also are relegated to nutritional restrictions that no normal human would endure, compromised speech and swallowing that can create a host of issues not the least being aspiration leading to pneumonia and possible death.

23.4.3 Treatment for the Surgically Reconstructed Mandible

As already alluded to, the development of procedures, materials, and techniques that can facilitate surgical reconstruction that provides for continuity of the mandible following tumor ablation surgery is a monumental advance that affords the patient an opportunity for more meaningful rehabilitation. This type of reconstruction can be used to address a composite mandibular resection, anterior arch composite resection or a complete resection of the entire mandible. The workhorse used to facilitate such reconstructive procedures largely is the micro-vascular fibula free flap. Other donor sites not as frequently used are the iliac crest (hip) and scapula (the shoulder blade's outer border). It should be noted, however, that despite what these types of reconstructive procedures offer as being an incredible advance in management they also offer the maxillofacial prosthodontist an array of challenges that are distinctly different from those associated with removable prostheses used to rehabilitate mandibular discontinuity.

Specifically, a reconstructed mandible does indeed provide for restored continuity and good restoration of facial form. One of the challenges related to the later is that the graft is generally placed so that it is aligned with the inferior border of the unaffected portion of the mandible. This approach is taken so as to replicate the inferior border of the portion of the mandible removed and provide for a good external symmetrical facial contour. This positioning of the graft creates an intra-oral discrepancy in the vertical axis because the fibula (a much smaller bone than the mandible it is replacing) that results in challenges the issue of the now having excess vertical space needing to be accommodated by the prosthesis. Sometimes reconstructive surgeons provide for a "double barrel" fibula reconstruction to modulate this concern (make the vertical discrepancy less) [23].

Radiographic assessments of these surgical reconstructions demonstrate what appears on x-ray to be a stable base onto which a prosthesis can rest. However, the clinical assessments of the intra-oral topography after a free flap reconstruction, in most circumstances, do not represent an anatomical base on which a conventional removable prosthesis can successfully rest and properly function. Usually, the soft tissue pedicle that comes along with the bone stock harvested from any of the donor sites, at least initially, appears to be more like a stuffed couch pillow rather than the desired attached tissue overlying what ordinarily would be a residual ridge of an intact mandible that presents following tooth loss. Unattached tissue is the bane of the prosthodontists' existence in his/her efforts to provide a prosthesis that offers appropriate support, stability, and retention, the basic tenants for any successful removable prosthdontic management. While admittedly the soft tissue pedicle can with subsequent surgical management be "debulked" but even if done so rarely approaches what is required for successful prosthodontic management. With that said, albeit controversial, even amongst prosthodontic colleagues providing surgically reconstructed mandibles with prosthodontic rehabilitation, it is the considered opinion of this author that rehabilitation for such reconstructed edentulous or for that matter partially edentulous lower jaws that a fixed (non-removable by the patient) implant supported prosthesis is the treatment of choice. While it is feasible to

attempt implant retained removable prostheses as some colleagues advocate, this type of management again, in the opinion of this author, is a step down from optimizing rehabilitation efforts for a patient with mandibular compromise who has undergone a surgical reconstruction.

23.4.4 Considerations for the Management of the Reconstructed Mandible Treated with a Implant Supported Prosthesis

The "new age" rehabilitation of a reconstructed mandible has associated with it an array of nuances that heretofore have not been tasked to the maxillofacial prosthodontist in his/her efforts in making patients with mandibular compromise "whole again". A reconstructed mandible, albeit having its continuity restored is not the equivalent of an intact functioning lower jaw. The lower jaw's neuromuscular physiology represents one of the, if not the most complex mechanisms of movement that occurs in the human anatomy. An array of muscle groups, joints, ligaments, all need to coordinate their movements in an exquisitely precise manner such that tooth contact can occur efficiently and appropriately. Inherent in the need to rid the patient of a malignant growth associated with the lower jaw, of necessity, causes a disruption in this incredibly complex neuromuscular web. By only replacing the lost portion of the jaw, the reestablishment of this complex mechanism is not fully restored. As previously noted, one major help with a patient dealing with such a compromised state is, in fact, the patient's incredible will to make work to his/her best advantage what is now available to restore function. Every patient in need of maxillofacial rehabilitation represents a unique experience as regards the prosthodontists' efforts to successfully achieve their rehabilitation management. The learning curve associated with providing this service has been for this author a very interesting adventure. It is not possible to provide all that has been accumulated regarding the knowledge accrued but certain themes evolve that can be highlighted.

It is very heartening/rewarding to see patients who have been rehabilitated with mandibular fixed implant prostheses years following surgical reconstruction to report that they are able to function, chew, eat, swallow and their prostheses have not only served them well but, in fact, in most circumstances have maintained a stable implant/bone interface. In most instances patients so treated are noted to require minimal need for management as regards their prostheses or peri-implant abutment tissues complement those findings. However, one of the common issues for management is fracture of teeth from the implant prosthesis that in most circumstances can be easily managed as a direct chair-side repair procedure.

Soft tissue complications do occur but their occurrences are not a across the board issue. However, it should be noted that soft tissue complications are indeed a bit of an annoying management problem for patient and provider alike. A variety of treatment strategies have been pursued with varying levels of success. These include daily application of Peridex (Chlorhexidine) by either topical application to the area of concern or as an oral rinse. In some circumstances, topical application of fluoride

gel that can change the chemistry of the peri-implant oral environment that has sometimes shown to offer some remedy. Surgical management to remove the compromised tissue that when assessed has been shown by pathology report to largely be granulation tissue sometimes containing hyphae (suggesting a possible contribution to this tissue insult by fungi, a common occurrence in the oral cavity following radiation treatment). Attempts to place a peri-implant spit thickness skin graft have been made and in some but not all circumstances achieving an attached tissue interface and thus offered resolution.

Patients who have undergone mandibular free flap reconstruction and subsequent oral rehabilitation with implant-supported prostheses in most circumstances is a 1-year undertaking. The time needed for healing post grafting, recuperation of oral tissues from the onslaught of radiation treatment effects, the likely intervention of using pre-and post-implant placement hyberbaric oxygen treatment, surgical placement of implants, soft tissue pedicle revision(s) and the follow-on procedures for fabrication of the prosthesis all fall in that time window. Once the completed prosthesis is placed, it is the beginning of approximately 1-year period of accommodation. This interval is needed for such patients to learn how to most effectively use what has been provided. It is somewhat akin to a baby learning how to walk. Most patients arrive at the destination and realization that this accommodation period is associated with adaptation of speech, chewing, and swallowing. Along the way there is a tendency for the patient to initially bite their lip, cheek, tongue, or all of these while the muscular movements about the prosthesis are "fine tuned" such that this no longer or very infrequently takes place. Developing a "feel" or understanding of forces applied for chewing is a major learning curve. Most tooth fractures occur during the first year following prosthesis placement in large measure due to the patient not having the intimate "proprioception" offered by the periodontal ligament found around natural teeth. This loss of proprioception not offered to the same degree of sophistication by an implant/bone interface that in essence is a poor substitute as a feedback mechanism for the brain to interpret the needed GPS system needing to evolve as a substitute to assess forces being applied to the system. Ultimately this huge change between God given anatomy and prosthetic replacement becomes modulated though the learning process of accommodation to this entirely different mechanism associated with chewing force application. Once accommodated patients commonly offer in an unsolicited way that they now feel "whole again".

23.5 Prosthodontic Rehabilitation of Facial Anatomy Following Tumor Ablation Surgery

As if the anatomical/functional compromises that result from the need for tumor ablation surgery for either the upper and/or lower jaw weren't enough, the thought of being confronted with loss of anatomy of the face necessitated by surgical management of malignancy, once again, for most individuals is indeed ….unimaginable.

Yet when patients are confronted with such a dilemma, the reality for the potential for such a devastating compromise of one's self-perception is indeed unimaginable. Given that our face is our three dimensional autograph and especially in American society where there is such an enormous focus of attention on appearance and all the attendant media hype associated with having a certain presentation deemed acceptable. Being confronted by necessity to deviate from the norm for any individual facing a life threatening disease whose management will create facial disfigurement has a huge impact on one's emotional well being.

For the Maxillofacial Prosthodontist to have the opportunity to interact pre-operatively with a patient confronted with anticipated loss of facial anatomy plays a huge role for the patient, his/her family, and the surgeon. Discussing the treatment options that can be considered are better reviewed with the patient and his/her family prior to tumor ablation surgery than after. In the past, the treatment options that could be considered were rather limited to either no treatment or an adhesive retained facial prosthesis. More commonly today, other options in most treatment centers have been expanded to surgical reconstruction or implant retained facial prostheses. As with intra-oral management the array of options, the myriad of patient factors, treatment schemes and a host of other variables creates a primordial soup of issues that need to synthesized and tailored to each patient such that an appropriate treatment approach can be chosen/facilitated. All of this from the patient's perspective is rather abstract and perhaps not able to be reasoned to arrive at a treatment decision. Moreover, it is not feasible for a patient seeking reconstruction vs. facial prosthetic rehabilitation to "test drive" the different options available such that a comparative choice decision can be made. In general terms, patients faced with this type of intervention are best served when they come to the realization that they wish to pursue rehabilitation of a facial deformity more so than the provider wanting to facilitate it for them. There is a very interesting and usual catharsis that most patients experience when undergoing this type of treatment. The psycho-social component plays a huge role in how this plays out during the course of management with patients' expectations initially being minimal or non-existent then evolving/reverting in many instances to their being fully involved/inculcated/obsessive about seeking the optimal end result. While this transition from the providers' perspective can at times be overwhelming, it nonetheless becomes an integral part of this type of patient management.

The ability to "make whole again" patients with compromised facial anatomy, simply stated, is incomparable to any other health care service. It is a service that is medically prescribed but the issues around making this service understandable is not possible.

23.5.1 Partial/Total Rhinectomy

Compromise of the external anatomy of the nose resulting from tumors emanating from the external skin such as basal cell carcinoma, or tumors within the nasal

cavity, or expansile lesions from adjacent maxillary sinuses necessitate complete extirpation of the external nose to offer control of progression of malignant disease or offer any hope for cure. Clearly, loss of the anatomical structure that is ground central of facial anatomy portends a host of esthetic and functional concerns. For example, the ability to wear glasses is significantly impaired once the nasal anatomy is resected. The external nose offers protection for the filtration system of the nasal cavity which is of critical need to prevent contaminants such as pollutants, noxious agents, viral, bacterial, or fungal egress into the lungs is impaired by loss of this anatomical structure. The impact of the cosmetic compromise goes without saying as being an emotionally devastating issue.

In some circumstances, only a portion of the nose need be excised. Regardless of the anatomical compromise prosthetic management of a partial rhinectomy is always more complicated and challenging than the removal of the entire external nasal complex. With the move for surgical reconstructive procedures for compromised nasal anatomy coming to the fore in the last few decades, a dichotomy of prosthodontic rehabilitation vs. surgical reconstruction has evolved. These two distinct approaches for reconfiguration of a compromised external nose run countercurrent to each other in that the surgical reconstructive management is desirous of maintaining tissue and the prosthetic approach having preference for eliminating unsupported tissues. Developing a realistic plan for rehabilitation needs to be sorted out before the planned tumor resection so optimized management for either a prosthesis or surgical reconstruction can be facilitated once tumor control is achieved.

For patients needing total removal of the external nose (total rhinectomy) there are also two distinct options for treatment, surgical or prosthetic. Inherently, the tumor location and extent dictates what needs to be sacrificed to rid the patient of the disease process, first and foremost. However, minimally invasive management, if offered, to address tumor management leaves patients with unsupported residual nasal anatomy that can present in such a way that obviates the ability of the prosthodontist to provide an anatomically correct representation of appropriate size, shape and contour of the prosthesis that would be anatomically correct and acceptable to the patient.

Prosthodontic rehabilitation for patients with partial or total rhinectomy, the most common approach used to retain such prostheses is to use a skin type of adhesive. On rare occasions the internal anatomy of the nasal cavity can be used for fabrication of a mechanically retained prosthesis. However, there is some inherent risk of creating complications using this approach if the residual anatomy following total rhinectomy has been radiated. In those circumstances, potential for pressure irritation of the internal nasal airway tissues should be avoided.

The contemporary approach for creating retention for nasal prostheses is to place craniofacial or conventional osseointegrated implants (Fig. 23.15). Typically two or three implants are sufficient to support and adequately retain a nasal prosthesis. The use of one or the other type of implant is dictated by the amount of available bone in the region of the lateral aspect of the nasal cavity and the midline along what was the nasal base. With conventional implants employed with those having greater

bone volume. Careful planning for placement of these implants regarding axial inclination and as well to avoid encroaching into the gingivo-buccal sulcus for those patients who are edentulous or transecting the root apices of maxillary anterior natural teeth for those who are not. It has been demonstrated that attempting to place implants in the region of the bridge of what was the nose has largely been unsuccessful and therefore should be avoided [24].

Implants offer an array of options to assist in retaining nasal prostheses. Various attachment systems using resilient attachments and/or magnet retention systems offer effective and reliable retention that surpasses that can be offered with adhesive systems.

23.5.2 Auriculectomy

Loss of one or in some instances both external ears (the later more commonly a result of trauma or congenital anomalies) create both functional as well as esthetic compromise. The external ear is responsible for funneling sound to the ear canal thus molding and shaping the sound so it can be interpreted by the brain as to where the sound is coming from, what is its intensity which are important aspects associated with normal hearing. Without an external ear, appropriate interpretation of sound is impaired [25]. Further, the ability to wear glasses is significantly impaired when one or both external ears are anatomically absent. Women who have a missing ear are limited in their choice of hairstyles in that the "up-do" is not an option because reveal of a missing auricle is a cosmetically debilitating. The counterpoint to that observation is a lost external ear can easily be camouflaged with longer hairstyles for either men or women.

Tumor resection of the external ear sometimes necessitates extension of the resection to include either the mastoid process and/or temporal bone. In these instances, a more significant cosmetic deformity results. Adjunctive radiotherapy complicates management for rehabilitation as circulatory capacity is impaired and hence surgical management has an additional element of risk.

While surgical reconstruction of an ear is possible, there are very few plastic and reconstructive surgeons who have excelled in this endeavor. Admittedly, this type of reconstructive procedure is acknowledged by surgeons as being the most challenging surgical exercise on their menu of treatment services [14]. As well, a reconstruction effort involves multiple stages and a donor site to harvest cartilage from the sternum/rib cage. Good circulatory capacity of the overlying skin in the region of the planned reconstruction is essential for promoting healing.

Prosthodontic management to provide for replacement of a missing external ear offers a predictable outcome as regards restoration of anatomically correct replacement in regard to size, shape, coloration, contour, orientation, etc. The down side to approaching this type of rehabilitation with a prosthesis is just that, it is an artificial replacement that is not a part of the patient in the same sense that which a tissue reconstruction offers. Inherent with that issue are overriding considerations that a

Fig. 23.14 Examples of an array of adhesives used to retain extra-oral prostheses

prosthesis needs replacement at varying intervals due to deterioration/discoloration of the material of which it is fabricated and the prosthesis is reliant on some form of mechanism to appropriately and predictably provide for its retention. The common method to retain extra-oral prostheses until fairly recently was use of a variety of skin adhesive, bi-face tapes, etc (Fig. 23.14). While the adhesive retained prosthesis did, in fact, provide a mechanism for retaining the prosthesis it was not consistently predictable. Moisture, heat, perspiration contributed to compromised retention of extra-oral prostheses reliant on this type of connection to the patient. This lack of predictable retention was a major concern for patients who, not infrequently encountered the embarrassment of having the prosthesis becoming detached [26, 27]. In and of itself, this type of outcome led patients to not use their prosthesis that is frustrating not only for the patient in need but also for the provider who devoted a significant effort to fabricate it.

With the introduction of specially designed craniofacial implants, a permutation of those used for intra-oral anchorage/retention of oral prostheses, a monumental advance for improvement that addresses the challenge of solving the problem of providing predictable retention for extra-oral prostheses came to the fore [28]. While this approach offers the desired improved retention the service requirement for such treatment, the increased cost to provide for placement of implants, etc. all create a new milieu with which patient and provider alike are confronted during the life-time service associated with this type of treatment (Fig. 23.16). One distinct advantage for the implant retained prosthesis when compared to that of the adhesive retained prosthesis is the former commonly is less challenged as regards maintenance and maintenance of the marginal integrity of the prosthesis.

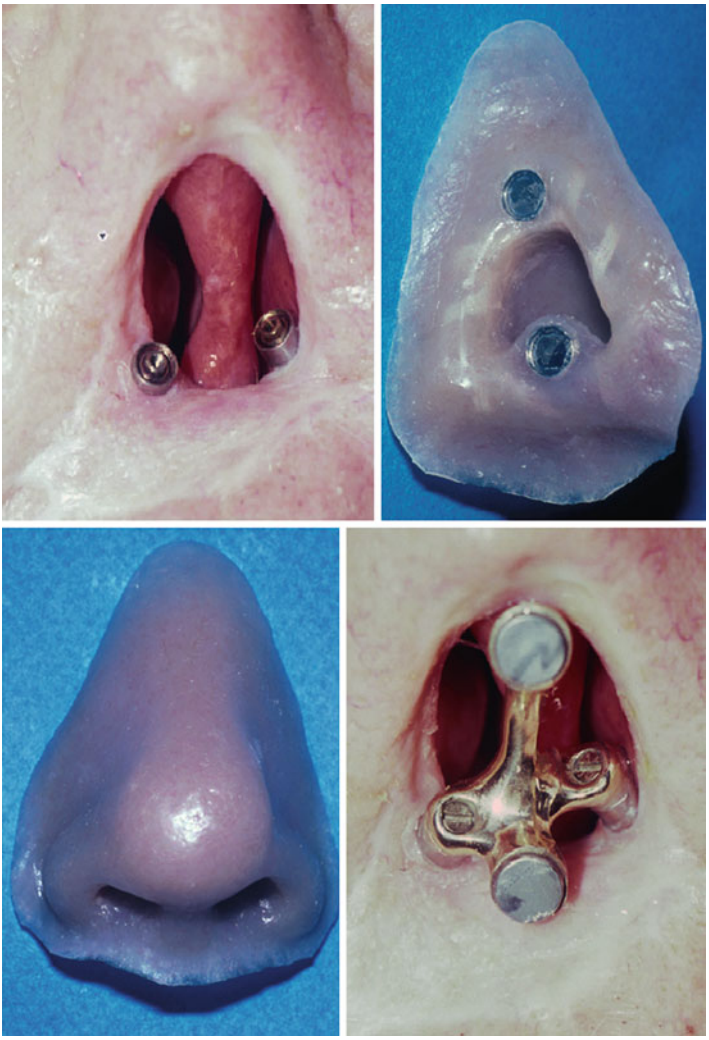

Fig. 23.15 Example of an implant magnet retained nasal prosthesis used to address a patient having a total rhinectomy, (**a**) view of the healed rhinectomy site with two trans-mucosal abutments in the lateral ala region that are anchored to two osseointegrated implants (*upper left*), (**b**) tissue surface view of the tissue colored silicone nasal prosthesis with two titanium encased cobalt samarium magnets (*upper right*), (**c**) the nasal prosthesis observe side (*lower left*), (**d**) the cast gold retaining component to which the prosthesis is seated and magnetically retained (*lower right*)

That results in affording the prosthesis a longer length of service. However, a trade off is that in some cases the peri-abutment tissues encounter management issues that can range from applying topical antibiotics or low dose steroid preparations to surgical management. Generally speaking, once craniofacial implants are placed and employed for use to retain extra-oral auricular prostheses they

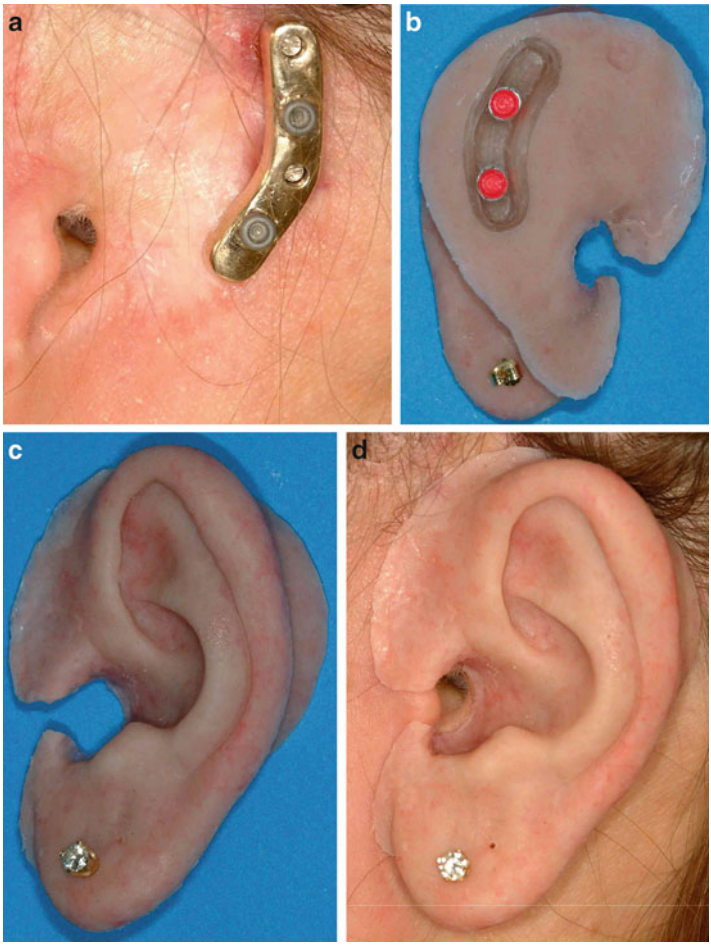

Fig. 23.16 Implant retained auricular prosthesis, (**a**) the implant retaining bar seated on two craniofacial implants (*upper left*), (**b**) the tissue side of the silicone auricular prosthesis demonstrating the two resilient attachments embedded/bonded in an acrylic housing that is affixed to the silicone of the prosthesis (*upper right*), (**c**) observe side of the completed prosthesis complete with pierced diamond stud earring (*lower left*), (**d**) the prosthesis seated in place (*lower right*)

commonly remain integrated and are not lost [29, 30]. The success/survival of these types of implants placed into areas that have received radiotherapy have a less favorable outcome as regards their achieving osseointegration or remaining osseointegrated. Use of pre-and post-adjunctive hyperbaric oxygen treatment may provide for improved success for craniofacial implants but more studies need to be conducted to support this assertion [31].

23.5.3 Orbital Enucleation… Surgical/Prosthetic Management

Given that our maker has given us only two eyes, two ears, and one nose, loss of any of these anatomical structures falls within the earlier assertion made of that being unimaginable and all the attendant issues associated with what impact that will have on one's self image along with the attendant functional impairment that is inherent in these types of anatomical compromises. Loss of an eye results in a monumental alteration in ones' life experience. With the loss of the globe of the eye, it usually is possible for an ocular prosthesis to be fabricated and provided such that is virtually undetectable when such a patient so treated interacts with the public. The caveat to that statement relates to the extent of surgical management and how the rehabilitation efforts are affected. Specifically, if the strap muscles attached to the globe of the eye do not need to be sacrificed as part of the tumor management they can be used by attaching them to various occlular implants that are made of a variety of materials such as titanium, hydroxylapatite, implantable silicone. When the muscles are attached to this type of ocular implant and the ocular prosthesis when placed in the eye socket this results in the ocular prosthesis being able to participate in tracking movement. The muscular contraction that occurs will, in effect, allow for the ocular prosthesis to "track" with the unaffected eye and hence will be more complimentary than distracting from what would be considered the "norm" when the patient moves his/her eyes from side to side, up and down, etc. With that said the prosthetic replacement for patients losing the globe of their eye still leaves them with the functional adaptation of accommodating to monocular vision from the norm of binocular vision. It is hoped with the rapid onslaught of technological advances that some time in the future a mechanism for not only replacing the lost eye but also making it such that binocular vision could be restored would be possible resulting in a huge advance in attempting to rehabilitate not only the lost anatomy but its function as well.

Individuals who fabricate the majority of ocular prostheses are known as Occularists. This is a stand-alone profession is separate from that of Maxillofacial Prosthodontists or Anaplastologists. However, there is some overlap amongst these disparate groups in regard to their training and experience. Occularists generally are trained in the time tested journeyman type of system where an individual interested in pursuit of this type of career first is a novice apprentice, then a journeyman, and then a master occularist. This process can take a number of years to accomplish. While the aforementioned specialty groups can also fabricate ocular prostheses, it would be fair to say that the overwhelming majority of ocular prostheses fabricated have largely been relegated to ocularists. Additionally, there are manufacturers of "stock" artificial eyes just like there are manufacturers who make teeth for denture prostheses.

In years past and especially in Europe, ocular prostheses were made of blown glass. While some ocular prostheses are still made with that technology, the majority of ocular prostheses fabricated today are of heat-polymerized methylmethacrylate (plastic).

23.5.4 Orbital Exenteration… Surgical/Prosthetic Management

The exenteration of the orbit i.e., the removal of the globe of the eye, the contents of the orbit, eye lids, and in some instances the bony architecture of the orbit, portends a more complex rehabilitation challenge than prosthetic management for that of an individual undergoing an enucleation (loss of the globe of the eye). The first challenge for this type of intervention is having the surgeon and the prosthodontist on the same page as regards how the residual anatomy will be addressed. There is a tendency for surgeons to close the resulting surgically exenterated orbit with vascularized free flaps such as radial forearm free flap that provides full thickness soft tissue coverage. The thinking behind this approach is to provide soft tissue coverage for the bone in the region of the orbit so it is, in effect, protecting it during the administration of post-operative radiotherapy. In so doing, the conventional wisdom suggests that development of radiation-induced osteoradionecrosis will be prevented. Clearly, the bony architecture of the orbit is in close proximity to the brain cavity and any potential for inducing complications associated with management of a malignancy in this region should at all costs be avoided.

With that said, this author has had any number of consults with patients having undergone an orbital exenteration without the benefit of having pre-operative communication with the surgeon performing the resection. The result of this type of management necessitates my having to tell the patient that their desire to seek fabrication of a prosthesis with that type of surgical management i.e. full thickness flap covering the orbit makes it such that any attempt for rehabilitation is not feasible. Further, if attempted, it will result in an esthetic compromise that out distances their post surgical presentation.

The reason for this assertion is that in order to fabricate an orbital prosthesis i.e., replacement of the eye and the surrounding soft tissues that being the lids, sometimes the supra-orbital rim, lateral border of the nose, infra-orbital rim, portion of the cheek, first an foremost necessitates having a deep socket into which the prosthesis can be placed. For the globe of the eye to be correctly positioned and to be made to appear symmetrical with that of the unaffected side it absolutely needs to be oriented in three-dimensional space correctly. For there to be any hope of creating a normal appearance resulting from a rehabilitation effort with the provision of an orbital prosthesis this essential mandate cannot be violated.

From a maxillofacial prosthodontic perspective, the ideal orbital exenteration leaves the patient with a deep orbit socket that is skin lined with a split thickness skin graft. Once, healed this type of socket is dry, with no communication with the frontal sinus, or nasopharynx or the oral cavity.

The conventional approach to retain an orbital prosthesis has been to use adhesive retention as already mentioned for nasal and auricular prostheses. In some circumstances, the anatomy of the orbital exenteration allows for the provision of a mechanically retained prosthesis [32, 33]. If a prosthesis can be designed with a mechanically retained approach the need for use of adhesive could be minimized or eliminated. The risk of using this type of design for those patients having an orbital

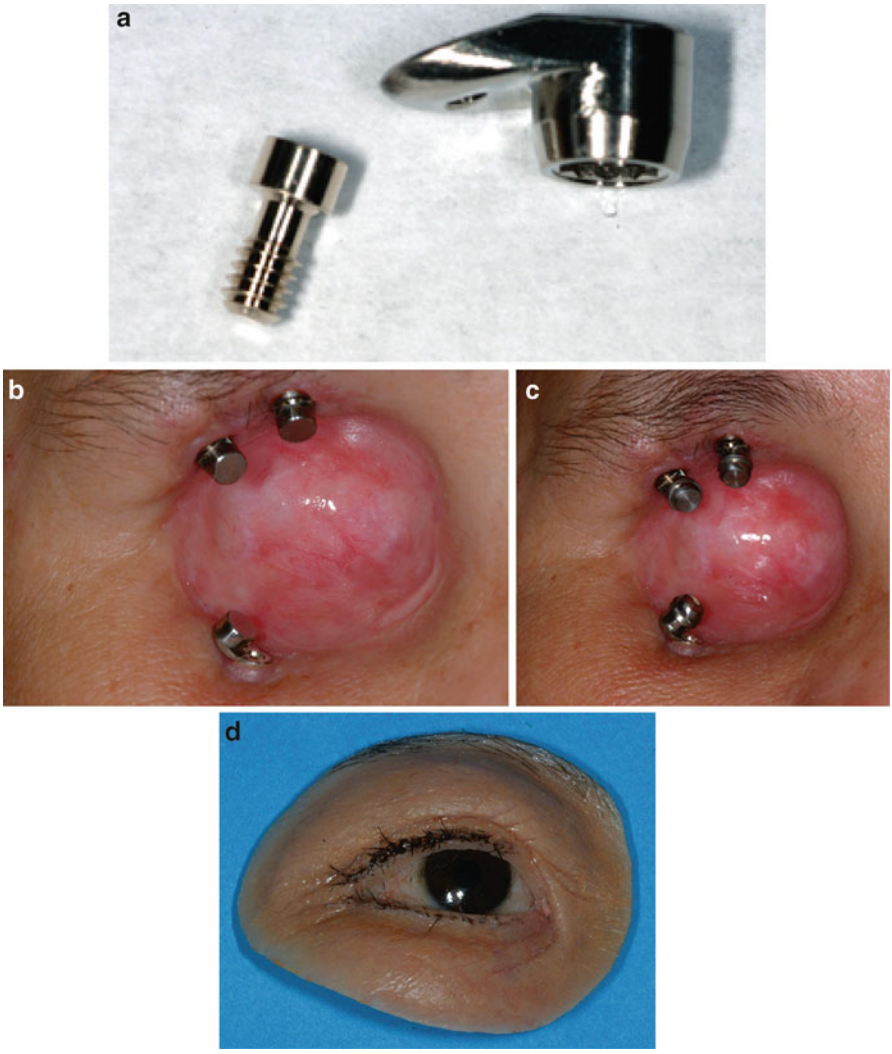

Fig. 23.17 One mechanism to retain an implant prosthesis for a patient having an orbital exenteration, (**a**) console abutment and screw used to redirect the retention component from the top of the implant. The lateral projections pod for placement of a magnet keep is provided in a number of angulations off the vertical axis of the implant position (*top image*), (**b**) console abutments in place with their magnet keepers affixed to the angulated pods (*middle left*), (**c**) titanium encased cobalt samarium magnets positioned on their respective keepers (*middle right*), (**d**) the visible (reveal) side of the orbital prosthesis, (**e**) the tissue surface of the orbital prosthesis now with the aforementioned magnets incorporated into an acrylic substructure bonded to the silicone tissue colored orbital prosthesis (*bottom*)

exenteration and radiotherapy might create soft tissue irritation that could lead to soft tissue and/or osteoradionecrosis. Clearly, the risk/benefit issues tilt toward not creating the potential for inducing this type of potential complication by employing this approach. As previously noted, the use of osseointegrated craniofacial implants

offers a contemporary approach to providing predictable base to retain an orbital prosthesis (Fig. 23.17). A variety of retention systems and designs have been shown effective in using an implant-based system to retain an orbital prosthesis. One challenge in fabricating such a prosthesis is the position, axial inclination of the implants in relationship to the overlying prosthesis. In some orbits space is significantly limited to correctly position the ocular prosthesis correctly in three-dimensional space and have the retentive elements incorporated to relate to the implants. Creative engineering frequently is challenged to a high degree for all the pieces of the puzzle to come together in a workable outcome.

Unfortunately, in some situations tumor ablation surgery necessitates removal of the maxilla along with an orbital exenteration. The result of this type of surgical intervention leaves a communication with the oral cavity, maxillary sinus, nasal cavity and the orbit. In such circumstances, the prosthodontic rehabilitation necessitates fabrication of an obturator and an orbital prosthesis. This type of prosthodontic management offers additional challenges as regards the prostheses inter-relationship and how that impacts stabilizing and retaining both prostheses such that they don't compromise the end result of either effort. In some instances and interface between the two prostheses is by design used to assist in each retaining/supporting the other.

23.5.5 Multi-site Extra-Oral Anatomical Compromise… Surgical/Prosthetic Management

The array of possible anatomical compromise that involves more than an isolated anatomical structure thus far described could, in and of itself is a stand-alone chapter. It is fortunate for patients so afflicted and the providers attempting to make such individuals "whole again" that such situations in contemporary head and neck cancer management are few and far between. The reason for this assertion results largely from most head and neck cancer surgeons not having a high degree of enthusiasm to attempt a "hemi-headectomy" a slang term for extensive multi-site facial disfigurement. Tumor management's goal in the region of the head and neck is to seek at the minimum local control. Faced with the need for extensive surgical resection the likelihood to predictably obtain local control has significantly diminished odds and hence more commonly today these patients are managed with palliative treatment rather than treatment with a hope to obtain cure.

Publications demonstrating Herculean efforts employing an array of craniofacial implants placed in multiple planes, onto which are placed extremely complex retaining structures for the ultimate placement of such multi-site extra-oral prostheses [34]. If nothing else, efforts such as this should be applauded and serve as the incredible will for the provider to make such patients "whole again". Perhaps this type of Sisyphisian effort could serve as the icon for Maxillofacial Prosthodontic Rehabilitation.

23.6 Conclusions

The challenges associated with the maxillofacial prosthetic rehabilitation for patients experiencing anatomical compromise of the oral and extra-oral anatomy associated with treatment resulting from a diagnosis of head and neck cancer has been presented. While a comprehensive description of treatment services and nuances associated with the provision of prostheses that provide for potential to rehabilitate there is far more to this story that can be provided in this chapter. The amazing aspect of the provision of this type of care is that each patient service while able to categorized as this or that type of prosthesis in actuality is a highly individualized unique treatment experience for both the patient receiving it and provider facilitating it.

Advances in surgical reconstruction have added a new dimension and have opened up a whole new arena of treatment options. This evolution has stimulated a whole array of new and heretofore uncharted challenges that require a much closer interaction amongst treatment team members so appropriate management can be provided.

The future for rehabilitation management for those patients diagnosed with head and neck cancer may eclipse the current and significant efforts needed for surgical reconstruction followed by prosthetic rehabilitation. Separate and apart for the dream of finding a cure for cancer would be the ability to genetically engineer replacement for anatomical compromises in the region of the head and neck so that the current albeit improved methods would be supplanted and eliminated. Clearly, this is the future but with the rapidity that scientific advances are unfolding it would be the hope and expectation that these dreams will soon become reality.

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Chapter 24
Complications from Surgical Treatment of Oral Cancer

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Contents

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Abstract Cancer of the oral cavity and oropharynx remains among the top ten most common malignancies in the United States, Europe, and worldwide (Shah et al., Oral cancer, Martin Dunitz an imprint of Taylor and Francis Group, London, 2003). Over the last 30 years the philosophies of treatment of oral cancer have changed very little with regards to primary tumor extirpation, with the exception of marginal mandibular resection. There have been major changes in the approach to cervical lymph nodes at risk for metastasis (Kim and Ord, Oral Maxillofac Surg Clin North Am 15:213–227, 2003). The radical neck dissection, once advocated by Dr. Crile as the only appropriate treatment for the neck, is now rarely performed in most centers (Shah, Cancer of the head and neck – atlas of clinical oncology. In: Management of cervical metastasis. BC Decker Inc, London, 2001). In addition, "organ preservation" protocols involving chemo-radiation therapy, although not without adverse effects, have significantly altered the quality of life for the cancer patient. Also, the ability to offer a variety of reconstruction options with the available hardware, local and regional flaps, as well as free tissue transfer from distant sites, has contributed to the overall significant improvements in functional and esthetic outcomes. The head and neck cancer patient in the new millennium has the opportunity to emerge from an extensive ablative surgical procedure with excellent functional and esthetic results. Despite these surgical advances, the ablative process still results in the sacrifice of several functional and esthetic organs during surgery for cancer of the oral cavity (Shah, Cancer of the head and neck – atlas of clinical oncology. In: Management of cervical metastasis. BC Decker Inc, London, 2001). Early complications from ablative surgery for oral cancer are, for the most part, similar to those from other sites. Long term complications however are quite challenging for the oncologic team as well as the patient who survives oral cancer, primarily due to the highly specialized regional tissues involved in the surgical field.

Keywords Complications • Treatment failure • Surgical airways • Neurologic dysfunction • Reconstruction • Quality of life

24.1 Introduction

Cancer of the oral cavity and oropharynx remains among the top ten most common malignancies in the United States, Europe, and worldwide [1]. Over the last 30 years the philosophies of treatment of oral cancer have changed very little with regards to primary tumor extirpation, with the exception of marginal mandibular

resection. There have been major changes in the approach to cervical lymph nodes at risk for metastasis [2]. The radical neck dissection, once advocated by Dr. Crile as the only appropriate treatment for the neck, is now rarely performed in most centers [3]. In addition, "organ preservation" protocols involving chemo-radiation therapy, although not without adverse effects, have significantly altered the quality of life for the cancer patient. Also, the ability to offer a variety of reconstruction options with the available hardware, local and regional flaps, as well as free tissue transfer from distant sites, has contributed to the overall significant improvements in functional and esthetic outcomes. The head and neck cancer patient in the new millennium has the opportunity to emerge from an extensive ablative surgical procedure with excellent functional and esthetic results. Despite these surgical advances, the ablative process still results in the sacrifice of several functional and esthetic organs during surgery for cancer of the oral cavity [3]. Early complications from ablative surgery for oral cancer are, for the most part, similar to those from other sites. Long term complications however are quite challenging for the oncologic team as well as the patient who survives oral cancer, primarily due to the highly specialized regional tissues involved in the surgical field.

This chapter addresses the chronic complications associated with surgical treatment of oral cancer and the management of these problems. The topics covered include treatment failure, speech and swallowing impairment, masticatory insufficiency, hardware failure, scar and fistula formation, trismus, tracheal stenosis, neurologic dysfunction and nutritional considerations. Long term donor site morbidities are discussed as well. Finally, psychological and quality of life issues associated with functional and facial esthetic outcomes are addressed.

24.2 Complications Associated with Cancer Resection

24.2.1 Treatment Failure

The most significant negative outcome for the oral cancer patient is failure to cure the disease. This failure may be due to local or regional recurrence, distant metastasis, or presence of second primary cancer (Figs. 24.1, 24.2, 24.3, 24.4). The vast majority of recurrences occur within the first 2–3 years following completion of treatment [1, 3]. Local recurrences are mainly the result of failure to eradicate the primary cancer with surgery and are often associated with failure to achieve negative surgical margins. In 1953 Slaughter put emphasis on the significance of examining healthy appearing tissues surrounding the tumor for risk assessment and disease control [4]. In general, the head and neck surgeon attempts to remove the primary cancer with a 1.0–1.5 cm margin of "healthy looking" tissue, if anatomically allowed, in order to achieve histopathologic "negative margins". Throughout the literature there is tremendous debate with regards to what precisely is considered a "negative margin". From a histopathologic point of view lack of dysplasia, carcinoma in situ or invasive cancer within 5 mm of the resection margins o f the pathologic specimen is reported as "negative." However, the validity of this interpretation and its association with

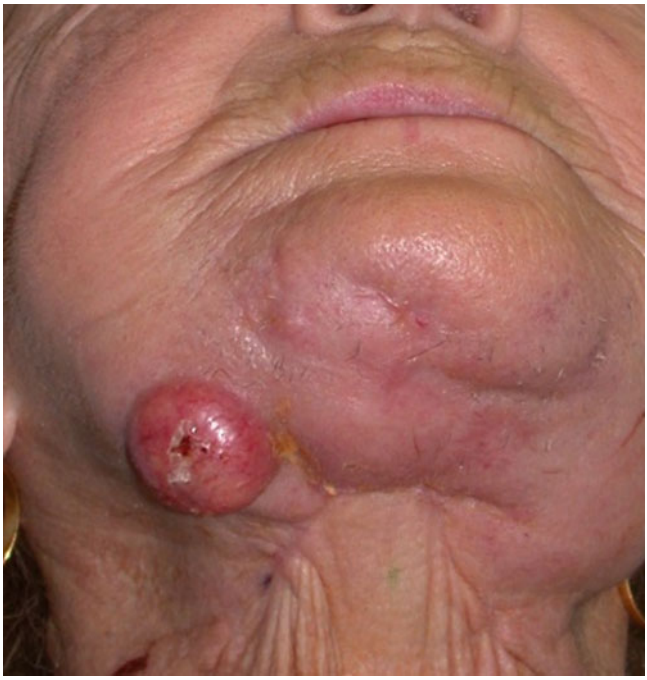

Fig. 24.1 Local failure with extraoral tumor extension

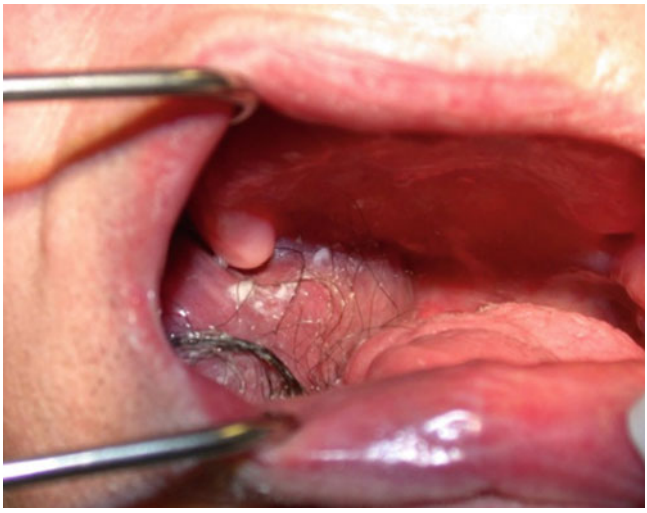

Fig. 24.2 Local failure under existing pectoralis major myocutaneous flap

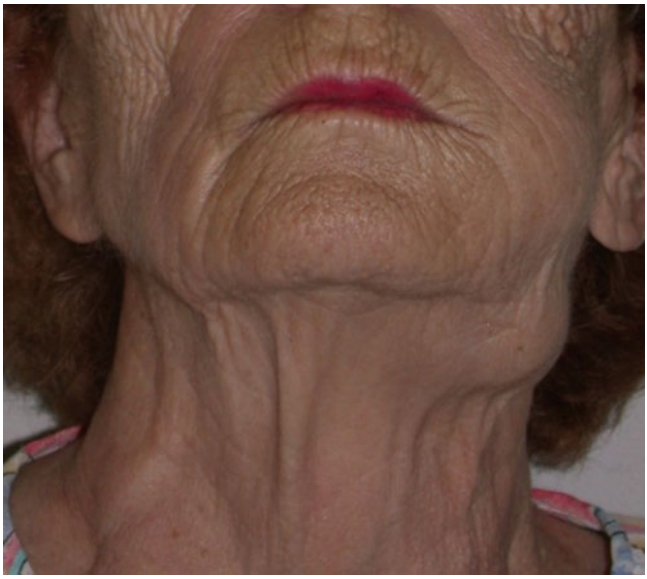

Fig. 24.3 Regional failure left neck post treatment

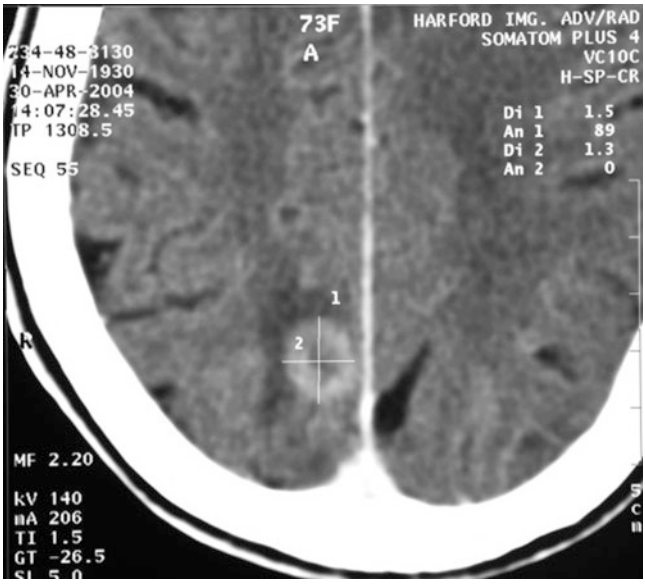

Fig. 24.4 Brain metastasis

local recurrence has been challenged in various studies. The lack of universally accepted standardized terms and definitions as well as clear distinction between mucosal and deep margins has been identified as a major deficit when the status of the margins is examined [2, 5–8].

To further ensure adequate tumor resection during surgery, frozen tissue sections have been traditionally submitted for analysis during the surgical resection. These have been proven to be valuable when found positive for disease, and this guides the need for additional tissue resection [9]. Diagnostic accuracy of frozen tissue specimens has been reported to be between 96 and 98%. "Sampling error," inability to perform frozen sections to examine for bone involvement, and difficulties with interpretation of histologic changes in radiated tissues are a few of the limitations that contribute to the lack of clinical reliability of frozen sections [10, 11]. Studies that have evaluated frozen section status, and the status of the resection margins, have demonstrated a clear association between positive margins of frozen sections and local failure of treatment. Recent advances in molecular biology of oral cancer, with the acceptance of field cancerization, and multicentricity along with primary tumor characteristics, may explain, at least in part, the failure to achieve local control [3, 12–15].

The benefit of removing the "at risk" lymph nodes of the neck in advanced stage (T3 and T4) tumors has been clearly demonstrated and is generally widely accepted. The eradication or prevention of neck disease be in the form of surgery via neck dissection alone, or with the addition of radiation or chemotherapy [1, 3, 16–18]. Controversy still exists as to whether one should treat or watch the neck nodes in early stage tumors with no clinical or radiographic evidence of nodal metastasis (N0 neck). This is an important issue clinically, since metastasis to the cervical lymph nodes has been shown to be a significant negative predictor of outcome and is associated with tumor aggressiveness [1, 3, 15, 19].

A follow up protocol is usually proposed by the treating team for all cancer patients; this recall includes frequent clinical examinations with radiographic surveillance, including computer tomography (CT) or magnetic resonance imaging (MRI), since these have been proven to be sensitive tests for assessing disease status.

Most recently positron emission tomography (PET), with or without computer tomography and magnetic resonance imaging, has been used for surveillance for local and regional tumor recurrence. The advantage of PET is that it may assist in the differentiation of post-surgical scarring and post-radiation treatment changes from tumor recurrence [20, 21]. Despite all current advances in diagnosis and treatment modalities, local and regional failures in oral cancer remain problematic issues.

In a non-radiated field, local and regional failure may be treated with additional surgery alone, or in combination with radiation and chemotherapy [22, 23]. One of the major clinical challenges is the case of local and or regional failure following a full course of postsurgical tumoricidal radiation treatment (Fig. 24.5). It is best to treat these patients with additional surgery whenever t is anatomically feasible to do so. If surgery is not possible, then additional radiation may be of use, but it is associated with serious complications and poor overall long-term therapeutic results [1, 22–25]. Another major problem with these patients who fail surgery and chemoradiation therapy is the presence of distant metastasis. This finding significantly

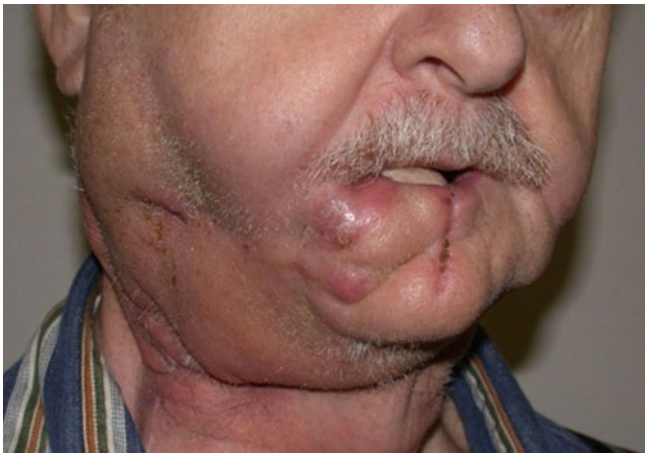

Fig. 24.5 Persistent disease during radiation and chemotherapy

decreases the chances of disease control and impacts negatively on the life expectancy of the patient. Recent studies have demonstrated that although local and regional control is achieved with current multimodality treatment, distant metastasis has significantly increased [15]. As new chemotherapeutic agents and combination therapies become available clinically, a delay in the progression of advanced disease may become a more reasonable expectation in the future [26–28].

24.2.2 Speech and Swallowing Impairment

Clearly surgical resection of malignancy within the vicinity of the oral cavity has a significant impact on speech and swallowing functions. More specifically, the oral preparatory phase (formation of a bolus) and the oral phase of normal deglutition, are significantly impaired following extirpative surgery. Loss of a significant portion of the tongue musculature will limit the ability to transfer food into the appropriate position for grinding by the dentition. Therefore, the first phase of swallowing is disrupted. The transfer of the bolus from the anterior portion of the oral cavity to the area of the tonsillar pillars, where the initiation of the swallowing reflex occurs, constitutes the second phase of swallowing. The harmonious coordination of the lips, tongue, buccal mucosa and maxillomandibular complex is required for completion of these phases and progression to the pharyngeal phases of swallowing. The same structures are associated with speech production and more specifically articulation. As a general rule, ablative surgery that involves the most anterior portion of the oral tongue is associated with significantly altered speech, while resections that incorporate the posterior tongue affect swallowing function. As postsurgical time progresses, surgical site cicatrix formation and fibrosis, along with decrease salivary flow from adjunctive radiotherapy if utilized, further impairs speech and swallowing [29–31].

The complexity of the function of the oral cavity structures cannot be restored to the pre-surgery status despite use of swallowing maneuvers and sensate free tissue transfer. Difficulties with articulation, chewing and swallowing remain long term problems for these patients, and adequate rehabilitation and support should be initiated early. Consultations with speech and swallowing services are imperative in assisting the patient to regain their pre–treatment status and possibly to avoid long term dependence on gastric tubes, recurrent aspiration, and communication difficulties [1, 3, 32–34]. The effects of swallowing and speech impairment on the quality of life are discussed further later in this chapter, and in other chapters of this book.

24.2.3 Masticatory Insufficiency/Trismus/Nutritional Considerations

Masticatory function is adversely influenced by the surgical management of oral cancer. The tongue, floor of mouth, maxilla and mandible with the adjacent tissues are vital structures used for mastication and their anatomic and functional integrity is altered during ablative surgery. For efficient mastication all three components of mastication (manipulation, trituration, and consolidation) are required, and are the result of synchronous interaction of hard and soft tissues [35]. Mandibular or maxillary resection affects the grinding ability either due to loss of stable and reproducible stomatognathic system relationships or due to loss of tooth-to-tooth contacts and diminished biting forces. In addition, loss of soft tissue bulk and sensation causes difficulties with the patient's ability to manipulate the food bolus to the occlusal table, retrieve the bolus, and then consolidate it prior to deglutition.

Numerous studies have evaluated the limitations associated with mastication status post cancer resection and the effects of reconstruction on masticatory function. Biting force testing, and those evaluating the tongue and cheek function, are employed to evaluate the specific aspects of mastication. Patient questionnaires are used to access the overall efficiency in masticating food and the quality of life following mandibular resection with respect to success of reconstruction utilization. Unfortunately, significant variability in the testing instruments utilized in these studies, has resulted in conflicting results and conclusions [36, 37].

It is universally accepted that reconstruction of defects in the oral cavity, at the minimum, result in decreased scar formation and reduced associated functional and cosmetic limitations. Soft tissue reconstruction with a pedicle flaps and the use of reconstruction plates to span the bony continuity defects has been shown to be superior to simple closure techniques alone. With the availability of free tissue transfer, composite flaps can restore not only tissue bulk and facial esthetics, but these can address masticatory function and recovery of sensation [38, 39].

Limited interincisal opening, less than 35 mm between the maxillary and mandibular incisors, is one criterion for trismus based on the restrictions in mouth opening

and mandibular function perceived by the patients. Trismus is a common complaint following oral cancer surgery. Fibrosis and scar contraction, in addition to contraction of the muscles of mastication, are the main reasons for inability of the patient to open the mouth. Common oral cancer procedures resulting in trismus include maxillary surgery involving the origin of the medial and lateral pterygoid muscles from the pterygoid plates, or mandibulectomy procedures involving any of the muscles of mastication, including the temporalis muscle insertion to the coronoid process, the masseter muscle insertion to the mandibular angle and ramus, and the pterygoid insertions to the medial ramus and condylar neck. Of course, adjuvant radiotherapy may lead to fibrotic changes which may exacerbate the magnitude of surgically-induced trismus. Finally, disarticulation of the temporomandibular joint for tumor eradication will certainly lead to similar limited mouth opening. Exercise regimens, and mouth opening assisting devices, either active or passive, are regularly prescribed to assist these patients. Unfortunately, if these steps are not incorporated early, before severe scarring has occurred, and maintained long-term, only limited improvement in trismus can be expected [1, 40–43].

As a result, the presence of these difficulties with mastication, swallowing, trismus, along with utilization of bulky tissue for coverage of defects that do not always address the functional needs of the cancer patient all contribute to limitations in food intake and compromise the nutritional status of patients. A significant number of these patients are forced to adapt specific diet modifications that may lead to nutritional deficits. The usual problems are inadequate protein intake and frequent episodes of dehydration, and some patients become dependent on feeding formulas through gastric tubes. Although these formulations are appropriately balanced with adequate calories, issues of intolerance, diarrhea, dehydration and electrolyte imbalance are very common. Nutritional education and support, along with close monitoring of the caloric and nutritional intake of these patients, will assist in preventing long term deficits and frequent hospital admissions [3, 44, 45].

Additionally, the patient population with oral cancer may have a social history significant for alcohol abuse, and preexisting nutritional deficiencies, and this may impact on continued malnutrition as well as poor wound healing postoperatively.

24.2.4 Facial Esthetic Considerations and Scar Formation

Of primary importance in the surgical management of oral malignancies is surgical access for visualization and assessment of margins and anatomic considerations for resection. This may be considerably complicated in cases where the tumor occupies the posterior aspect of the lateral tongue and floor of mouth as well as the retromolar fossa, the mandibular gingiva, or the maxilla. The complex anatomy of the oral cavity makes surgery more challenging and requires incorporation of various incisions and flap designs to facilitate adequate exposure and subsequent tension free closure.

For the neck dissection, on the other hand, the need to protect the carotid sheath and its contents has led to incision and flap designs that specifically address this

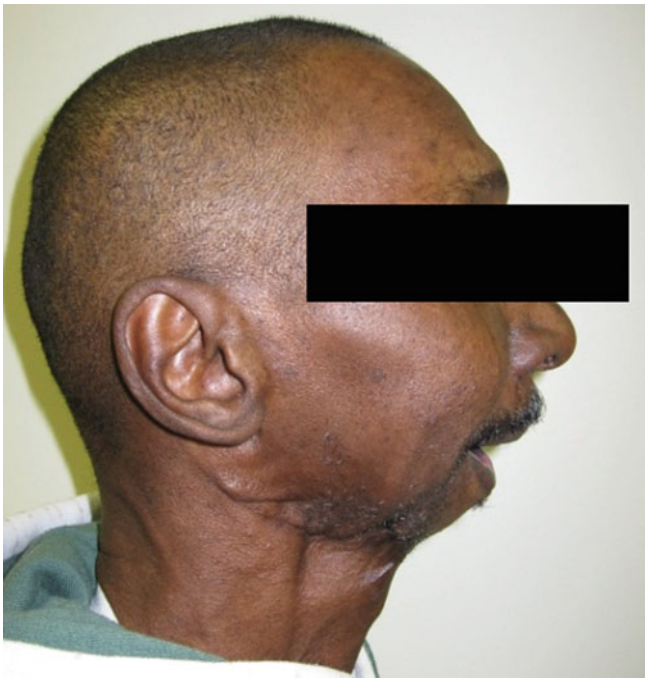

Fig. 24.6 Severe facial defect post resection of anterior mandible SCCA without reconstruction

anatomic limitation. Esthetic considerations have not, until recently, been a primary concern when access for tumor resection is planned. Lip split and extensive facial incisions have been utilized over the years, recognizing that the main concern has been adequate exposure, and not esthetics.

The change in the patient population demographics suffering from oral cancer, along with concerns about long term facial scarring, has forced surgeons to consider incision and flap design based upon facial esthetic units. The stigmata of oral cancer surgery are no longer acceptable in the face and neck regions due to a desire for continued social interactions and reasonable quality of life, especially when survival rates improve, and patients live longer lives following treatment [46–51].

Incisions in the neck, with trifurcation extensions, that do not follow natural skin creases, have a higher incidence of dehiscence and unesthetic scar formation. In addition, the effects of radiation treatment further worsen the appearance of the scars and risk exposure of the carotid artery, or other vessels, if superficial skin necrosis occurs [1, 2, 52, 53] (Fig. 24.6). Also, unesthetic tracheostomy scars are very common, especially when the need for the tracheostomy is delayed, or the site has been infected. The advantages and disadvantages of vertical versus horizontal incisions for access to the trachea with regards to scarring and esthetics are debated extensively due to individual surgeon preference and experience. Attempts should be made to handle tissue gently, to provide protection of the skin from iatrogenic trauma from

traction or electrocautery, to consider elevation of thick soft tissue flaps, with adequate blood supply, in order to minimize the creation of unesthetic scars [53, 54].

For surgical access to some of the tumors in the oral cavity, the lips may need to be divided, and incisions on the face may be required. The original description of the lower lip split procedure in the 1900s placed the incision at the middle of the lip and chin causing severe scarring post-operatively. Since that time, various modifications have been described to this technique, with the main endpoint the achievement of an esthetically acceptable result that does not compromise access or restrict adequate resection. Precise alignment and restoration of the vermilion border of the lip, and alignment and interdigitation of the orbicularis oris muscle, and reorientation of the lip skin and oral mucosa are paramount in order to achieve excellent lip competence, function and esthetics [48–50, 55].

For maxillectomy procedures, it is often necessary to elevate the skin over the midface region to gain access to the underlying tumor. The classic Weber-Ferguson incision, with or without an extension to involve the lower eyelid, has been used for many years to accomplish wide surgical access in the midfacial area. This incision incorporates splitting of the upper lip, and failure to realign the vermilion border of the upper lip, or to reconstruct the philtral columns of Cupid's bow, can lead to esthetic and functional limitations. The lower lid incision extension, if required, can cause severe scarring, especially if post-operative infection further delays healing. Despite accurate surgical attention to detail during flap elevation, normal postsurgical scarring of the lower lid incision can result in lower lid retraction and ectropion with ophthalmologic consequences, and present a difficult esthetic and functional dilemma [56–58].

Reconstruction of maxillectomy defects is commonly accomplished with a prosthetic device or surgical "stent," that serves to obturate the surgical site defect. While less than ideal, the obturator provides adequate support of the soft tissues, and speech and swallowing are preserved. However, major esthetic concerns and functional limitations are apparent when the device is removed (Figs. 24.7, 24.8). These patients

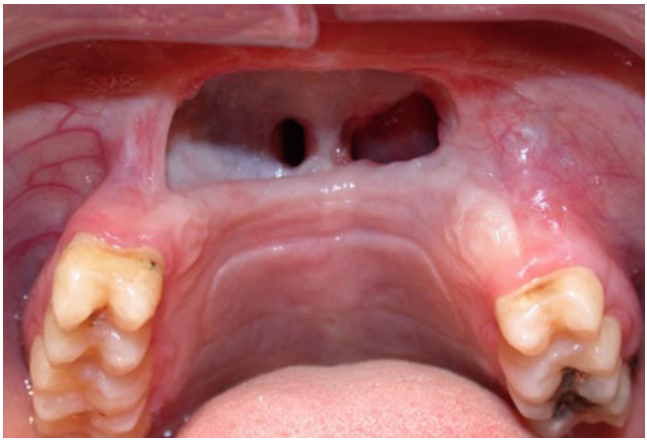

Fig. 24.7 Oral nasal communication post anterior maxillectomy without the obturator in place

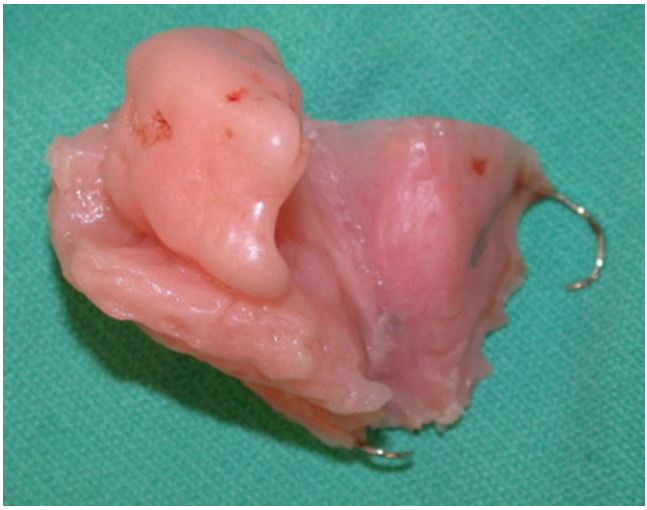

Fig. 24.8 Maxillary stent/obturator for use post maxillectomy procedures for speech, swallowing and esthetics correction

cannot perform normal speech, mastication, or swallowing functions without the maxillary obturator in place. Also, lack of stability of the obturator, even with an experienced maxillofacial prosthodontist, can be a clinical challenge [1, 3, 53, 59].

Recently with the increasing regional availability of free flap reconstruction, many of these limitations are no longer significant, provided that the patient is a good surgical candidate, and the surgical team is capable of performing the reconstructive procedure [60–63].

Often there is the need for local or regional flap coverage to obturate major defects, and these procedures are not without esthetic consequences. Traditionally the tongue, buccal mucosa, palate, and the temporalis and deltopectoral systems have been the reconstructive workhorses for oncologic surgeons for many years [64–66]. A myriad of esthetic and functional limitations have been described throughout the years in the literature using these types of soft tissue flap reconstructions.

It should be noted that the majority of patients who undergo partial or total maxillectomy or mandibulectomy procedures for tumor resection, or mandibulotomy for surgical access, will require post-operative radiation which may further worsen soft tissue scarring. The deleterious effects of radiation and the use of chemotherapeutic agents on the skin and existing scars have been discussed in the literature [1–3] (Fig. 24.6).

Additionally, many oral cancer patients have a significant social history of tobacco use and abuse due to its etiologic relationship with oral cancer, and therefore, the skin and other soft and hard tissue vascularity may be already severely compromised. This prior history, and possibly continued smoking by a majority of patients, may contribute not only to poor wound healing, but also to postoperative wound dehiscence, compromised flap viability, and resultant unesthetic scarring.

24.2.5 Chronic Fistulas

Any procedure that involves entering the mucosa of the upper aerodigestive tract via a neck incision may lead to formation of a fistulous tract due to persistent salivary leakage into the neck wound. Fistulas occur often following oral oncologic surgeries, and depend to a great deal on the general physical and nutritional status of the patient, the incision design, and the tumor type and stage, all of which may lead to an increased risk of this problem. These fistulas are more difficult to manage and completely eradicate when radiation therapy (XRT) has been employed. The effects of radiation in delaying surgical wound closure or preventing healing are generally attributed to low oxygen tensions and vasculitis that promote infection, as well as endothelial fibrosis and decreased blood supply to the surgical site. The higher the dose of radiation, and the longer the interval between radiation treatment and surgery, the higher the rate of wound complications when XRT is used pre-operatively. When XRT is employed post-tumor resection, adequate time is required in order to prevent delayed healing, fistula formation, and wound dehiscence.

Salivary fistulas can occur as early as 1 week, to as late as 3–4 weeks, post surgery. Fistulas that are present at 1 month after surgery are considered chronic, or persistent fistulas. Patients may present with a low grade fever of unknown origin, and other vague complaints indicating chronic inflammation. Usually the skin flap under the area of dependant drainage becomes inflamed and indurated. The best treatment involves prevention; but, if a developing fistula is noted, then surgical exploration of the wound with an attempt to direct saliva away from vital structures, such as the carotid vessels, is clinically indicated. The wound should be irrigated and packed open, and the patient should be prescribed empiric antimicrobial therapy for oral and skin flora, supportive care, and hyperalimentation, or, at the minimum, adequate nutritional support. If drainage is persistent for more than 4 weeks, then excision of the fistulous tract with closure of the oral mucosa and the skin should be attempted [1, 2, 52, 53, 67]. This surgery may be combined with attempts to transiently decrease salivary flow, with anti-cholinergic medications, if not contraindicated.

Loose or contaminated hardware from previous infections and or wound breakdown may be another reason for chronic fistulas (Figs. 24.9, 24.10). Usually there is a nidus of bacteria that cannot be eliminated with antibiotics alone, and local debridement, removal and/or replacement of existing hardware, and closure with local and regional flaps are indicated [1].

24.2.6 Surgical Airway Complications

Surgical treatment of oral cancer, especially advanced stages, interferes with maintenance of airway patency. Post-surgical edema, in addition to radiation and chemotherapy associated swelling, increase the risk of late airway complications (Table 24.1). This concern may require either prolonged intubation or surgically securing the airway with a tracheostomy. Surgical complications associated with

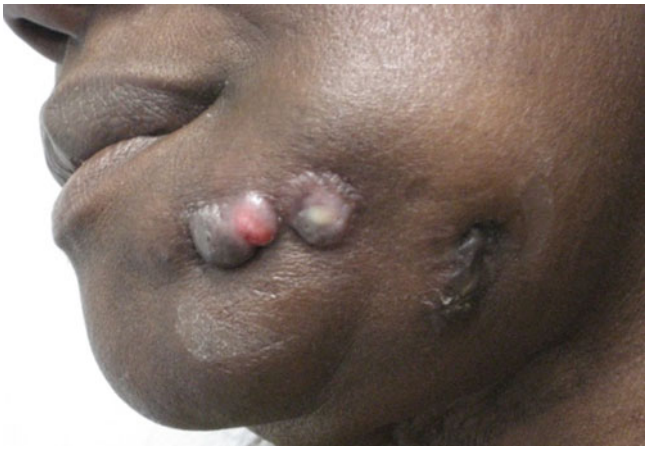

Fig. 24.9 Chronic fistulas with drainage on the face and neck due to saliva leak and bacterial contamination of existing hardware

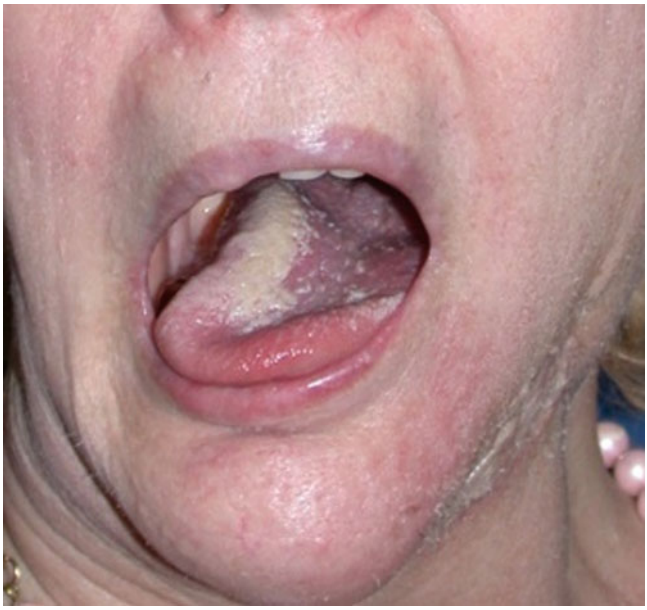

Fig. 24.10 Right hypoglossal nerve dysfunction

tracheostomy are traditionally divided into peri-operative, immediate post-operative and late post-operative, based on the time of occurrence. Tracheal stenosis, tracheomalacia, tracheoesophageal fistulas (TEF) and life threatening bleeding are among the potential late post-surgical complications [53, 68–70].

Table 24.1 Late surgical airway complications

1. Tracheal stenosis
2. Tracheomalecia
3. Tracheoesophangyal fistula (TEF)
4. Tracheo-Innominate artery erosion
5. Chronic aspiration and pneumonia
6. Esthetic considerations

Table 24.2 Risks associated with tracheal stenosis

1. Sepsis
2. Stomal stenosis
3. Advanced age
4. Male sex
5. Hypotension
6. Steroid use
7. Ill fitting cannula
8. Oversized cannula
9. Excessive mobility
10. Excessive removal or tracheal cartilage
11. Prolonged use

24.2.6.1 Tracheal Stenosis

Nearly all patients with a tracheostomy have some degree of trachea narrowing at the site of the stoma. About 3–12% of these patients develop a clinically significant stenosis that requires intervention. Tracheal stenosis is defined as an abnormal narrowing of the tracheal lumen that occurs most commonly at the level of or above the stoma and below the vocal cords. Two additional locations of potential stenosis include the site where the cuff and the tip the tracheostomy tube are located.

Stenosis is believed to be the result of bacterial contamination of granulation tissue and subsequent peri-chondritis that weakens the tracheal walls. Formation of granulation tissue is the result of microtrauma around the stoma, the cuff, or the tip of the tracheal tube. The natural progression is maturation of this tissue to fibrous tissue that is covered with epithelium, and subsequent fibrosis that causes narrowing. Multiple risks factors are associated with this complication (Table 24.2). A high index of suspicion is the key to diagnosis of this problem. Difficulty clearing secretions and a persistent cough may be subtle clinical findings, but these symptoms may not occur until 50–75% of the tracheal lumen has decreased. Ultimately, diagnosis with determination of the site and extent of the stenosis is made by direct laryngoscopy or bronchoscopy. Excision of the granulation tissue, rigid bronchoscope serial dilations, stent placement, and surgical resection with anastomosis of the remaining tissue, are some of the techniques employed to correct this problem if the tracheal stenosis is persistent or symptomatic.

24.2.6.2 Tracheomalacia

As with tracheal stenosis, a high index of suspicion is important for the early diagnosis of this complication. Tracheomalacia is a weakening of the tracheal wall. Ischemic injury leads to chondritis and results in destruction and necrosis of the involved cartilage. This causes the airway to collapse during expiration, causing air trapping and difficulty with clearing of respiratory secretions. Treatment is based upon the severity of the condition, and may range from nonsurgical conservative observation in mild cases, to tracheal resection and reconstruction in the more severe or persistent cases.

24.2.6.3 Tracheoesophangyal Fistula (TEF) and Tracheo-innominate Artery Erosion

Both of these complications are rare, occurring in less than 1% of patients who have had tracheostomies; but, when present, are usually acute and severe problems.

TEF is either an iatrogenic complication due to direct trauma during the surgical procedure, or due to prolonged pressure from the cuff or the tip of the tube in contact with the posterior tracheal wall. Perforation or erosion causes formation of a fistula with the esophagus. Gastric distention due to air leak into the stomach, persistent cuff leak, and food aspiration are some of the reasons that a persistent TEF may be present. Diagnosis is made with barium esophagoscopy or a CT scan of the mediastinum. If the patient is a surgical candidate, repair via a thoracotomy approach may be attempted by a thoracic surgeon. Otherwise a double lumen stent can be used to manage this problem. In either clinical scenario, the prognosis is poor.

Erosion of the innominate artery from a tracheostomy is a complication with nearly 100% mortality rate. This is either due to error in surgical technique, by placing the tracheostomy too low in the neck, or due to erosion of the anterior wall of the trachea from the cuff or the tip of the tube. Mild bleeding around the tube, can commonly be the first sign, and usually occurs 3–4 weeks following surgery. Massive bleeding, or hemoptysis, can alternatively be the first sign, and urgent surgical exploration, with attempts to identify and ligate the vessel, is indicated. The success of this repair is reported to be very low, and prevention remains the best treatment of this complication.

24.2.6.4 Chronic Aspiration and Pneumonia

Tracheostomy interferes with swallowing, and places the patient at risk for aspiration. Silent aspiration is reported in over 70% of these patients. In addition, chronically ventilated tracheostomy patients, especially in a hospital setting, are found to be at highest risk for ventilator-associated pneumonitis and pneumonia. Both of these complications are commonly associated with older age, prolonged hospitalization, and co-morbid conditions, such as chronic obstructive pulmonary disease due to smoking. A significant number of oral cancer patients present with either advanced stage disease, or are medically compromised, and therefore are at increased risk for developing either of these pulmonary complications. Treatment of these problems includes medical management and physical therapy.

Table 24.3 Cranial nerves at risk for post-surgery dysfunction

1. Spinal accessory nerve
2. Phrenic nerve
3. Hypoglossal nerve
4. Lingual nerve
5. Vagus nerve
Recurrent laryngeal N.
Superior laryngeal N.
6. Sympathetic trunk
7. Marginal mandibular branch of facial nerve

24.3 Neurologic Dysfunction

24.3.1 Spinal Accessory Nerve

There are several nerves at risk for iatrogenic injury during extirpative surgery in the head and neck due to their anatomic proximity to the surgical field, especially when the surgery involves a nodal dissection (Table 24.3). Nodal metastasis has long been considered an ominous sign in head and neck cancer, and radical resection of the cervical lymph nodes, with adjacent muscles, vessels and nerves was advocated. This was based upon the same principles applied in breast cancer surgery, and it was considered the primary method of managing this disease process. This type of radical surgery was accompanied by serious post-operative functional and esthetic complications.

Shoulder pain and spinal accessory nerve dysfunction are reasons to that have led surgeons to consider less aggressive surgical techniques to manage cervical nodal metastasis in the head and neck cancer patient. Nerve preservation, is not synonymous with nerve function preservation, and "shoulder syndrome" can develop even when the spinal accessory nerve is not sacrificed. Pain, muscle weakness, shoulder girdle deformity and inability to abduct the upper extremity above 90° are the results of denervation of the trapezius muscle. Transection of the eleventh cranial nerve during radical surgery, or excessive manipulation during less radical procedures, as well as severing the anastomosis with the cervical plexus, may all result in this complication (Fig. 24.11).

Some debate exists in the literature regarding the actual incidence of developing shoulder syndrome even after preserving the spinal accessory nerve [71, 72]. All studies have clearly demonstrated that when the nerve trunk and its anastomosis with the cervical plexus are preserved, patients have better post-operative function and significantly less pain and deformity. Careful dissection around the vicinity of the nerve, limited use of electrocautery, and early identification based on known anatomical landmarks, may help to limit surgically-induced neural trauma.

Direct primary anastomosis of the iatrogenically severed nerve is possible, and has been described in the literature, however, there are no available techniques to restore the esthetic component of "shoulder syndrome," but aggressive immediate physical therapy can improve functional outcomes [1, 2, 53].

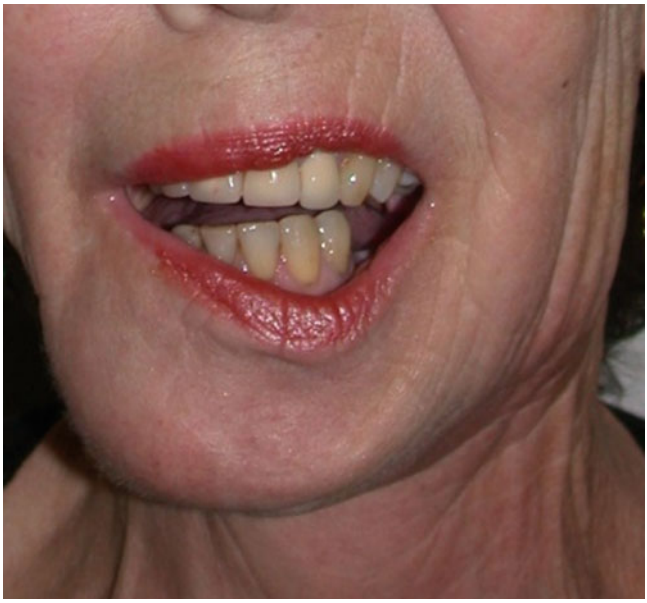

Fig. 24.11 Dysfunction of right marginal mandibular nerve evident upon animation

24.3.2 Phrenic Nerve

Another neurologic complication that may be encountered during neck dissection is injury to the phrenic nerve. This causes paralysis to the ipsilateral diaphragm since the phrenic nerve is the only motor innervation to this muscle.

The diaphragm is responsible for 70% of the respiratory movement and long term pulmonary complications can originate from this type of injury.

An attempt to limit the surgical dissection to a layer superficial to the pre-vertebral fascia, with identification of the nerve, may assist surgeons in preventing this complication [1, 2, 53, 73].

24.3.3 Hypoglossal and Lingual Nerves

The hypoglossal nerve (C.N. XII) provides motor innervation to the ipsilateral tongue, and the lingual nerve (C.N. V3) provides sensation and gustatory innervation, via the chorda tympani branch of the facial nerve (C.N. VII), to the anterior two-thirds of the ipsilateral tongue. Both nerves may be injured iatrogenically during neck dissection, and excision of the tongue and floor of mouth may further endanger the lingual nerve. Unless there is gross neural invasion by

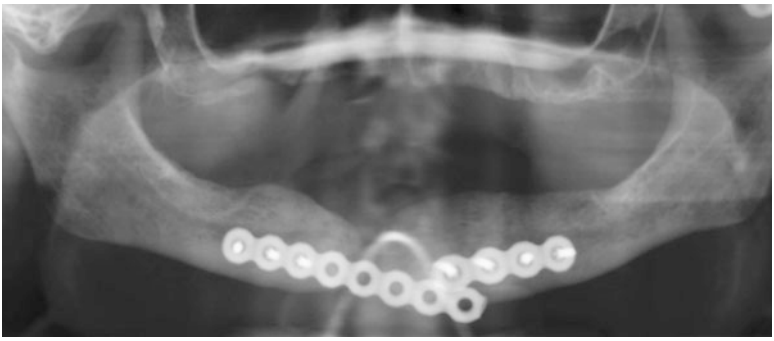

Fig. 24.12 Fractured displaced plate anterior mandible

the cancer, or the path of the nerve runs directly through the tumor, both nerves are usually preserved. Hypoglossal nerve dysfunction can present with subclinical symptoms with deviation of the tongue to the ipsilateral side of injury, accidental tongue biting, and dysarthria (Fig. 24.12). Patients may also experience an exaggeration of their difficulties with mastication and deglutition that are already present following surgery. In cases of bilateral hypoglossal nerve injury, upper airway obstruction can occur when the patient is placed in a supine position. Additionally, atrophy of the muscles of the tongue can occur and add to the functional difficulties experienced by these patients.

Ipsilateral loss of sensation to the tongue from lingual nerve injury can further impact on the difficulties with mastication, speech, swallowing and injury to the tongue during speech and mastication.

These injuries can occur from traction or dissection around the lingual nerve during surgery, and may not always be recognized until later in the post-operative course. A compromised ability to taste foods due to chorda tympani nerve injury may also contribute to decreased food intake and malnutrition. Rehabilitation for speech and swallowing, using physical therapy, is usually beneficial for these patients [53, 73].

24.3.4 Vagus, Recurrent Laryngeal and Superior Laryngeal Nerves

Direct or indirect injury to the vagus nerve (C.N. X) or its branches, specifically the recurrent and superior laryngeal nerves, can occur during dissection around the carotid sheath. This is mostly due to the traction on the main trunk of the nerve, or lack of identification of the nerve during neck dissection, or placement of hemostatic clips to control hemorrhage during surgery. Unilateral true vocal cord paralysis, in the median or paramedian position, is the result of injury to the recurrent laryngeal nerve, and is generally well tolerated due to compensation from the intact contralateral vocal cord. However, mild to moderate hoarseness and diminished cough efforts

are commonly experienced by patients. This problem becomes even more concerning in cases of bilateral injury when upper airway obstruction may result.

Injury to the branches of the superior laryngeal nerve can occur during dissection around the superior thyroid branch of the external carotid artery. This may result in minor swallowing difficulties due to decreased sensation at the laryngeal inlet, or decreased tensor capability of the true vocal cord. Early fatigability and decreased ability to phonate high pitched sounds may seriously affect professional vocalists or public speakers.

Direct laryngoscopy alone, or in combination with motor speech evaluation, and a high index of suspicion, can all assist in the accurate diagnosis of these neurologic injuries. Prevention remains the best management, and patients who depend on their voice professionally, require a detailed consultation and evaluation before and after surgery [53, 73].

24.3.5 Sympathetic Trunk

Disruption of the sympathetic trunk nerve fibers may cause ipsilateral Horner's syndrome. This is usually due to a surgical dissection that extends too far medially behind the carotid sheath. Horner's syndrome involves blepharoptosis due to disruption of the innervation to Mueller's muscle, miosis or pupillary constriction, anhidrosis with lack of perspiration of the forehead skin, apparent enophthalmos, and vascular dilation ipsilateral to the injury. Although the physical findings are pathognomonic for the diagnosis of Horner's syndrome, the clinical presentation can be occult and often variable. In addition, since Horner's syndrome findings may be due to variety of other factors, such as metastasis or vascular injuries, early recognition is of high importance [1, 53, 74].

24.3.6 Marginal Mandibular Branch of the Facial Nerve

The marginal mandibular branch of the facial nerve (C.N. VII) is at risk during incision and elevation of the flaps for standard neck dissections, and access to the oral cavity for composite resections. The nerve runs at the undersurface of the platysma muscle and is superficial to the facial vein at the submandibular gland region. Dingman and Grabb [75] have described the anatomic location of this nerve, with a position superior to the inferior border of the mandible in 81% of cadavers proximal to the facial vessels, and in 100% of specimens distal to the facial vessels [75].

On occasion, it may be more hazardous to dissect and mobilize the nerve so that the facial vein can be used to retract it away from the surgical field. Nodal dissection around the facial vessel, however, is not compromised with this surgical maneuver.

Injury to this nerve causes alteration of the mobility of the corner of the mouth due to disruption of the innervation to the orbicularis oris and depressor angulae oris muscles. In addition to the functional disturbance, transduction of this branch has

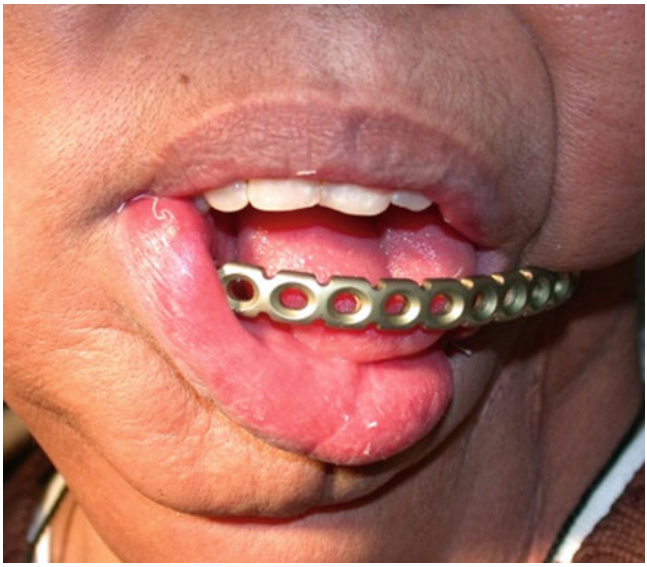

Fig. 24.13 Exposed reconstruction plate due to contraction and scarring of the soft tissues

adverse cosmetic consequences. Inability to control the movement of the lower lip can interfere with liquid consumption, and gives the patient the appearance of having sustained an injury similar to a cerebrovascular accident (Fig. 24.13).

Careful planning of the incisions, taking into consideration the route of the nerve and identification early during flap elevation, is the best way of preventing inadvertent iatrogenic injury to this branch of the facial nerve. Some functionality is normally restored if the neurologic injury is due to traction and not severance of the nerve, but it may take several months for spontaneous neurosensory recovery [1, 2, 53].

24.4 Complications Associated with Reconstruction and Donor Site Morbidity

24.4.1 Hardware Failure

Mandibular resections, or osteotomies, of the mandible used for access purposes require utilization of plates and screws to span continuity defects, stabilize bone segments, or secure bone flaps. The complex bony anatomy and muscle attachments require careful planning for hardware placement. Failure to adhere to basic reconstruction principles, fatigue of the metal due to over-manipulation during contouring and adaptation, extensive defects and unbalanced masticatory force distribution may all lead to hardware failure. Usual problems with hardware include fracture of the reconstruction plates, or

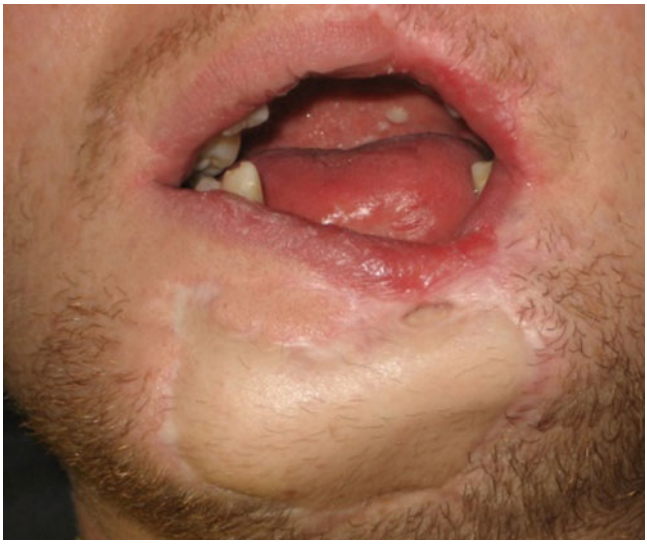

Fig. 24.14 Radial forearm free flap, severe cosmetic defect and lip incompetence

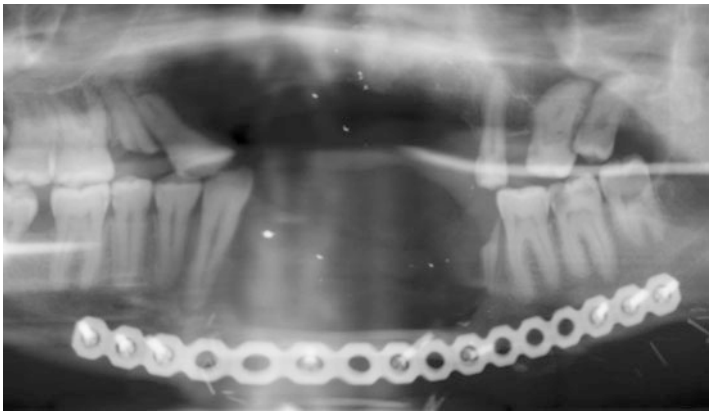

Fig. 24.15 Radial forearm composite free flap in the anterior mandible with inadequate bone height for prosthetic rehabilitation

loosening of the screws with mobility of the mandibular segments (Fig. 24.14). The plates may become exposed through the overlying soft tissues and secondarily infected. This leads to drainage further damage of the adjacent tissues and chronic fistulas.

Hardware exposure may occur even without fracture or mobility if the overlying tissue is of inadequate thickness due to the resection, or scarring due to the effects of radiation (Fig. 24.15). Careful incision planning, adequate soft tissue coverage of plates used, careful consideration of the defect size, and adherence to reconstruction

principles is critical in order to avoid plate exposure. Serious consideration should be given toward complete and appropriate coverage of any hardware used for reconstruction with local, regional or free flaps.

In the cases of fractured, or loose and infected plates and screws with cutaneous fistulas, removal of the existing hardware is usually required. Early intervention is preferred, but the majority of the patients requiring bone resection receive adjuvant radiation therapy. Radiation therapy causes severe scarring of the soft tissues and compromises healing ability. Preoperative preparation with hyperbaric oxygen treatments may be indicated to improve the healing abilities of the soft tissue envelope prior to removal and replacement of hardware [1, 76, 77].

24.4.2 Prosthetic Rehabilitation Considerations

The ultimate goal once disease is controlled and the patient is cancer-free is appropriate prosthetic and functional rehabilitation. Reestablishment of a functional maxillomandibular complex that provides an adequate dentition for mastication, adequate underling bony support for the facial features, and adequate soft tissue for restoration of speech and swallowing represent the desired endpoint, and there are many potential options for reconstruction (Table 24.4). Local tissue re-arrangement and local and regional flaps do not always provide restoration of function, but can serve to obturate the surgical defects. It is difficult to provide a patient with a functional denture prosthesis using a reconstruction plate as the sole underlying support. This scenario frequently leads to chronic plate exposure with inflammation, and possibly the need for plate removal with or without replacement. With the wide use of composite free flaps, surgeons can provide adequate soft tissue bulk and bone support to re-establish continuity, function and potentially provide sufficient bone for osseointegration of dental implants to restore masticatory function [59–63, 75]. Great debate regarding which osseous flap is best for implant placement exist in the literature and various techniques are been proposed to provide the most ideal flap for this purpose [78, 79]. Unfortunately, not all patients are candidates for free tissue transfer and oral rehabilitation is not always considered during all phases of the resection and reconstruction. Composite bone flaps may be used, but placement may not be appropriate for dental implant placement; or, implants may be placed into the bone, but restoration may not be achievable (Fig. 24.16). Several factors may contribute to this prosthetic problem. Since this is a multidisciplinary issue, it is not always feasible to convene all members of the treatment team to discuss the treatment plan of the oral cancer patient prior to resection, so the plans for reconstruction may be created post-operatively and may not be ideal. Also, the extent of the resection may not allow ideal rehabilitation. Several post-surgical and radiation associated complications may prohibit execution of the ideal restorative plan. Finally, patients' compliance and financial issues contribute to delays or actually not achieving the final restorative goal.

Table 24.4 Potential reconstruction options

1. Simple closure
(a) Skin grafts
(b) Allogenic material
(c) Primary closure
(d) Healing by secondary intention
(e) Prosthetic devises
2. Local flaps
(a) Tongue flaps
(b) Buccal mucosa advancement flap
(c) Buccal fat pad
(d) Palatal flap
3. Regional flaps
(a) Temporalis myocuteneous flap
(b) Deltopectoral muscle flap
(c) Latissimus muscle flap
(d) Nasolabial flap
4. Free flaps
(a) Soft tissue free flaps
(i) Radial forearm free flap
(ii) Anterolateral thigh free flap
(iii) Rectus Abdominus free flap
(iv) Latissimus free flap
(b) Hard tissue free flaps
(i) Fibula free flap (osseous or composite)
(ii) Deep circumflex Iliac artery free flap
(iii) Scapula free flap
(iv) Radial composite free flap

24.4.3 Aesthetic Considerations and Functional Limitations at Donor Site

Local and regional flaps, and free tissue transfer, employed for reconstruction of surgical defects inherently create an additional defect at the donor site. Even with the most carefully planned incisions, these defects may lead to unesthetic scars, contraction, and tissue deficits at the donor site.

The tongue, buccal mucosa, and buccal fat pad are local tissues frequently used to address small defects in the oral cavity. Usual limitations from use of these sites are functional due to scarring and postsurgical tissue contraction.

For larger defects, regional tissue such as the delto-pectoral, temporalis and latissimus myocutaneous flaps are used. These tissues have served well over the years, but the defect at the donor site remains a testament to the procedure performed [80–82]. Composite tissue transfer from distant sites such as the fibula or the radius and the iliac crest are considered the gold standard for reconstruction of defects of

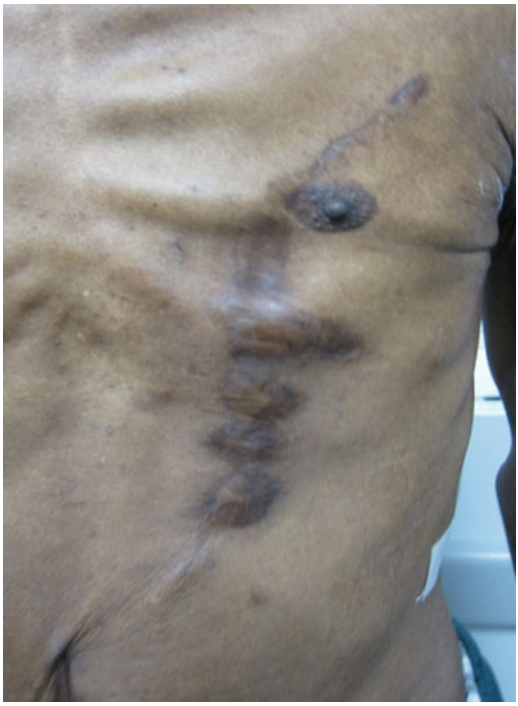

Fig. 24.16 Donor site scarring post pectoralis major myocutaneous flap harvest

the oral cavity. Excellent functional outcomes and very acceptable esthetic results at the recipient sites can be achieved with the potential for future dental rehabilitation. However, the donor sites are usually plagued by long scars and occasionally tissue mismatching and other bulk-related defects. Functional limitations such as trismus, limitation in range of motion, and gait disturbances are some of the undesired long term sequelae at the donor sites. Aggressive physical therapy is required early and employed until near normal function is regained, while scar revisions may be employed to address the esthetic considerations.

24.5 Long Term Quality of Life and Psychological Considerations

Quality of life issues for the oral cancer patient are addressed in detail in other chapters of this text, but for completeness, the influence of surgical intervention on quality of life is briefly discussed here. Quality of life is a critical outcome measure in head and neck cancer management, mainly due to the inability to improve survival, especially in cases of advanced disease. Unlike other malignancies, oral cancer treatment has not drastically changed over the last 30 years. Except for modifications in the types and extent of neck dissections, surgery remains, for the most part, the treatment

modality most commonly offered, with addition of radiation and chemotherapy when indicated. The focus on patient care has shifted towards preservation of form and function with the careful selection of appropriate reconstruction techniques [37, 83].

Chronic pain, difficulty with chewing, swallowing, and speech influences function and adversely impacts on the quality of life. In general, studies have demonstrated that improved function post-resection is achieved with utilization of free tissue composite flaps that correct bone continuity defects and can support dental implants as well as a future prosthesis. Furthermore, free tissue transfer for reconstruction of tongue defects, and avoidance of primary closure typically improves tongue mobility. These reconstruction options improve patients' ability to chew and swallow their food appropriately, and to articulate and speak fluently. Both patient subjective perception of improved quality of life, and objectively measured improvement, has been demonstrated in multiple studies in the head and neck cancer literature [38, 39, 83, 84].

Chronic pain issues from the temporomandibular joint and muscles of mastication are unique to the oral cancer patient. Together with some of the potential neurological complications mentioned earlier, as well as functional limitations, these factors impact on activities of daily living, and contribute to an overall poor quality of life. Finally, facial disfigurement, scarring, speech impairment, inability to control secretions, loss of taste, the need for removable prosthetic appliances, and difficulties with mastication have serious psychological impact on the oral cancer survivor. In conclusion, the oncology surgical principles that ensure adequate tumor resection in order to prevent recurrence or limit metastasis, should be combined with the principles of reconstruction that will provide the best long term form and functional results.

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Chapter 25
Psychological Issues in Head and Neck Cancer

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Contents

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Abstract Head and neck cancer (HNC) brings a host of issues of importance to patients, families, and treatment providers. Beginning at the time of initial diagnosis, individuals often struggle with fear and guilt due to concerns that they bear some responsibility for the diagnosis. Once treatment is underway, patients frequently must cope with disfiguring consequences, with changes in communication, eating, and body image. Over time, expected adjustment issues can develop into depression and other serious psychological problems. Even several years after treatment is over, patients may need to deal with ongoing pain, communication, and substance use problems, as well as anxieties about disease recurrence. Individuals may report some psychological benefit as a result of the diagnosis and treatment of HNC, even though some ultimately face the end of their lives. Suggestions as to how providers can help patients manage these issues are provided, as well as resources for patients.

Keywords Psychological issues • Adjustment • Depression • Anxiety • Pain • Substance Use

25.1 Initial Diagnosis Phase

In spite of the medical progress that has been made in the treatment of cancer in recent years, a diagnosis of cancer frightens most people. Patients have thoughts of suffering horrible pain, disability, and have fears of death. Even for individuals who are treated successfully, the treatment will likely impact their ability to work and their financial situation, and it may result in a future inability to return to work. Their social/familial roles will change, and they may be unable to fulfill obligations

to their family and friends. People want to maintain independence; many will be unable to be independent during treatment, and some will lose their independence for the rest of their lives. Finally, a diagnosis of cancer may significantly shorten one's life. Each of these issues is an expected concern when an individual receives a diagnosis of any type of cancer. Head and neck cancer (HNC) brings all these and also additional challenges.

25.1.1 Psychosocial Risk Factors

HNC has traditionally been diagnosed more frequently in men over age 50 [1, 2] with a history of heavy cigarette and alcohol use [3]. HNC is strongly linked to tobacco use (85%), and individuals who use both tobacco and alcohol are at greatest risk of developing HNC [2].

More recently, a new subgroup of individuals who develop HNC has been identified. These are people who tend to be younger (40s–50s), both men and women, and they do not necessarily have the history of heavy alcohol and cigarette use as the traditional group [4]. In this group, alcohol and smoking do play a role, but the main risk factor is oral HPV infection [1, 5]. A recent study reported a 225% increase in the number of oral cavity cancers related to HPV infection [6]. Individuals with HNC that is associated with human papillomavirus (HPV) tend to have better outcomes than the older male group, as they respond more favorably to treatment [4, 6–8].

Both groups may have to deal with some degree of social stigma – the traditional group because they may be seen as substance abusers who brought this on themselves. The newer subgroup, those with HPV infection, may be seen as substance abusers even though they may not have that history. They may also be viewed as promiscuous, as some research suggests that individuals in this group have had a higher number of sex partners [9], although HPV infection can occur without that sexual history (e.g., from mouth to mouth contact [10]).

25.1.2 Delay in Diagnosis

Delay in seeking medical treatment is a significant problem, resulting in approximately half of patients with HNC being diagnosed with advanced disease when they finally are diagnosed [11]. Studies have reported that 25–50% of patients wait longer than 3 months after the development of initial symptoms to seek treatment [12-14]. Treatment of advanced disease is associated with poorer outcomes, including high morbidity and higher treatment costs [15]. There is a substantial body of literature on delays in seeking treatment that addresses both patient and system factors. System factors include lack of access to medical professionals, and waiting for appointments and test results. While these may play a role, in most cases the patient factors are more responsible for delays in diagnosis [16].

Twenty years ago, research demonstrated that many alcohol and drug abusers did not seek treatment for their abuse because they wanted to handle it on their own and felt that treatment was stigmatizing [17]. This logic has been used to explain the delay in seeking treatment for HNC, even though seeking treatment for a medical problem is likely somewhat different than seeking treatment for alcohol/drug abuse. Recently, while there are some conflicting reports [18], most studies do *not* find that drinking alcohol is associated with delay in seeking treatment for HNC [11, 19].

Much of the delay in seeking treatment appears to be due to a universal cognitive and emotional process that many individuals experience, starting when they first notice a symptom, described by Scott and colleagues [12]. Specifically, most individuals do not view their initial symptom (such as sore throat or tongue, lump, or swelling) as a serious symptom that warrants seeking treatment; rather they interpret their symptom as a problem other than cancer [12, 16]. This interpretation of the initial symptom as non-serious seems to occur across cultures, with evidence that individuals tend to self-treat the symptom initially, and wait to see if that is successful [12, 20, 21]. They do not generally attribute the initial symptoms to cancer, so they do not react with distress that might motivate a consultation with a medical professional. At some point it becomes clear to the individual that the symptom is not improving – this elicits a reappraisal process in which they begin to think that the symptom might be indicative of a more serious problem [12]. At this point they are more likely to seek treatment, although valuable time in beginning treatment has already been lost. Data on delay for several different types of cancers support this process of initial misattribution of symptoms to non-cancer causes, then a trial of self-medication prior to seeking medical treatment [22].

Factors such as age, gender, and marital status are not predictive of delay in seeking treatment [14]. Deprivation and socioeconomic status have been cited as reasons for patient delay, although the evidence has been mixed [14, 23]. Delay has also been associated with less perceived control over one's health and lower levels of competence to effect change in one's health [24] as well as a lack of social support seeking [13].

25.1.3 Emotional Adjustment to Diagnosis

The diagnosis of HNC brings other challenges in addition to those associated with a diagnosis of cancer generally, and can be a time of significant distress and anxiety. At diagnosis, HNC is less familiar than many other cancers (such as lung or breast cancer), as it occurs less frequently than many other cancers [7]. As a result, most people know little about the treatment and implications of a diagnosis of one of these cancers. Several studies have documented poor awareness of symptoms and risk factors for HNC in the general public [20, 25] as well as in those who are at-risk for HNC [26].

While distress can present at any stage of the cancer process, monitoring for distress and vulnerability to psychopathology should begin as early as possible after

diagnosis and can aid in the identification of patients that may be at risk for more significant psychopathology. One way for providers to assess patient distress is through the use of the Distress Thermometer, a brief visual analogue measure that allows patients to rate their level of subjective distress on a scale of 0–10 [27]. The Distress Thermometer has been demonstrated to adequately identify distress that may lead to psychological difficulty in a variety of cancer patients including HNC [28]. The distress thermometer is often supplemented with specifiers for social, psychological, and physical problems to further elucidate the sources of the patient's distress. Referrals for medical, social work, or psychological follow-up can then be provided to the patient based upon their ratings of the severity and causes of their distress. The distress thermometer is recommended by the National Comprehensive Cancer Network (NCCN) [2] as a screening tool to be administered at multiple time points throughout the process of cancer care [29]. Additional information about the distress thermometer and screening guidelines for distress in patients with cancer can be found at www.nccn.org. The Patient Health Questionnaire-2 (PHQ-2) [30] is another brief, well validated, and reliable measure that can be easily implemented to screen for psychological distress in patients with cancer [31]. Patients rate their experience of two common symptoms of depression, anhedonia and hopelessness, on this two item measure. Scores on the PHQ-2 provide indication if further assessment is needed.

25.1.4 Information and Educational Needs

As treatment typically begins quickly, individuals often need to rapidly process a large amount of information about their new diagnosis and its implications. Patients may need to consider treatment options that include surgery, radiation, chemotherapy, or a combination of these treatments. Especially relevant for HNC patients is information on the potentially significant negative outcomes of treatment (e.g., disfigurement, pain, difficulty speaking) that may occur even if the treatment is successful in terms of disease management. Individuals have differing needs for information about the disease, potential treatments, and possible outcomes. In a qualitative study of information and expectations, patients complained about receiving "too little" or "too much" information [32]. These information needs are likely reflective of coping styles that dictate the individual's preference for information and their reactions to information that is provided to them [33].

Some basic level of information is required for patients to make an informed decision about treatment, but some patients are not provided with enough information about what to expect during and after treatment. For example, Zeine and Larson [34] reported that 21% of patients who had laryngectomies were not aware that they would have no voice after surgery, and 94% of the patients felt this topic was an important one to address. Further, 61% felt they were not given enough information on physiological changes, and 54% felt they needed more information on social issues that they might need to deal with after surgery. While most of the patients

reported that they were given opportunities to ask questions of medical professionals prior to the surgery, 54% of them reported that they did not know what questions to ask. Llewelyn and colleagues [32] suggested providing both verbal and written information on a "timely and individual basis" in an attempt to meet the information needs of HNC patients.

Patients with low literacy may face additional challenges in understanding and processing information about their cancer and treatment options, risks, and benefits. It is estimated that as many as 90 million Americans, or 25%, have difficulty with health literacy, [35, 36]. Low literacy is associated with a number of negative outcomes in patients with medical problems including decreased adherence to treatment regimens and increased hospitalizations [37]. Patients with cancers that impact the ability to communicate may be especially vulnerable if they also have low literacy [35].

In English, the Rapid Estimate of Adult Literacy (REALM) [38, 39] and short-form (REALM-sf) [40] are well-validated measures of health literacy that provide estimates of reading ability. The Short Assessment of Health Literacy for Spanish Adults (SAHLSA-50) [41] is a reliable and valid measure of reading ability for Spanish Speaking adults. Brief screening of literacy can reveal potential problems in understanding that can then be avoided by additional education.

25.1.5 Maladaptive Coping Reactions

Adaptation to illness is often shaped by the patient's beliefs about their illness and the coping strategies they employ (e.g., avoidant, approach, or emotion-focused) [42, 43]. People have a basic desire to understand negative life events, such as the diagnosis of cancer. Thus, people try to look for meaning and assign causation to these events (e.g., "what does it mean?", "why did it happen?", "why me?" "what will the future hold?") [44]. Similarly, people have beliefs about how management of an illness is best approached. When individuals feel they are directly to blame for the cancer through past actions or life choices, heightened distress or feelings of guilt may occur. Guilt may play an exaggerated role for HNC patients due to the relationship between HNC and alcohol use, tobacco use, and sexual transmission of HPV. Alcohol users may feel that they themselves have caused this cancer, that this cancer could have been avoided if they had been able to stop drinking or that the cancer serves as a punishment for alcohol abuse. As HNC becomes more prevalent among younger women and men due to the connection with HPV, these individuals may have guilt about sexual interactions that could have led to cancer. The stigma associated with oral sexual contact may heighten feelings of guilt in this subset of the population [45].

Feelings of guilt and shame may lead to avoidant coping, causing patients to delay seeking treatment, to hide their illness from friends, family, and employers, and to hide continued substance use from medical professionals [13]. If excessive guilt threatens feelings of self-worth, patients may be more hesitant to seek social support, potentially leading to strained relationships, social isolation, and depres-

sion. However, some research asserts that feelings of guilt and self-blame that are moderated by beliefs of control can facilitate adjustment [46]. For example, self-blame associated with specific behaviors might enhance the perception of control because the behavior can be changed. On the other hand, self-blame that is attributed to enduring characteristics of one's personality can result in greater distress and helplessness [44, 47]. In a study of HNC patients, those who believed their cancer was caused by their past smoking and who also had higher perceived control that the long-term course of their cancer was dependent on their own behavior, tended to smoke less [48]. In contrast, self-blame without self-control beliefs was associated with higher rates of smoking, even after controlling for depression [48]. In the same study, self-blame and control beliefs did not affect continued alcohol use, possibly because the link between alcohol use and cancer is not as well-known among the general public [48]. In other words, patients might not have realized that decreasing their alcohol use could improve their outcomes.

Others can also make these causal attributions contributing to blame and stigma in the face of illness. When people have engaged in behaviors believed to have contributed to their illness, increased negative attitudes, harsh judgment, reduced sympathy, and greater stigma are directed toward them, possibly resulting in a withdrawal of social support [49]. Perceiving the cultural stigma, some patients feel unfairly blamed, especially if they did not engage in the behavior or if they stopped (e.g., smoking) many years prior [50]. In this way, causal attributions by others can contribute to feelings of shame, embarrassment, and anger. When there is continued substance use among HNC patients, or when significant others disapprove of how a patient manages their disease, relationship strain can result. Guilt may also emerge among significant others who engaged in the perceived causal behavior with the patient or for those who continue to smoke and drink following the patient's diagnosis [51].

25.2 Active Treatment Phase

Treatment for HNC may involve surgery, radiation, chemotherapy or a combination of these modalities. One frequent outcome of traditional surgical and radiation treatments for HNC, especially due to organ removal through surgery, is that individuals are unable to speak, eat, and swallow normally. Chemotherapy is now playing a larger role in the treatment of HNC, in an effort to preserve the organs necessary for proper speech and eating [52]. Each of these treatments, however, brings with it toxicities that patients need to endure during, and often after active treatment.

Chemotherapy and radiation therapy (used separately or in combination) are associated with many significant side-effects, including oral mucositis and pain, nausea/diarrhea, decreased appetite, dysphagia (problems swallowing), changes in taste, and skin reactions [53–58]. These ultimately can lead to weight loss and malnutrition [59]. Not all patients experience each of these, and the intensity of the reactions varies depending upon the specific chemotherapy and/or radiation dosage

given. At best, for many patients these toxicities are uncomfortable. At their worst, they are responsible for dramatic decreases in life quality.

One study explored HNC patient hopes for outcomes prior to initiating their treatment [60]. Patients were asked to rate a list of 12 potential treatment effects. Seventy-five percent of the patients rated being cured as their top priority, and 93% rated being cured in the top three of their priorities. Living as long as possible, having no pain, having normal energy, and returning to regular activities quickly, were also chosen by a large number as one of the top three priorities. Other possible priorities (e.g., being able to swallow, keeping appearance unchanged), were rated much less frequently as top priorities.

Other researchers have asked patients to rate their priorities 6 months after treatment [8]. Patients listed their priorities as (1) being cured of cancer, (2) living as long as possible, (3) having no pain, and (4) being able to swallow all foods. Clearly the most important priority for patients is being cured, and individuals are willing to undergo a variety of treatments that may have negative consequences, in an effort to achieve cure. These authors [8] also reported that 87% of the HNC patients said that undergoing their treatment "was the right decision," indicating little regret, in spite of the ongoing problems that many had to manage.

25.2.1 Eating and Breathing Problems

A major challenge of HNC treatment is the effect on the basic functions of eating and breathing. Eating problems resulting from pain in the mouth and throat, difficulty swallowing (dysphagia), difficulty chewing, changes in or reduction in saliva (xerostomia), dry mouth, mouth sores (mucositis), changes to or loss of taste (dysgeusia), and loss of appetite, are common among HNC patients and may persist over time. Eating problems and weight loss have been reported in 44% of patients prior to starting treatment, effect up to 100% of patients during treatment [61], and continue to be a significant problem for the majority of patients for the first year after treatment [61, 62]. Among HNC patients, the highest rated problem 1 year after treatment was dry mouth, and dry mouth continued to be reported as a problem up to 5 years after diagnosis [63]. In a descriptive study, HNC patients described dry mouth as contributing to loss of appetite and taste, as well as difficulty chewing and swallowing [61], and more than half of HNC patients have problems swallowing up to 5 years later [64]. Similar long-term difficulties with swallowing were reported for HNC patients following laryngectomy or pharyngolaryngectomy [65].

Eating problems resulting from HNC treatments have been found to negatively impact quality of life. Van den Berg and colleagues [66] reported that malnutrition (greater than or equal to 10% unintended weight loss) within the first 6 months of diagnosis was related to significantly lower global quality of life during and after treatment. Dysphagia is associated with poorer quality of life at diagnosis, and through the first year after treatment [67]. Oral cavity complaints (i.e., teeth problems, difficulty opening mouth, and swallowing difficulty) have also been associated with

decreased survival because these domains are related to overall oral health and nutritional status [68]. Again highlighting the importance of nutrition, Capuano and colleagues reported that greater than 20% loss of pre-diagnosis weight was significantly correlated with treatment interruptions, infections, readmission, mortality, and survival [69].

There are significant psychological, functional, and social consequences of eating problems and weight loss. During treatment for cancer, eating problems become intimately tied to the experience of having cancer [70]. Thus, eating difficulty and weight loss are continual reminders of the disease and of the threat to one's life. The emotional distress caused by the cancer diagnosis can also impact appetite as decreased appetite is often a consequence of depressed mood. Further, poor appetite and intake lead to decreased nutritional status, which contributes to fatigue and low energy. Conditioned nausea from chemotherapy can also impact appetite.

Problems eating can impact quality of life and social functioning as HNC patients can become more socially withdrawn and self-conscious due to issues with oral hygiene (e.g., bad breath, drooling), atypical eating behaviors, difficulty eating with family or in public, the presence of nasogastric tubes, appearance changes and weight loss, and feelings of shame and disgust surrounding these issues [70–72]. Eating problems can threaten the ability to experience "togetherness" through shared meals [73], and problems eating out socially 2 years after treatment were also associated with decreased quality of life [74]. Further, because eating and cooking are valued activities for many, changes in this area may result in decreased pleasure and comfort, as people often turn to special foods to cope during times of stress [61, 73]. In this way, problems with eating can compromise morale and challenge coping resources.

Larsson and colleagues found that as mucositis, pain, xerostomia, loss of appetite, and changes in taste mounted, the drive and desire to eat was reduced. Diminishing will and desire to eat made it more difficult to engage in the work necessary to chew and swallow, which only further exacerbated eating and nutrition problems [73]. In addition, many patients require enteral or parenteral feeding, and must adjust to the presence of the tubes on their body and learn how to care for the equipment. During treatment, patients anticipate the return of their ability to eat normally, to taste foods, and to experience the pleasure of eating once again [70].

Psychological strategies may be employed to help address eating problems. These include relaxation, breathing, and imagery techniques to help manage conditioned nausea, anxiety, and pain that may occur when eating. Nutritional goal-setting, along with practical advice (e.g., eat small amounts of food throughout the day) can aid patients in meeting these goals. Cognitive restructuring techniques derived from cognitive behavioral therapy can help patients reframe the act of eating as something that is a medically necessary activity for nutrition, not necessarily an activity for enjoyment or taste. Similarly, helping patients focus on surviving side effects on a daily basis may help them better manage these problems and increase their sense of control [73]. If the loss of social eating is something that is very distressing to a patient, they might be encouraged to brainstorm ideas for how they might compensate for that loss in other ways (e.g., engage in other shared activities that do not involve

eating). Alternately, they can be encouraged to slowly engage in more demanding social eating activities so that they become increasingly acclimated to and skilled at eating in a modified way in front of others (e.g., eating small snacks at home in the presence of supportive others, going out for coffee).

In addition to eating problems, difficulty or discomfort when breathing (dyspnea) is also reported among HNC patients [75]. In one study, more than half of the HNC patients surveyed indicated that they experienced shortness of breath, a rate second only to that of lung cancer patients [76]. Difficulty breathing is frequently one of the symptoms leading to diagnosis (e.g., cancer of nasopharynx) and can be exacerbated by inflammation and pain of the mouth and throat as side effects of treatment; problems breathing can also result from surgical procedures (e.g., tracheotomies, neck dissections, resections of pharynx) [61, 71]. A history of smoking, asthma, or COPD can increase the likelihood of breathing problems [76]. For some, it may become more difficult to breathe lying down, which can disturb sleep. From a psychological perspective, difficulty breathing often causes anxiety [77]. Patients have reported that difficulty breathing during radiation treatments intensified feelings of claustrophobia and helplessness and caused severe anxiety. Some patients may become hypervigilant and overly focused on suffocation [71].

25.2.2 Communication Difficulties

Communication problems, including difficulties with speech, voice, and facial expression, can present significant functional and psychosocial challenges. Alterations in speech can vary from vocal changes (e.g., hoarseness) to voicelessness [78]. Clarity of speech can be reduced due to side effects of treatment such as dry mouth, swelling, and pain [73]. Such changes can be temporary (e.g., tracheostomy in the post-operative period), or permanent (e.g., total laryngectomy or glossectomy), and some patients may need to use assistive devices (e.g., electrolarynx) or alternate speaking techniques (e.g., tracheoesophageal speech) in order to communicate [79].

Speech and communication serve important functions and are essential components of self identity and personality; these are typically ranked highly as important quality of life domains [78]. Difficulty being understood can be associated with affective distress, negative self-image, and disturbed interpersonal relationships [78, 80, 81]. Research has demonstrated that talking about traumatic events in a way that facilitates emotional expression and reinterpretation decreases distress [82, 83]. However, HNC patients may lose their ability to express themselves and to discuss new coping skills at a critical time [84].

Head and neck patients have relayed stories of fear and frustration when attempting to communicate with care providers and family in the immediate post-operative period [78]. In particular, HNC patients have reported difficulty communicating their physical needs (e.g., suctioning, difficulty breathing, pain, toileting, and feeding) and difficulty communicating their questions postoperatively [85]. It follows that

negative emotional responses can be magnified when combined with the helplessness associated with an inability to communicate. For example, Menzel [86] described a strong link between the inability to speak among intubated patients and emotional responses of anger, worry, and fear. As noted above [34], 21% of head and neck cancer patients were unaware preoperatively of the inability to speak after surgery and 29% of their spouses were also unaware. Pre-surgical preparation is important to help patients manage their expectations following surgery and maintain a sense of control following loss of speech [79], though realization of the difficulty ahead may also cause distress.

In the ideal situation, patients will explore options for new communication systems prior to surgery, and be prepared with alternate forms of communication (e.g., signs, gestures, writing, assistive devices) for the immediate post-operative period [78, 79]. Communication in the post-operative period is an important aspect of resocialization [87], and new methods of successful communication reflect the individual's integration of post-operative changes into a redefined sense of self. Pre-surgical preparation for communication impairment will have other benefits as well, as patients who have already contemplated and planned for alternate communication systems may have a greater investment in and sense of control over aspects of the rehabilitation process. This is important as engagement in rehabilitation and restoration of speech can depend on factors such as motivation and social support, in addition to medical variables [79].

Problems with speech and communication can also be addressed through speech therapy. Health care providers can also help patients with impaired communication become more comfortable and communicate more effectively by being patient and creative in their own communications with them [84]. For example, use of both verbal and nonverbal messages can improve understanding. Mouthing words, gesturing, and head nods can help facilitate communication with voiceless adults [78]. Putting questions to people in a form that requires a less wordy response (e.g., yes/no questions) [78], summarizing what a patient has said, checking for understanding, and asking for clarification can also improve communication [88]. Accepting reports from family members can also be useful, but it is necessary to ask the patient to agree or disagree with what has been said on his/her behalf [88]. Offering the option to write, developing a system of gestures, and therapeutic journaling can also be helpful in overcoming communication challenges [84]. Newer technologies, such as communication applications on tablets, may also help ease the burden of communication impairment among HNC patients [88].

25.2.3 Changes in Appearance

25.2.3.1 Importance of the Face

The face has special psychological significance and can contribute to self-identity (the basic understanding of who we are), body image (the way we perceive our bodies),

and self-image (the assessment of our social worth) [89–91]. Faces are the image reflected in the mirror [91]; they provide information about mood, personality, ancestry, health, and age [89]. Faces are typically the focal point during conversation and social interaction, and often how a person is distinguished and remembered by others [84].

Visible disfigurement of the face and neck is a salient and potentially traumatic consequence of HNC and can affect self-identity, self-expression, and social interaction. Disfigurement, including changes in facial integrity, contour, skin texture, dentition, facial expressions, and weight loss, can result from the cancer or as sequelae of treatment (i.e., surgical access, ablation, scarring, and changes related to radiotherapy and/or chemotherapy) [90, 92]. While the likelihood and severity of disfigurement have decreased with advancements in surgical procedures and reconstructive techniques [93], disfigurement remains a significant concern among patients [84, 94, 95]. For HNC patients, fears about facial disfigurement and dysfunction after treatment may be as prominent as fears of cancer recurrence. In a study of surgically treated HNC patients, 75% reported concerns or embarrassment about at least one bodily change during treatment [96]. In another study of patients with oral and oropharyngeal squamous cell carcinoma treated by surgery, 24% continued to be bothered by their appearance 5–10 years after surgery [97].

25.2.3.2 Negative Social Experiences

Visible disfigurement of the head and neck can have a significant impact on social functioning. Because there is frequently no option of hiding these physical changes, they are easily recognized by others, increasing the stress for patients who would prefer to keep their medical problems private. Disfigurement can result in lower perceived attractiveness, which can impair confidence and increase feelings of embarrassment or shame during social interactions. Patients with disfigurement frequently report that people stare, make uncomfortable comments, and ask unpleasant questions about their condition [98]. The visibility of facial and neck disfigurement may also elicit blame or unsympathetic reactions from others because of the association of HNC with controllable behaviors such as smoking [49, 50].

Changes in facial appearance can also degrade social interaction through diminished self-expression, as nonverbal communication may be impaired. Difficulties communicating or feeling understood by others may contribute to a sense of isolation which is a common feature of depressive disorders.

25.2.3.3 Patient Reactions

Following surgery, there may be a discrepancy between a patient's memory of their pre-surgical appearance and function, their idealized image, and their perception of their current body image [99]. Patients have reported that treatment has aged them and feel as if they look older or not like the "old me" [100]. The dissonance caused

by a profound discrepancy between preexisting beliefs and the current situation can lead to emotional distress, intrusive thoughts, and avoidance of the discrepant material. People may attempt to avoid social interactions, and may find it difficult to leave the house, resulting in limited activities or social isolation, which decreases quality of life [101, 102]. Issues with visible disfigurement and poor body-image may also make it difficult to fully reintegrate within the social community (i.e., make new friends, find a job) and return to normal levels of functioning.

Stress-appraisal models [103] that are adapted to HNC patients are useful for understanding the range of reactions that patients may experience [87]. Appearance-related changes can be interpreted as a threat, a loss, or a challenge, depending on how the situation is appraised (how bad is it?) and whether the patient believes that they have the coping resources to manage it (can I deal with it?)[87]. Such appraisals impact the coping strategy that is employed. When patients feel overwhelmed and helpless to handle a situation, emotion-focused coping strategies, such as avoidance or disengagement are more common than problem-focused strategies [104]. In the case of HNC, this may manifest as behavioral avoidance (e.g., reluctance to look in the mirror, touch the affected area, engage in self-care behaviors, or interact with others) and/or cognitive avoidance of the thoughts, images, and emotions associated with changes in appearance [105]. Avoidance may also be demonstrated by increases in smoking, drinking, and other forms of behavioral disengagement. Those who avoid may prolong and intensify problems as avoidance prevents cognitive processing and is associated with greater unwanted thought intrusions and distress [83]. That is, if individuals do not reappraise the new situation and adjust their prior beliefs, they might continually be haunted by the changes and might not successfully adjust to their new situation. Avoidance is therefore problematic, because incorporating the physical changes that have occurred into a reformulated and acceptable sense of self is necessary for long-term adjustment [99]. However, not all patients respond with avoidance. Positive adaptation in HNC patients is demonstrated by involvement in self-care, participating in dressing changes, and socialization while still in the hospital. Self-care is also associated with reduced anxiety and social reintegration [87, 99, 106].

25.2.3.4 Managing Changes in Appearance

Pre-operative preparation is important to help patients develop realistic expectations and to begin to prepare psychologically and concretely for changes that will occur [84]. However, in one study, about 25% of HNC patients reported they were not satisfied with the information they received about the amount of potential scarring or disfigurement they should expect after surgery [96]. The patient's perceptions play an important role in their adjustment to facial changes, and there is no clear evidence that the size or degree of disfigurement determines subsequent adjustment [107]. Rather, studies of burn victims show that perceived severity of disfigurement is the main factor determining a person's reaction to the disfigurement [107]. While it is expected that patients with HNC will experience

a range of grief reactions including anger and depression, they may feel reluctant or embarrassed to raise these issues with their doctors [90, 96]. The Body Image Reintegration Behaviors Scale [105] is an assessment instrument that can assist with uncovering significant appearance related issues and directing recommendations for treatment.

It is also useful to help patients prepare for questions that others will ask about their changes in appearance. Medical professionals can help HNC patients prepare by helping them to understand more about the social dynamics of interactions and how the patient might best influence the outcome of these situations [108]. For example, allowing patients to practice how they might respond in situations in which others stare or make comments can empower them with the skills and confidence to better handle these situations. Patients may also be guided to restructure maladaptive thoughts regarding their appearance. For instance, negative expectations about social interactions can change behavior in subtle ways that can increase the likelihood of negative outcomes. Similarly, the attributions that patients make regarding reasons for staring or awkward social interactions can impact self-esteem (e.g., "They are staring because I'm hideous" versus "They are staring because they're curious") [108]. Appraising negative outcomes to an enduring, permanent aspect of the self can be detrimental in that patients might feel helpless to change the situation. Patients can be encouraged to engage in feared activities so that they gradually test expectations, rather than limiting themselves socially or professionally due to fears of others' reactions. Medical professionals should also help patients reevaluate thoughts about the ideal-real body image discrepancy [89], especially when patients seem excessively focused on one aspect of their physical appearance. The goal is to help clients formulate new beliefs in which they incorporate other aspects of personality and functioning into their self-identity for a more complete view of themselves as an entire person.

It is also important to remember that not everyone is ready to deal with problems immediately. Therefore, patients need to be reminded that resources for support and information are available when they are ready to utilize them, including internet and phone resources which may be a useful first step for those less ready to interact socially [109]. If further treatment options are possible, such as prosthetic rehabilitation, further refinement surgery, and camouflage techniques, information about these should also be offered [90].

For those patients struggling with appearance concerns, psychotherapeutic interventions (e.g., groups, social skills training, cognitive behavioral therapy) can be helpful. Participation in groups or social networks may be especially useful to promote camaraderie [89], normalize injury, allow patients opportunities to learn to navigate social situations, and provide opportunities to practice their responses. Helping patients practice skills for socialization is important because behavior rather than disfigurement influences successful outcome in social situations [110]. Research has demonstrated that teaching social interaction skills to patients following facial disfigurement resulted in decreased social avoidance and distress [111]. Another study showed that skills training for patients with appearance changes reduced social anxiety and decreased problems with speech, eating, and self-confidence [112].

25.2.4 Problems with Sexuality and Intimacy

Although the terms are often used interchangeably, sexuality refers to interest in sexual activity, the expression of sexual needs to a partner, and the capacity to have satisfying sexual experiences [113]. Intimacy is a broader term that involves the emotional support, affection, and sense of connection derived from close, personal relationships. Sexual problems in HNC can derive from multiple sources: appearance changes, oral functioning, self-esteem, fatigue, pain, anxiety and depression, and other relationship issues. As crucial components to recovery and quality of life, it is fortunate that awareness and treatment for sexual problems among HNC patients is growing [102]. For many years, avoidance of this issue was common due to the assumption of low importance of sexuality among older populations or those faced with a life threatening illness, as well as discomfort in discussing this topic on the part of both patients and providers [114].

25.2.4.1 Frequency of Sexuality/Intimacy Problems

Low and colleagues [102] surveyed cancer-free HNC patients about their sexual functioning and intimacy, and reported that one-third acknowledged decreased sexual interest and enjoyment and one-fourth of patients endorsed problems with intimacy. In another study of HNC patients, about 85% of patients reported continued interest in sex, but less than half (49%) were satisfied with their current sexual functioning, and a majority cited problems with arousal and orgasm [115]. Patients with HNC have also reported that decreased sexual interest is one of the top three health-related quality of life problems that they faced [75].

For HNC patients, most sexual problems occur early after treatment. Problems in marital and sexual functioning increase from 1-month to 1-year following diagnosis, while physical problems generally decline [62]. In broader cancer populations, sexual problems commonly reported include reduced libido, erectile dysfunction, vaginal dryness, painful intercourse (dyspareunia), and difficulty achieving orgasm [116]. Overall, higher rates of sexual problems occur among younger, female, and unmarried patients [102, 115], and problems with sexuality and intimacy generally have little correlation with medical variables such as cancer site, stage of disease, type of treatment, and time since surgery.

25.2.4.2 Physical Changes

Changes to the mouth and tongue, and oral problems more generally, affect sexuality and intimacy. For example, Wilmoth [117] described a woman who could no longer kiss her husband because part of her jaw bone and tongue were removed and there was interference from a nasogastric tube, eliciting significant disruption and distress. This example underscores the importance of inquiring about intimacy in the larger sense, as well as sexuality specifically. Others have also

described self-consciousness from changes in saliva, drooling, and odors – HNC patients often worry about others' reactions to these changes and fear rejection from their partners [118]. It is important to encourage patients to openly discuss these issues with their partners [118], as this is one way to increase intimacy, self-acceptance, and relationship satisfaction in the midst of sexual problems.

The physical toll of illness and treatment can affect sexual functioning and desire. For example, fatigue is a much reported side effect of treatment, which can leave patients feeling too exhausted for sex or any other activity. In addition, shoulder and back pain are commonly reported as a lingering side effect from treatment [119], and it is well-understood that pain can diminish sexual desire or lead to avoidance behaviors [113]. Similarly, hormonal changes as a result of chemotherapy and radiation (e.g., thyroid problems [120]) can affect sex drive. Decreased hormone levels in women can lead to vaginal dryness and atrophy, decreased libido, uncomfortable hot flashes, irritability, and changes in mood [116], which can decrease feelings of femininity or the sense of oneself as a sexual being.

25.2.4.3 Psychological Impacts

Psychological distress is associated with sexual problems [121], and decreased interest in sex is more common in patients who are depressed and coping poorly with cancer [102]. Similarly, anxiety can cause fears regarding performance and interfere with sexual enjoyment in the moment and the ability to maintain arousal. Also, changes in appearance due to surgery, weight loss, hair loss, or scarring, can decrease feelings of attractiveness [102]; and because of their prominent role in intimate and sexual interactions, changes to the face and mouth can be especially detrimental [115]. In Gamba and colleagues' [101] study, HNC patients (an average of 3.2 years following surgery), were divided into groups based on the extent of appearance changes. Results demonstrated that the group with the most extensive disfigurement reported more change in self image (57 versus 25%), decreased sexuality (75 versus 39%), and greater social isolation (36 versus 12%). However, other studies have stressed the importance of self-perception or investment in appearance as predictors of psychological difficulty, rather than the severity of the physical changes, per se [98, 107].

25.2.4.4 Relationship Changes

Finally, relationship problems may cause or exacerbate sexual problems and sexual problems may cause strained relationships. The reciprocal influence between relationship quality and sexual functioning is indicated by the fact that markers of marital and sexual satisfaction tend to decrease together [62]. Attention to strained relationships is important because research involving cancer patients and their partners suggests that the quality of the relationship (e.g., intimacy, satisfaction, communication) influences adjustment, distress, and quality of life for both the patient and the

partner. In a study of patients with HNC or lung cancer and their partners, Manne and colleagues [122] reported that higher baseline distress was associated with more negative communication, as well as higher levels of distress and decreased intimacy over time. Relationships can suffer with the loss of shared intimacy (i.e., affection and togetherness, sense of closeness), shared activities (eating, socializing), and possibly through fears of causing more distress by talking about the issues. It is also possible that relationship problems may have preceded the HNC diagnosis. For example, in families dealing with substance abuse problems, there is often a high degree of distress which may also be exacerbated by current stressors related to HNC [123].

Another source of dissatisfaction in relationships is related to issues of balance and benefit in relationships. That is, partners and caregivers may feel overly burdened or "under-benefitted" due to the patient's high support needs, which is associated with greater psychological distress among partners [123]. Patients may feel "over-benefitted" and report higher levels of satisfaction, or such an imbalance can lead to feelings of guilt.

25.2.4.5 Addressing the Issues

Due to discomfort surrounding this topic, sexual problems are thought to be underreported [102] and under-treated [117]. This is nicely demonstrated in Low and colleagues' [102] study which reported patterns of response to sexual function and intimacy questions in 518 cancer-free HNC patients. Based on the number of answered questions, patients seemed more comfortable answering questions about intimacy rather than sexuality. Further, they found that patients who were older, unmarried, and female were less likely to answer questions about sexual functioning [102].

To address potential sexuality and intimacy problems, it is important that providers ask, listen, and inform their patients about potential sexual problems and ways to manage them [118]. Solutions exist for many common problems and treatments are available (e.g., individual or couples counseling, sex therapy). For younger patients and those who may be considering having a child in the future, it is important to talk about the possibility of infertility [116]. Oncofertility is a growing field which gives cancer patients an opportunity to preserve their fertility if action is taken before treatment begins [124]. This is an important option, as one study found that young women with early-stage breast cancer would choose a less toxic chemotherapy treatment, even if it delivered less protection from recurrence, in the hope of preserving fertility or decreasing the risk of early menopause [125].

25.2.5 Role Changes

Role changes associated with HNC can challenge an individual's personal identity. Personal identity, or the basic understanding of who we are [126], is believed to be

both stable and dynamic over time [127], and is partially shaped through social roles (e.g., man or woman, professional, parent). Engagement in these roles provides the evidence to reinforce beliefs about the self [128]. In this way, identity and self-esteem derive from fulfilling our social roles and through the response of others [128]. As people enter new life phases and partake in different activities, some social roles will change [129], but the diagnosis of a serious illness can forcibly alter social roles, limit opportunities for role-fulfillment, and bestow new illness-related identities [130]. The role changes associated with HNC can cause significant interpersonal distress, diminished self-esteem, and create feelings of loss.

If the cancer experience subsumes other aspects of the patient's life, increasing identification with the illness can occur [129, 130]. This can lead to a new self-identity as a "cancer patient." HNC patients must suddenly learn to negotiate their role during an increasing number of interactions with medical providers, either by asserting themselves or by taking on a more passive role. HNC patients may also perceive that others' views of them have changed, feeling they are viewed as someone who is sick, weak, defective, or "repugnant" [50]. Many patients also need to negotiate a role change from care giver to care receiver. Many patients derive their identity through care-taking activities for their spouses and families (e.g., parenting, cooking, cleaning) or through their jobs (e.g., nurse). Changes in this role can be especially difficult as patients must come to rely on others to meet these needs for themselves and their families, and they may believe that others value them less if they are unable to fulfill social roles in the same way as before. Patients might perceive a diminution of status as they become increasingly dependent on others [128], and they may be unaccustomed to asking for help and support during treatment. With HNC, visible disfigurement, weight loss, and functional changes in the ability to eat and communicate can make it difficult to conceal or overcome this outward image.

HNC patients also report guilt for the impact that cancer has on their family and caregivers [93]. As patients' sense of contribution is challenged, their caretaking needs simultaneously increase (e.g., transportation to medical appointments, hospitalizations, sickness, side effects). This may create a deficit in which patients feel as if they are taking more than they are giving. HNC patients have expressed feeling like a "burden" – guilty that they cannot contribute in the same way, and guilty for putting their family through the stress and changes brought on by their illness.

A major role change for many patients occurs with disruptions to employment. Many people derive a large part of their identity from their work. A basic component of self-esteem comes from being productive, making a contribution, and feeling that one's skills are valued. Therefore, without this reinforcement, periods of unemployment can be very stressful and have a significant impact on mental health. Multiple studies have shown that unemployment is associated with increased rates of depression, substance use, suicide, and violence [131].

For HNC patients, disruption in employment or job loss and reduced income occurs at a time when financial strain may be growing due to medical bills. Some families will have greater difficulty surviving without the financial contribution of the patient and may lose their homes or fall behind on other bills [132]. Thus, patients may be in a position of feeling responsible for the situation, yet helpless to change it.

Though some social roles may decrease in prominence, it is important to help patients think flexibly about their contributions so that aspects of the patient's most valued roles can be preserved. This can be achieved, for example, by modifying duties rather than eliminating them. Alternately, patients might expand their definition of what it means to be a good parent, spouse, caretaker, or professional. The goal is to help patients re-establish a sense of continuity in their identity between their past, their current experience, and their future [133]. Patients who fail to integrate these changes may feel a sense of alienation from themselves and their family and friends [133].

The cancer experience can also inform or broaden a patient's identity in a positive way. Significant life events, such as the diagnosis and treatment of cancer, can motivate a reassessment of priorities [129] and a renewed commitment to "a life worth living." Many adults who have survived cancer identify as cancer survivors [129], and this identity is related to greater well-being. Involvement in cancer-related advocacy activities is more adaptive than identifying as a "person with cancer" or "a victim" [134]. Furthermore, social norms surrounding cancer and illness behavior are changing and others may not attach the same stigma to cancer patients as before [130]. With improvements in medical technology and growing public awareness of cancer survivorship, cancer is increasingly perceived as an illness that can befall anyone and as an illness that takes courage and strength to endure.

25.2.6 Cognitive Changes

Cognitive issues, such as decreased attention, memory, and concentration can occur following chemotherapy and radiotherapy [135–137]. Psychoeducation regarding the possibility of short-term cognitive effects can help reassure patients and their caregivers that the patient is not going crazy or developing dementia [135]. To alleviate the impact of inattention or memory problems, patients can also be advised to use compensatory behavioral strategies [137]. These include avoiding multi-tasking and avoiding distractions, as well as energy conservation plans (e.g., increased sleep, decreased workload, delegating tasks, taking breaks, and asking for assistance) To support memory, compensatory strategies include asking for information to be repeated, using organizational aids (e.g., hand held device or notebook/binder), lists, posted reminders, mnemonic devices, calendars, timers, alarms, developing new routines, and using cues within the environment as reminders [135]. However, if cognitive problems interfere with return to work or functioning, referral to a neuropsychologist for further evaluation can be made [135].

25.2.7 Social Support

Social support, both emotional and instrumental, is generally helpful for cancer patients, in terms of helping them to manage and adjust to issues associated with

cancer [138]. For HNC patients specifically, social support is associated with less depression [139]. Dissatisfaction with social support has been associated with poorer psychological adjustment [140]. However, even in the presence of adequate social support, depressive symptoms are related to lower perceived quality of life [141]. External sources of social support from group therapy and, importantly, support from physicians has been shown to improve psychological functioning and quality of life [142, 143].

Patients have described changed relationships following cancer diagnosis; friends or family seemed to push away or avoid them during this time. Perceived unsupportive social environments can be especially detrimental for cancer patients. In HNC patients and their partners, marital relationship satisfaction predicted higher quality of life and lower psychological distress [123]. The broader cancer literature also refers to the negative impact of social constraints, which occur when an individual feels they must inhibit their expression of cancer-related thoughts and feelings in order to protect others or to avoid a dismissive, negative, or unhelpful response. Perceived social constraints have been associated with higher levels of distress [144], greater depression, and lower quality of life [145] among cancer patients. Friendships might also be challenged as cancer treatment consumes a greater part of the patient's life. As involvement in shared activities and experiences decreases, it can become difficult to talk about topics other than cancer.

25.3 Psychological and Behavioral Problems

25.3.1 Depression and Suicide

Clinical depression is a common problem in HNC patients, and is qualitatively different from expected difficulties adjusting to the cancer diagnosis and treatment. HNC patients experience depression more than patients with other cancers, with a reported incidence of 15–50% [45, 146]. The presence of depressive symptoms in HNC survivors is also greater than in the general population, with estimates from 16 to 44% [147, 148]. Pervasive sadness that is not passing, but remains for an extended period of time or leads to a further disruption in functioning, is indicative of depression. Table 25.1 lists the diagnostic criteria for depression [149]. Fatigue, loss of appetite, weight loss and insomnia or hypersomnia are common symptoms of cancer treatment; while these are also symptoms of depression, they are not sufficient to diagnose depression alone, unless the intensity of these symptoms exceeds expected levels [150].

Several medical problems, such as hypothyroidism and electrolyte disturbances, and side effects from medication, such as from opiates or steroids, can mimic symptoms of depression and need to be considered before the diagnosis of depression is made. (For list of medical conditions and medication side effects that mimic depression, see chapter by Breitbart and colleagues [151].) Depression symptoms that present in the context of delirium or encephalopathy may remit once cognitive functioning is

Table 25.1 Criteria for diagnosis of major depression

Individuals demonstrate at least five of the following symptoms (one must be either depressed mood or loss of interest) present for at least 2 weeks:
Depressed mood
Decreased interest in activities
Change in appetite
Change in sleep
Psychomotor agitation/retardation
Fatigue
Feelings of worthlessness or guilt
Decreased concentration
Suicidal ideation, plan or attempt

restored and preclude any depression diagnosis. Emphasis on the non-neurovegetative symptoms of guilt, hopelessness, social withdrawal, and loss of pleasure that are less influenced by the cancer process and treatment may be more informative in diagnosing depression [152, 153]. Suicidal ideation, intent, and attempts are also indicative of a clinical depression as they are not normal reactions to medical illness.

Suicidal ideation is the thought that one should take his/her own life and includes wishes to die, consideration of taking action to end one's life, and envisioning a plan for how to do so. Passive suicidal ideation may be expressed as a wish that God would "take me" or that the illness would escalate. Patients with solely passive suicidal ideation (those wishing for death without the idea of taking any action) are at less risk of suicide attempts and completions than those patients with active suicidal ideation (those with a plan for how to bring about one's own death and an intention to take action). Past suicide attempts, family history of completed suicide, and impulsivity [154] as well as being white, male, and unmarried are risk factors for suicide [155]; note that these are common characteristics of HNC patients for whom alcohol use is a contributing factor. The suicide rate among cancer patients is higher than in the general population: 31.4 per 100,000 vs. 16.7, and is higher for HNC patients compared to individuals with other cancers [155]. Amongst HNC patients, more advanced disease, an inability to swallow, and depression are associated with higher risk of suicide [45, 156]. Chronic, uncontrolled pain also places patients at risk for suicide; these patients have twice the risk of suicide compared to patients without chronic pain [157].

Premorbid depression is the best predictor of depression during treatment and post treatment [139, 148]. After an initial episode of depression, a patient is more likely to experience subsequent episodes. As depressive episodes are often triggered by stressful events, the HNC patient has increased vulnerability to depression during and after treatment. The stress associated with HNC diagnosis, treatment, deficits, and prognosis may exacerbate already existing symptoms or result in a new episode onset.

During treatment, a high incidence of depression is thought to be secondary to the immediacy of invasive treatment, the disfigurement from treatment, the disruption of vital functions such as eating and speaking, and because of the association between HNC and alcohol use. Greater physical symptoms, impairments in eating ability

[148], and continued use of alcohol and tobacco [158] have all been associated with increased rates of depression in the post treatment period. Higher rates of depression in the post treatment period are likely related to the lasting changes in physical appearance, reduced functioning, and impairments in basic functions of eating and communicating that often result from aggressive HNC treatments. Some patients may feel that treatment made them worse due to losses in function. Social isolation secondary to functional deficits is also associated with increased risk for depression.

Depression has a negative impact on a number of post-treatment outcomes for HNC survivors. Depression is a predictor of functional pain (e.g., with mobility or eating) up to 5 years after treatment. Howren [159] reported that presence of depressive symptoms predicted lower quality of life for a number of domains including eating, speech, aesthetics, and social disruption 12 months following treatment. While most HNC survivors return to baseline quality of life within 12 months, individuals with depression demonstrate continued deficits in quality of life over the long term [75]. Findings on the impact of depression on survival are mixed, with several studies demonstrating no impact of emotional well being on survival [160, 161]. It may be that depressive symptoms in themselves and emotional well being do not relate linearly to depression, but rather through the relationship of depression to self care and social factors that lead to decline in health status and functioning.

There are several brief and easily administered measures that can be utilized in the care of HNC patients to assess for current symptoms of depression. These include the Beck Depression Inventory [162], The Center for Epidemiology Scale-Depression (CES-D) [163], the Hospital Anxiety and Depression Scale [164], and the Geriatric Depression Scale [165]. Once identified, depression may be addressed with therapy, medication, or both. Many antidepressant medications, particularly selective serotonin reuptake inhibitors (SSRIs), have low incidence of side effects and are safe to use in the context of medical problems.

25.3.2 Anxiety

Persistent anxiety that disrupts functioning distinguishes problematic anxiety from what might be considered a normal reaction to HNC. A significant number of patients experience anxiety, especially during the initial diagnostic and treatment phase of their illness. Estimates of anxiety in HNC patients range from 25% [166] to 39.4% [167]. In a study of inpatients newly diagnosed with HNC and facing surgery, 40% reported significant anxiety [167]. Patients also ranked their top unmet care needs – both groups (those with and without significant anxiety) reported that coping with anxiety about their treatment/surgery was the top need for which they needed care. The patients with anxiety ranked coping with sleep and dealing with fears of cancer spreading/returning as their 2nd and 3rd most significant unmet needs, while patients without significant anxiety ranked being informed about benefits and adverse effects of treatment and being informed about the effects of cancer that could shorten their lives as the 2nd and 3rd most important needs.

Table 25.2 Symptoms of panic attack

Individuals demonstrate four or more of the following symptoms; these develop abruptly and peak within 10 min:
Palpitations or accelerated heart rate
Sweating
Trembling or shaking
Shortness of breath
Feeling of choking
Chest pain
Nausea
Dizziness or lightheadedness
Feelings of unreality or being detached from oneself
Fear of losing control or going crazy
Fear of dying
Numbness or tingling
Chills or hot flashes

As with depression, medical problems, such as asthma or congestive heart failure and side effects from medication, such as steroids and hypertensive agents can mimic anxiety symptoms and need to be considered when assessing symptoms. For a list of medical conditions and medication side effects that mimic anxiety, see Breitbart and colleagues [151].

Panic attacks are acute periods of anxiety that manifest with many bodily symptoms and can be thought of as an autonomic fight or flight reaction in the absence of any tangible threat. Shortness of breath, sensations of choking, and chest discomfort are components of a panic attack, see Table 25.2 [149]. New onset of panic attacks during HNC treatment was described by Shimizu and colleagues [168], and panic was related to a bodily sensation interpreted as terrifying or life threatening to the patient. Panic attacks often start with a physical problem that is misinterpreted or misunderstood by the patient. The patient's focus on this problem then triggers the autonomic arousal found in life threatening situations. Pain is also a significant contributor to the development of panic attacks [168].

Post Traumatic Stress Disorder (PTSD), involves continuing to react as if one remains in a threatening situation well after the situation has ended, and is characterized by a reliving of the situation, avoidance of circumstances related to the situation, and prolonged hyperarousal. Acute Stress Disorder differs from PTSD only in timing of presentation and is an appropriate diagnosis when these symptoms present in the month following the actual situation (see Table 25.3). In a combined sample of HNC and lung cancer patients, the incidence of Acute Stress Disorder prior to treatment was 28% and incidence of PTSD at 6 months post cancer diagnosis was 22% [169].

There is significant overlap between depression and anxiety such that both problems may present together. Twenty-four percent of cancer patients and 15% of HNC patients have mixed depression and anxiety, and HNC was among the highest six cancer types with mixed depression and anxiety [170]. Shorter time

Table 25.3 Stress disorders

A Reaction following a traumatic event that includes:
Re experiencing the event through
1. Intrusive thoughts
2. Distressing dreams
3. Flashbacks
4. Emotional distress when exposed to something similar
5. Physiologic distress when exposed to something similar
Avoidance of things associated with the traumatic event
1. Avoiding thoughts or discussion of the event
2. Avoiding places or people associated with the event
3. Inability to recall important aspects of the event
4. Decreased interest and participation in activities
5. Feeling estranged from others
6. Restricted range of affect
7. Sense of foreshortened future
Persistent symptoms of increased arousal
1. Difficulty falling or staying asleep
2. Irritability or angry outbursts
3. Difficulty concentrating
4. Hypervigilance
5. Exaggerated startle response
Acute stress disorder: symptoms occur in the month after the traumatic event
Post traumatic stress disorder: symptoms persist more than 1 month after the traumatic event

from diagnosis to treatment and greater physical impact of disease correlated with greater psychological needs, including anxiety [167]. Negative coping styles (such as denial, venting, substance use, and behavioral disengagement) have also been found to be correlated with anxiety [166].

There are several brief and well validated assessment tools that can be used to screen for the presence of significant anxiety. These include the Beck Anxiety Inventory [171] and Hospital Anxiety and Depression Scale [164]; both provide measures of physical and cognitive symptoms of anxiety and also give an indication of the severity of the symptoms. The Impact of Events Scale-Revised [172] provides a measure of the severity of the impact of a stressful event and can provide information regarding the risk for the experience of PTSD symptoms.

25.3.3 Alcohol and Tobacco Use

25.3.3.1 Frequency of Alcohol and Tobacco Use

Alcohol use and smoking are directly related to the occurrence of HNC and many patients are dependent on alcohol or are problem drinkers. Duffy and colleagues,

[146] reported that 41% of HNC patients were drinking at the time of diagnosis, and 22% of HNC patients have been diagnosed as "problem drinkers" [173]. Lifetime prevalence rates of alcohol dependence in the general population are estimated at 12.5% [174], making alcohol abuse about two times more likely in the HNC population. In the general population, 7.6% smoke 1 pack per day or more [175] but smoking rates range from 23 to 40% in HNC patients [158, 176-178]. There is a positive relationship between smoking and drinking such that greater cigarette use is found with greater alcohol consumption [179, 180]. Similarly in the HNC group, smoking and drinking frequently co-occur.

When individuals are diagnosed with a potentially life-threatening disease, it is expected that they will make changes in their lifestyle to comply with medical treatment and to improve their health behaviors. Abstinence from alcohol and smoking cessation are difficult to achieve, even in the absence of any medical problems. Smoking cessation rates in the general population are about 7% for those quitting without assistance, and 15–30% for those quitting with help from various behavioral and pharmacological intervention [181].

Many HNC patients (40–79%) quit smoking after diagnosis [182], and those who do not quit report more psychological distress [13]. However, only 20% of the patients who drink three or more alcoholic drinks per day stop drinking after the diagnosis of HNC [146, 177], and only 9% of problem drinkers are interested in alcohol cessation treatment [146].

In a study of over 4,000 adults in the US, Dawson and colleagues [183] reported that only 18.2% of those with alcohol dependence achieved abstinence [181]. For HNC patients, typical rates of alcohol and tobacco use range from 23 to 40% for tobacco [158, 176-178] and 37 to 54% for alcohol [173, 184-186]. Potash and colleagues [173] reported that 43% of problem drinkers continued to drink 1 year after diagnosis, and 44.5% of those with poor oral functioning continued to drink alcohol at 12 months after treatment despite their functional deficits.

Complete abstinence is a difficult goal to achieve for many HNC patients. In a general population sample, 25.9% of alcoholics experienced a relapse to problematic alcohol use during a 3 year period [187]. Given the difficulties in decreasing or abstaining from alcohol use [183], formal treatment for substance use in the HNC patient is often warranted. However, the HNC patient's medical situation, intense treatment, and physical limitations may inhibit the patient's ability to participate in formal addiction programs, making recovery more difficult. As programs for both alcohol and smoking cessation have the highest rates of success, engagement in formal substance abuse treatment should be encouraged as soon as it is medically appropriate. Social support also helps individuals with smoking cessation [62], and should be enlisted whenever possible.

25.3.3.2 Negative Outcomes Associated with Continued Substance Use

Continued use of alcohol and tobacco is associated with worse medical, psychological, and social outcomes for HNC patients. Specifically, continued substance use is related to greater side effects from treatment, undetected withdrawal symptoms

during treatment, and decreased treatment response [188]. Continued use of alcohol and tobacco is also associated with as much as a fourfold increase in cancer recurrence [189, 190], as well as increased mortality from cancer related causes [48, 186, 191]. The lower survival rates for individuals that persist in using substances may in part be related to additional medical (e.g., cardiovascular and respiratory) and psychological (e.g., untreated depression) comorbidities that also are associated with poor survival rates [192].

Patients who quit smoking have improved treatment outcomes and report better quality of life when compared to continued smokers [62]. Continued use of tobacco appears to be a greater risk factor for poor outcomes compared to continued use of alcohol. The relationship between alcohol use and poor outcomes is less consistent and may depend on how and when alcohol is used. Moderate, social, drinking does not demonstrate the negative impact that heavier problem drinking does [185, 193], and can have positive results on quality of life, social relationships, and health outcomes [194].

25.3.3.3 Reasons for Continued Use

Individuals who persist in smoking and drinking alcohol against medical advice may do so for a number of reasons. Both smoking and drinking can be addictions, that is, people continue to engage in the behavior even when negative consequences are present and despite attempts to cut back or discontinue use. Smoking and drinking are frequently used by HNC patients to avoid the negative emotions associated with the diagnosis [194], perpetuating the addiction.

Another contributor to continued smoking and drinking is an association between addiction behaviors and depression and anxiety. Many individuals with alcohol abuse or dependence have co-existing depression or anxiety (37–62%) that is not treated [195] and the abuse can be an effort to self medicate. Individuals that smoke also commonly report using cigarettes as a method of anxiety reduction, and anxiety is likely to be increased during diagnosis and treatment for HNC.

Attributional style and self-efficacy may also play a role in the continued use of tobacco. In a study of patients that had been active users of tobacco prior to diagnosis, Christensen and colleagues reported that patients that attributed the cause of their cancer to tobacco use and had feelings of personal control over the recurrence of cancer were less likely to continue smoking in the post treatment period compared to a group that felt they had less personal control over cancer recurrence [48].

25.3.3.4 Assessment and Intervention

Initially, an evaluation of the presence and extent of the patient's smoking and alcohol use is needed. Educating the patient is also important, as many patients are initially unaware of the connection between alcohol, tobacco, and HNC, and continued use of

alcohol may be partly related to the medical provider's reluctance to address issues of substance use with the patient [173]. Further, discussion of the importance of smoking cessation with the medical provider increases the likelihood of abstinence [181].

Screening for alcohol abuse and dependence can be achieved quickly and efficiently with the use of brief well validated measures. One of the best screenings for alcohol abuse/dependence is the four item CAGE questionnaire in which patients rate their use of alcohol on four items: need to cut down, annoyance about others' complaints of patient's drinking, guilt about drinking, and consumption of alcohol first thing in the morning) [196]. Two (or more) positive responses on the CAGE indicate the presence of an alcohol use disorder. The CAGE questionnaire has been used extensively, and has been used with HNC populations at diagnosis, during treatment, and during palliative care to describe alcohol habits and attitudes [197-199].

The Alcohol Use Disorders Identification Test (AUDIT) [200] is another brief, well validated, and widely used measure of potential alcohol abuse and dependence. Developed by the World Health Organization, the AUDIT was designed for use with international populations and has been standardized in several countries, as well as translated into different languages including Spanish, Russian, and Swahili [201].

25.3.3.5 Special Problems

Withdrawal from substances is a significant issue in HNC patients, and identification of withdrawal symptoms and management of these symptoms is important to treatment outcomes. Withdrawal from alcohol may include symptoms such as autonomic hyperactivity, hand tremor, insomnia, nausea or vomiting, visual, tactile or auditory hallucinations, psychomotor agitation, anxiety and grand mal seizures [149]. Withdrawal symptoms can occur with abstinence, but are also seen with a decrease in usual alcohol consumption, and may present in 6–24 h after a drop in blood alcohol level [202]. Cognitive problems are also more prevalent in alcoholics and may persistent even after recovery or prolonged abstinence [203]. Withdrawal symptoms post surgery are associated with increased morbidity and complications, but decreased ICU transfers, delirium, and violence were achieved when HNC patients were assessed for these symptoms frequently and treated promptly [204].

Identification and management of alcohol withdrawal is achieved in many hospital settings with the use of the Clinical Institute Withdrawal Assessment [205]. This is a ten item scale (administered by nursing staff) that addresses common symptoms of alcohol withdrawal and their severity. It is the most common measure of alcohol withdrawal used in hospital settings due to its brevity and ease of administration [206], although it requires training to ensure reliability and proper scoring.

Withdrawal from tobacco can present with anger, anxiety, depression, difficulty concentrating, impatience, insomnia, and restlessness. Withdrawal symptoms present within the first week after smoking stops and can last 2–4 weeks [207]. Unidentified withdrawal from tobacco can complicate the treatment of HNC patients and make coping with the disease and treatment more difficult for the patient. If left undiagnosed and untreated, depression and anxiety may aggravate

preexisting ineffective coping strategies (such as smoking) and may lead to further withdrawal, isolation and disinterest in rehabilitation [203].

25.4 Pain and Pain Management

Pain can be problematic throughout the course of HNC. In a study of orofacial pain in patients with normal mucosa, oral precancer, and newly diagnosed HNC, only the patients with new HNC reported spontaneous pain and functional restrictions from pain [208]; smokers also reported greater pain and interference from pain than non-smokers [209]. Further, pain is the presenting symptom in 19% of patients newly diagnosed with HNC [210]. Patients reported 12 different types of pain; the most common were sore throat, tongue and mouth pain, and pain when swallowing.

Pain during treatment for HNC can be due to a surgical procedure, mucositis, infections, neuropathic pain, and musculoskeletal pain [211]. Much attention has been paid to mucositis (lesions in the mucousal lining of the mouth), from either radiation or chemotherapy. During radiation therapy specifically, over 90% of patients experience oral pain [212]. Wong and colleagues [213] reported that the pain typically begins during the 2nd week of radiation therapy, and continues throughout treatment. At 1 month follow-up, pain has typically lessened. Patients in this study used a variety of oral analgesics to help manage the pain, and also used mouth rinses, but none of these had much of an impact on swallowing pain which was often very severe and difficult to manage.

Difficulties with pain management often continue long after treatment has ended. Pain and physical pain sites tend to correspond with areas that were involved in HNC treatment and include shoulder pain, oral cavity pain, noxious phantom tastes, and fatigue. The report of continued pain experience after treatment varies widely by study with rates from 15 to 50% of patients reporting continued pain experience in the 1–5 years after treatment [214, 215]. Increased experience of pain in the post-treatment period is associated with decreased quality of life [216]. In patients with recurrent disease, pain is the initial symptom in 70% of cases [217]. Continued presence of pain is also associated with increased mortality in patients that were disease free for at least 1 year following treatment [68].

Assessment of the cause of the pain, with attention to the timing of pain in the course of the disease (e.g., during treatment or after), as well as social variables that may impact the management strategy (e.g., alcohol use), are all critical to adequate pain management. Severity of pain can be assessed simply by asking patients to rate their pain on a scale from 0 (no pain) to 10 (worst pain ever). Treatment of HNC pain can then be accomplished through the use of medications, nerve blocks, or myofascial trigger point injections; see Sist and Wong for a series of case reports that highlight diagnostic and treatment issues [218]. Of note, many patients report that the pain treatments provided do not provide adequate relief [213]. Chronic, uncontrolled pain places patients at risk for suicide; these patients have twice the risk of suicide than patients without chronic pain [157].

Pain management is an especially difficult issue for an alcoholic patient who may have more difficulty achieving adequate pain control. Staff may blame the patient for the development of the disease, and may be less likely to attend to complaints of pain. Continued requests for pain medication are often seen as evidence of addictive behavior or considered an exaggeration in the addicted patient, leading staff to view the patient's complaints of pain as invalid [219]. While pain management in these patients is more complicated than in those who are not using alcohol, these patients still deserve to have pain complaints believed and pain controlled. Patients with a history of problem drinking may have less tolerance to pain in the absence of alcohol, may have co-existing anxiety that decreases pain tolerance, and may more quickly develop a tolerance to opioids; all arguing for the need for more pain medication in these patients rather than less [220]. Poorly controlled pain can result in the maintenance of the addiction as patients seek relief from the pain and the stress of dealing with pain through already established addiction behaviors [195].

25.5 Long Term Challenges

Premorbid functioning, residual effects of treatment, and new challenges in the post treatment period may all impact psychological functioning in the months and years following treatment for HNC. This post treatment period represents a time of continued psychological vulnerability involving fears of recurrence, employment difficulty and disability, and in some cases, encountering issues that arise at the end of life. However, there may also be positive long term psychological consequences of HNC. Research suggests that the majority of patients find some benefit from their cancer experience [221-223]. The post-treatment psychological consequences of HNC treatment, whether positive or negative, predict long term quality of life, often better than medical and physical factors [224, 225]. Understanding the long term social and psychological implications of HNC is essential as patients are living longer with available cancer treatments. For the patients for whom HNC represents the end of life, understanding the unique psychological issues that accompany this stage of life can help providers make this transition as comfortable and effective as possible for patients.

25.5.1 Psychological Factors and Post-treatment Adjustment

Stable personality factors influence how HNC patients respond to the post treatment period. Dispositional pessimism is the stable tendency to maintain a negative outlook and expect poor outcomes; this attitudinal style can be applied to a wide variety of situations. A patient's tendency toward optimism or pessimism may impact quality of life as well as their ability to cope with long standing consequences of the illness long after treatment has ended. Holloway reported that a pessimistic style was associated

with decreased quality of life in several areas including social support satisfaction, physical well being, and specific physical functioning (eating, breathing, and communication) in patients that had been free of HNC for at least 3 years [225]. In this study, dispositional pessimism was actually a better predictor of poor functioning than objective physical measurement of xerostomia and shoulder dysfunction. People with a pessimistic style are less likely to see their efforts as having an impact on the situation, so they may make less effort to change or cope with their situation.

Use of ineffective coping strategies, particularly avoidant coping, has been associated with negative outcomes for HNC patients. Avoidant coping includes any behavior that helps the individual *not* confront an undesired event. Avoidant coping is demonstrated by alcohol or other substance use, rejecting support, missing medical appointments, or noncompliance with medications. Use of avoidant coping in HNC patients has been associated with increased mortality [68].

The personality construct of neuroticism has also been linked to poor outcomes in HNC populations. Neuroticism is one of the Big Five personality factors along with openness, conscientiousness, extraversion, and agreeableness [226], and neuroticism is characterized by emotional instability. Individuals high in neuroticism are more apt to demonstrate psychological distress in anxiety provoking situations and to use more ineffective coping styles such as avoidant coping (described above). Neuroticism is associated with poor health-related quality of life [224] and increased mortality [68].

25.5.2 Fears of Recurrence

Thoughts and feelings about a cancer experience are not likely to end at the completion of treatment. Approximately 50% of patients continue to experience thoughts about their cancer even 8 years after diagnosis and 25% think about their cancer regularly [228]. Fears of recurrence are especially pronounced immediately prior to clinic follow-up appointments [100], when talking with other cancer patients, or when experiencing physical symptoms [227].

Several factors appear to place individuals at increased risk for experiencing fears of cancer recurrence. HNC patients with disfigurement or lasting functional impairments (including pain and difficulties with eating) have been found to be at greater risk to experience continued fears of recurrence even 3 years after cancer remission [229]. Fear of recurrence has also been associated with heavy tobacco use in HNC patients [158]. In this instance, smoking behavior that is likely an attempt to decrease anxiety actually produces the opposite effect as HNC patients that continue to smoke and drink are at increased risk for a recurrence of cancer [190].

25.5.3 Employment Concerns

Problems with identity and employment can also continue beyond the treatment period. Patients with HNC are also more likely than patients with most other cancers

to remain on disability after treatment [230, 231]. A study of laryngectomy patients reported that a quarter of near-total laryngectomy patients and close to half of total laryngectomy patients stopped working after treatment [232]. A newer study of [233] HNC patients who were less than 65 years old and who had finished treatment at least 2 years prior showed a surprisingly high return to work rate: 71% of patients returned to work within 6 months following treatment and 83% of patients returned to work within 2 years. The factors most related to unemployment were problems with the mouth, teeth, and eating difficulties (e.g., xerostomia, sticky saliva, poor appetite), as well as problems with anxiety and aspects of social functioning (e.g., social eating) [233]. Other factors associated with becoming disabled in HNC patients are advanced disease stage, use of alcohol, and low educational level [132].

Unemployment and disability have also been associated with specific treatment factors including pain, fatigue, disfigurement, and speech and eating difficulties. In HNC, the likelihood of remaining on disability after treatment increases when multiple treatment modalities are utilized [232]. Among patients that were working at the time of diagnosis, participation in chemotherapy appears to have a particularly negative impact. This is of importance as treatments for HNC are now more likely to include chemotherapy as a component of treatment. Taylor and colleagues [231] reported that HNC patients who had undergone chemotherapy were 3.5 times more likely to be disabled at 1 year follow-up than those that had undergone only surgery or radiation therapy or both. The relationship between chemotherapy treatment and high rates of disability appears to be at least partially attributable to fatigue resulting from chemotherapy. In a study of patient reported factors for not returning to work, fatigue was most frequently endorsed with 58.5% rating it as an important factor in their decision [234]. Additional factors reported by patients included variables associated with the treatment process itself, including difficulties with speech and eating. Interestingly, appearance was not frequently rated as an important in this study.

Pain is also predictive of disability following HNC treatment [231], with approximately 38% of patients reporting pain as an important reason for not returning to work [234]. There are several reasons why pain may be related to increased disability. Patients may find it difficult to return to work due to the perceptions that participation in work activities exacerbates the pain experience. Additionally, the use of narcotic medications for treatment of pain may lead to difficulty with resuming work due to medication side effects such as sedation. Finally, patients may perceive the continued experience of pain as a sign of disease progression and they may be less likely to return to work if they believe their illness to be worsening.

25.5.4 Post-traumatic Growth and Meaning

There has been a recent interest in the potential benefits and growth that result from the experience of health related difficulties, including cancer [235]. Posttraumatic

growth involves gaining a new sense of personal meaning or benefit from a traumatic experience [236]. Research on benefit finding consistently identifies four types of benefit: Improved personal resources (awareness that available social and instrumental supports are greater than previously thought), enhanced sense of purpose, development of closer relationships, and change of life priorities [221, 227].

Due to the aggressive nature of HNC and its treatment, as well as long-term consequences (including disfigurement and difficulties in communication and speech), benefit finding after HNC could be questioned. However, even though the cancer itself and the subsequent treatment can be threatening and distressing, it appears that benefit finding after the cancer experience is the norm rather than the exception. The majority of cancer patients, 60–90%, report finding at least some benefit from undergoing the experience of cancer [222, 223], and benefit finding occurs at similar levels with HNC patients [221]. While cancer survivors do not have a better overall view of life compared to their healthier peers, they are more likely to attribute their positive attitudes to their cancer experience [227]. Optimism and positive reframing have also been associated with increased benefit finding in patients with HNC [221, 237].

25.5.5 End of Life Issues

For some, HNC is a terminal illness. One of the difficult adjustments that often accompanies terminal illness is the psychological letting go of the possibility of a return to normal functioning and a life without the presence of cancer. End of life may be associated with loss of roles, feelings of isolation from healthy others, and the beginnings of detachment from life. End of life and associated increased symptom burden may impact several arenas of the patient's life including relationships with family and friends, loss of control of functional capabilities and life choices, and feelings that important issues may be left unresolved. This adjustment process may lead patients to experience psychological distress. This distress may be manifested as hopelessness, loss of meaning and purpose to one's life, loss of personal dignity, and feelings that one has become a burden to others [238, 239]. Hopelessness at end of life is of particular importance as these patients are at increased risk for suicidal ideation and suicide completion [240, 241]. For some patients the end of life journey may result in an acceptance and an evolution of hope. Hope for extension of life is gradually replaced by hope for peacefulness, dignity, and a spiritual afterlife [242].

Therapies have been aimed at mitigating the more maladaptive psychological processes that may occur at end of life. These therapies are aimed at preserving and strengthening personal dignity and sense of self as described in Breitbart and Chochinov's models [238, 243]. As symptom burden and hospitalizations increase with disease progression, patients may become focused on their illness and the loss of personal identity and dignity. Dignity preservation therapies involve shifting the patient's focus from aspects of the illness process to areas of continued personal strength and valued areas of the self. These goals are achieved through several methods including maintenance of autonomy, development and maintenance of

hope, and honoring personal spiritual needs. Maintenance of autonomy may mean being mindful of patient requests for privacy during medical hospitalizations and treatments, designating family members to assist with personal hygiene and toileting tasks, and structuring the medical and home environment to allow the patient to maintain their greatest level of functional independence [238]. Spiritual needs may be honored through requesting chaplain services when appropriate and creating room for the patient to feel comfortable expressing their spiritual needs and concerns. These approaches have been found to increase feelings of dignity and to provide a sense of meaning and purpose at the end of life [238, 244].

As end of life draws closer, families often need to become more involved in treatment planning and decision making and may struggle with their own feelings regarding end of life issues [245, 246]. Engagement and education of family throughout the treatment process about aspects of the patient's illness and potential outcomes can help prepare patients and families for the reality of palliative and hospice care. Preparing patients and families for end of life is an essential task that can be achieved through effective and honest communication about end of life issues [245, 247]. Completion of Advance Directives and Power of Attorney documentation can assist patients and families in preparing for end of life treatment decisions. These documents may also assist in lessening confusion and potential conflicts amongst family members regarding palliative and hospice decisions if patients become unable to communicate. Honest communications with families of hospitalized and incapacitated patients at end of life has been associated with improved adjustment for families [246]. For a more complete description of psychological processes and issues during end of life see Breitbart [248].

25.6 How Medical Professionals Can Help

Patients with HNC are at increased risk for a host of psychological and social difficulties, with different challenges occurring at different stages of treatment. Problems can range from specific issues that cause distress and impact quality of life (e.g., eating difficulties), to health behaviors that interfere with treatment (e.g., alcohol use), and/or to more serious forms of psychopathology (e.g., depression). The presence of psychological symptoms at any point in the cancer process is associated with poorer coping, functioning, and quality of life. As a result, it is important for medical professionals to be attentive to the psychological issues and to address them properly. Specific suggestions are provided below.

25.6.1 Assess and Monitor Psychological Status

A vital first step toward treatment is assessment. If we do not ask about problems or raise issues, we will miss opportunities to provide assistance. As a first-line intervention, simply asking patients about potential problems can validate and normalize their

concerns. Further, assessment of psychological symptoms, especially depression, anxiety, and suicidality, is essential when treating the HNC patient. (Brief measures to assess these issues have been described above.) These are easy to use, and can provide information that could result in a referral for further treatment by mental health professionals. The National Comprehensive Cancer Network has formulated distress management guidelines which regard the assessment and treatment of distress from diagnosis through treatment and survivorship as a standard component of care [29]. The assessment of distress is also associated with increased patient satisfaction [249].

In addition to screening measures, it is helpful for patients to discuss their concerns with their providers. The belief that discussing suicide, for example, would implant the thought in the mind of a patient who would otherwise not consider it is untrue [250]. Detecting suicide risk may go a long way towards prevention, as completed suicides are often done in the absence of discussion or are not advertised by the patient. Rather, it can be therapeutic when patients are allowed an opportunity to voice their concerns to an empathic listener [135]. Additionally, given the strain that cancer treatment can put on relationships, and as caregiver burn-out or family conflict can negatively impact the patient during a vulnerable time, it can be helpful to ask the patient's caregivers how they are doing and to make referrals for individual, couples, or family therapy if necessary [135].

An additional benefit of routinely asking about distress and other problem areas is that it may help socialize patients into a model of care that regards emotional well-being and self-care behaviors as important aspects of successful outcome and valid targets of intervention. This is especially important in HNC because patients with premorbid alcohol and tobacco abuse/dependence, depression, or other psychopathology may be especially vulnerable to the development of psychological and social problems throughout treatment and over the long-term. Yet despite being at greater risk for distress, research also suggests that HNC patients may be less likely than other patients to participate and follow through with psychological interventions [251, 252]. Therefore, a benefit of routine assessment and early introduction to supportive services is that it may help to destigmatize the use of psychosocial services [232] for this at-risk group.

25.6.2 Provide Education and Support

The general public is not knowledgeable about HNC, so providing education to patients is critical. The initial education should be done by the physicians and nurses most involved in the patient's treatment, as these individuals know the case and have the most credibility with the patient. This initial education should then be supplemented by other resources, such as websites, brochures, support groups, or discussions with previous patients. Throughout the course of treatment, the provision of informed, well-timed, practical advice can decrease stress for patients and families [100]. As treatment progresses, it will also be important for the main treatment providers to continue to be sure the patient understands what is occurring and what can be expected as a result of the specific intervention or procedure. Specific websites that can be helpful for patients are listed in Table 25.4.

Table 25.4 Web resources for patients

For education about HNC, treatments, and much more:
www.cancer.gov/cancertopics/types/head-and-neck/
www.cancer.gov/cancertopics/types/oral
For books, a newsletter, and information on support groups in the U.S.:
www.spohnc.org/
For patients with laryngectomies (information on strategies to address communication, eating, and other oral problems):
www.webwhispers.org
www.theial.com
For help with appearance changes:
www.lets-face-it.org.uk
For help with issues of sexuality:
www.cancer.org

A simple intervention that highlights the benefit of providing information was described by McQuellon and colleagues [253]. In this study, new patients to an oncology clinic were given a brief, 15–20 min orientation consisting of a tour of the reception, nursing, blood draw, and chemotherapy areas, handouts on clinic hours and operations, and an opportunity to ask questions. One-week later, intervention patients reported lower mood disturbance, anxiety, and depressive symptoms, as well as more confidence in their doctors, greater satisfaction, hope about their illness, and understanding of clinic operations compared with a no-treatment control [253]. This simple intervention helped patients feel more comfortable at the beginning of treatment, a time when distress is typically high. Psychoeducational interventions can also be used to help patients build skills that will assist them in coping with future treatment challenges [254].

Family and friends are unlikely to understand the psychosocial problems the patients may experience (at least initially). As social support will be useful to these patients as they navigate the challenges associated with HNC, encouraging the education of and support from significant others will also be useful to patients in the long-term. For example, one study showed that incorporating significant others into a skill building intervention resulted in less patient distress for up to 1 year after the intervention [255]. In this way, patients and their families can learn to work together to solve problems presented by cancer and its treatment.

25.6.3 Encourage Decreased Use of Substances in a Non-judgmental Way

Professionals and patients agree that decreasing/quitting alcohol and tobacco use is difficult for anyone, and it is more difficult for individuals with a longer history of substance use and for those under stress. We would do well as providers to educate ourselves regarding interventions to help people decrease substance use

(i.e., nicotine replacement therapy, pharmacotherapy, group treatments, AA, quit lines, etc.) and to encourage patients to utilize these resources. Keeping in mind the guilt and frustration these patients may be experiencing, approaching this issue and providing encouragement in a non-judgmental way will increase the likelihood of a positive response from the patient.

It is often useful to assess where patients are in their readiness to stop using substances, and to initiate a conversation that might lead them further in the direction of quitting (e.g., "Do you ever think about quitting? What are some of the things that get in the way? What are some of the reasons you want to quit?"). Clinical guidelines have been developed for the treatment of tobacco dependence that offer concrete suggestions on how a medical professional might approach the conversation of discontinuing substance use with patients [256].

25.6.4 Manage Pain

Pain is a problem for many patients before, during, and after treatment for HNC. As noted above, pain management may be complicated in individuals with a history of addiction. Regardless of the role the patient's lifestyle may have played in the development of the disease, *all patients deserve adequate pain management*, and medical professionals need to determine how to best provide this. In addition to medical management of pain, pain self-management and coping skills can also be taught. These include instruction in breathing techniques, imagery, progressive muscle relaxation, and other exercises to induce the relaxation response, cognitive techniques focused on restructuring the way patients think about their pain (i.e., something to be managed, rather than eliminated, reducing catastrophization and increasing acceptance), goal and activity scheduling, pacing, managing diet, sleep, and exercise, improving communication, and problem solving [257]. See Caudill [258] for a patient-centered workbook with pain management techniques.

25.6.5 Refer for More Focused Mental Health Treatment

Regardless of location or setting, most mental health providers have experience with the treatment of depression, anxiety, and suicidality. In many settings, health psychologists who specialize in addressing the interplay among physical and psychosocial issues are uniquely positioned to aid the coping of HNC patients. These providers can aid with the adjustment to facial changes, adjunctive strategies for pain management, addressing barriers to compliance, problems with intimacy, and also in the treatment of the more traditional psychological problems (depression, anxiety). Health psychologists use a variety of strategies to help patients cope with their illness and related issues, such as cognitive-behavioral techniques, motivational interviewing, relaxation and stress management training, and mindfulness techniques. Treatment does not need to involve a long-term commitment from

patients, but it can be quite useful if patients do not seem to be coping effectively on their own. It is striking that despite the psychiatric difficulties present in the HNC population, only 32% of HNC patients participate in formal psychological interventions [156].

25.7 Future Research Directions

The increasing prevalence of HPV related HNC and the decrease in heavy smoking rates in recent years has important medical and psychological implications. With rates of heavy smoking decreasing from 23.2% of the population to only 7.6% of the population in 2007 [175], the landscape of who is impacted by HNC is changing. Issues of long-term survivorship with this new group of HNC patients should receive more attention as people will live longer and will likely need to deal with more chronic problems that will impact their quality of life. Also, while the current stigma associated with HNC is centered on the use of tobacco and alcohol, the association of oral sex with HPV infection may create a new source of stigma for this next generation of HNC patients. Future research should delineate the psychological issues that are shared and also those unique to this new population.

Patients with HNC are at higher risk to experience a variety of psychological and social problems after surgery and are often in need of psychological and psychiatric services after treatment. Because of impairments in communication and physical functioning, traditional individual psychotherapy may not be easily achieved. There is a recent movement toward the development and implementation of new methods to reach populations that may not otherwise have access to services. These involve utilization of the internet, cell phones, and other types of media to better serve patients who have difficulty communicating or attending traditional treatment [259]. A recent study demonstrated the usefulness of an internet-based intervention for depressed individuals [260], and research is now focusing on methods to implement smart phone technology to assist patients with management of psychological symptoms [261]. When speech difficulties or appearance concerns make traditional avenues of seeking treatment uncomfortable or impossible, these emerging technologies could be of great use to patients coping with HNC.

25.8 Summary

A diagnosis of HNC brings many new issues and life changing events for patients – events that would challenge the coping resources of anyone. Patients typically have little knowledge about aspects of HNC, so need providers to educate and guide them as they make treatment decisions and then undergo treatment, cope with changes in their body and its functioning, and then make longer-term adjustments in their lives. Awareness of these issues and their management will enable providers to deliver suitable guidance, support, and resources to aid HNC patients and their families.

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Chapter 26
Quality of Life Issues in Research and Clinical Practice

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Abstract This chapter summarizes current knowledge related to quality of life in general and application of this knowledge to the head and neck cancer patient. People diagnosed with head and neck cancer often experience a wide range of symptoms and substantial impairment in basic human functions, such as difficulty eating, speaking, and breathing. These problems may occur as a result of the cancer and/or treatment. While many of these problems are associated with treatment and are time-limited, others may be long-lasting and irreversible. Information related to quality of life is essential for understanding the full impact of head and neck cancer and how people's lives change as a result. How to best assess quality of life in people with head and neck cancer, however, remains controversial given the lack of a gold standard for quality of life assessment. This chapter will address: (1) definitions and conceptual issues associated with quality of life; (2) factors influencing quality of life measurement, such as choosing an appropriate instrument; (3) common quality of life issues in people with head and neck cancer; (4) using quality of life information in research; and (5) using quality of life information in clinical practice.

Keywords Quality of life • Symptoms • Functional status • Functional ability

Abbreviations

CARES	Cancer Rehabilitation Evaluation System
COH QOL-CA	City of Hope Quality of Life Scale for Cancer
EORTC QLQ C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-H&N35	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Head and Neck
FACT-G	Functional Assessment of Cancer Therapy – General
FACT-HN	Functional Assessment of Cancer Therapy – Head and Neck
FLIC	Functional Living Index
HNRQ	Head and Neck Radiotherapy Questionnaire
HNQOL	University of Michigan Head and Neck Quality of Life instrument
LORQv3	Liverpool Oral Rehabilitation Questionnaire (version 3)
MOS SF-36	Medical Outcomes Survey-Short Form 36

QLI	Quality of Life Index
SIP	Sickness Impact Profile
SLDS	Satisfaction with Life Domain Scale
UW-QOL	University of Washington Quality of Life Instruments
WHOQOL-100	World Health Organization Quality of Life Questionnaire – 100
WHOQOL-BREF	World Health Organization Quality of Life Questionnaire – 26 Items brief questionnaire

26.1 Introduction

Head and neck cancer and the resulting treatment frequently results in highly distressing symptoms along with significant impairments in basic functions, such as eating, speaking, and breathing. These devastating changes in physical functioning influence all aspects of a patient's life. It is for this reason that quality of life assessment and evaluation in people with head and neck cancer is so meaningful. Although length of survival and disease free intervals are widely accepted as primary outcomes for head and neck cancer treatment, quality of life information provides patients/families and health care providers with important supplementary information to guide treatment decisions. Furthermore, understanding quality of life issues across the head and neck cancer trajectory from diagnosis and treatment through palliation/end-of-life or long-term survivorship is essential for providing quality cancer care. Quality of life information from people with head and neck cancer informs patients/families, health care providers and society how well one lives, not just how long one lives.

26.2 Defining Quality of Life

While everyone agrees that evaluating quality of life in people with head and neck cancer is essential for providing quality cancer care, how to best do this remains a question. Multiple definitions of quality of life have been published in the health care literature, although no one definition is universally accepted. Table 26.1 lists examples of quality of life definitions found in the cancer literature. One of the most frequently cited defines quality of life as "a state of well being that is a composite of two components: (1) the ability to perform everyday activities that reflect physical, psychological, and social well being and (2) patient satisfaction with levels of functioning and the control of disease and/or treatment-related symptoms" [1]. Importantly, this definition reflects two areas of theoretical agreement among quality of life experts [2]. First, the individualistic perspective is a fundamental component. This means that the individual is the most suitable judge of his/her own quality of life. Second, quality of life is a multi-dimensional concept that encompasses all aspects of life.

Table 26.1 Quality of life definitions found in the cancer literature

Author	Definitions (direct quotes)
Andrykowski et al. [3]	A multidimensional construct, incorporating information regarding individuals' current physical symptoms and general health perceptions as well as information regarding physical, emotional, occupational and interpersonal functioning
Belec [4]	The degree of satisfaction with present life circumstances as perceived by the individual
Cella and Tulsky [5]	Patient's appraisal of and satisfaction with their current level of functioning as compared to what they perceive to be possible or ideal
Ferrans and Powers [6]	An individual's perceptions of well-being that stems from satisfaction or dissatisfaction with dimensions of life that are important to the individual
Gaston-Johansson and Foxall [7]	The degree of satisfaction with present life circumstances as perceived by the individual. QOL is influenced by present as well as past and future experiences
Gotay et al. [1]	A state of well-being which is a composite of two components: the ability to perform everyday activities which reflect physical, psychological and social well-being, and patient satisfaction with levels of functioning and the control of disease and/or treatment related symptoms
Grant et al. [8]	A personal statement of the positivity or negativity of attributes that characterizes one's life
Molassiotis et al. [9]	A concept referring to the individual's own perceptions about the degree of satisfaction and ability to perform in life
Testa and Simonson [10]	The physical, psychological, and social domains of health, seen as distinct areas that are influenced by a person's experiences, beliefs, expectations, and perceptions
World Health Organization Quality of Life Group [11]	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, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships and their relationships to salient features of the environment

26.3 Conceptualizations of Quality of Life in Health Care

While most quality of life definitions in the cancer literature address the individualistic perspective and multidimensional nature of the concept, the focus or overall conceptualization of quality of life may differ substantially. The importance of understanding the underlying conceptualization of quality of life cannot be overemphasized as evaluating quality of life from different conceptualizations may lead to dissimilar and even conflicting results. For example, people with head and neck cancer may experience substantial negative changes in functional ability, and yet, report little to no change in overall life satisfaction. These conflicting results often lead to confusion; however, they may be explained by the different conceptualizations of quality of life found in the

cancer literature. Understanding the different conceptualizations is vital when considering quality of life issues and outcomes in people with head and neck cancer. Ferrans identified five of the most common conceptualizations of quality of life found in the health care literature: (1) the ability to lead a normal life; (2) the ability to lead a socially useful life; (3) the ability to fulfill personal goals; (4) feeling happy about one's life; and, (5) feeling satisfied with one's life [12]. These five conceptualizations are summarized in Table 26.2. Each conceptualization will be briefly discussed along with implications for head and neck cancer.

26.3.1 The Ability to Lead a Normal Life

The first conceptualization refers to the person's ability to lead a normal life. The closer one gets to the standard of normal, the better the QOL. One of the difficulties associated with normal life conceptualizations of quality of life is deciding upon a standard of normal. In caring for people with cancer, one standard of normal is perfect health. The closer one gets to perfect health, the better the quality of life. Another approach is to compare individuals to a reference group of healthy individuals or a typical individual of a comparable age and/or disease. Quality of life is better when one can function at a level similar to a healthy individual or a typical individual of a comparable age and/or disease. Using the individual as their own standard of normalcy is a third approach. This approach delineates changes in health status before, during, and after an illness in terms of symptoms, level of functioning, ability to return to work, etc. In this context, quality of life is better when comparisons among various time points, such as before, during, and/or after an illness, reveal few, if any, differences.

Assessing quality of life from a normal life conceptualization is a very useful approach for characterizing quality of life changes in the head and neck cancer population. Understanding deviations from perfect health are helpful when trying to determine the impact of health and neck cancer and its treatment on various aspects of life. One problem with making comparisons to perfect health is that perfect health as a standard is rarely attained by anyone, let alone someone with head and neck cancer. This makes the comparisons unrealistic as the goal of perfect health may be impossible to achieve, particularly for someone with advanced disease. More commonly, comparisons to a typical individual of a comparable age or a reference group with the same disease are considered the standard of normal. This type of comparison provides a more realistic picture of the impact on head and neck cancer on quality of life. One disadvantage to this approach is that the reference group may or may not view health in the same way. Using the head and neck cancer patient as their own standard of normal alleviates the difficulties associated with using a reference group and, at the same time, provides the needed information regarding the impact of head and neck cancer treatment on quality of life. Determining "pre-illness" criteria or expecting the patient to remember "pre-illness" health may prove difficult at least for some patients. This is particularly problematic when treatment extends over time, and the individual adapts to a new "normal." This adaptation is called "response shift."

Table 26.2 Conceptualizations of quality of life in the health care literature

Conceptualization
The ability to lead a normal life
Refers to the person's ability to lead a "normal" life
Primarily addresses deviations from normal functioning
Closer one gets to the standard of normal, the better the quality of life
Underlying conceptualization of many quality of life instruments used in the head and neck cancer population
Standard of normal varies and/or not explicitly stated (e.g., perfect health, comparable health to a defined reference group, pre-illness health)
The ability to lead a socially useful life
Refer to the patient's ability to lead a socially useful life
Focuses on the ability of the person to make contributions to society through gainful employment or fulfillment of commonly defined social such as worker, mother, teacher, etc.
Quality of life is better when the individual is able to fulfill socially useful roles
Conceptualization most often used by policy makers
Objective measures of quality of life typically fall in this category (e.g. return to work, economic impact, etc.)
The ability to fulfill personal goals
Focus is on achievement of personal goals. Relates to the congruence between desired and achieved goals
The person feels satisfied or happy when personal goals which are important to him/her are achieved
May not be culturally relevant for all groups
Goals may change over time resulting in ability to accurately assess achievement
Feeling happy about one's life
Focus is on the range of affective states from depression to euphoria
Relates to the balance between positive and negative feeling states
Those who are happier have a better quality of life than those who are unhappy
Affective states are frequently transitory and quick to fluctuate
Feeling satisfied about one's life
Refers to a cognitive assessment of life's experiences based on comparisons between desired and actual conditions of life
Those who have a better QOL are the ones who are most satisfied with their lives
Considered the most appropriate conceptualization of quality of life
Comprehensive approach to quality of life assessment in head and neck cancer patients would be measure quality of life that reflects the life satisfaction and ability to lead a normal life
Life satisfaction not likely to change as a result of life's minor inconveniences
Areas of life that are most important to individual may change over time and/or as a result of life-limiting or life-threatening illness

26.3.2 The Ability to Lead a Socially Useful Life

The ability to lead a socially useful life is another conceptualization of quality of life. This conceptualization refers to the patient's ability to lead a socially useful life. It most commonly focuses on the ability of the person to make contributions to society through gainful employment or fulfillment of commonly defined social roles

such as worker, mother, teacher, etc. Under this conceptualization, quality of life is better when the individual is able to fulfill socially useful roles. This conceptualization is more frequently used by policy makers because of their propensity to consider economic conditions of the populace. Objective measures of quality of life, such as employment status, hours worked per week, patients' perception of their ability to work, financial status, and dependence on state financial aid, are frequently used to reflect the social utility conceptualization.

There are advantages and disadvantages to using the social utility conceptualization in the head and neck cancer population. For policy makers, the ability to contribute to society during or following head and neck cancer treatment may be of particular interest. Depending on the stage of disease, people undergoing treatment for head and neck cancer may be out of work for an extended period or permanently. In addition, treating head and neck cancer can be a very costly endeavor, particularly if multimodal therapy is required. As health care dollars become scarce, policy makers may rely on information related to socially useful functions, such as potential for future employment, when considering quality of life outcomes to inform decisions regarding health care resource allocation.

There are a number of difficulties associated with using social utility definitions of quality of life in the head and neck cancer population, particularly if this is being used for allocation of health care resources. As in the normal life conceptualization, there are a wide range of meanings in terms of socially useful behavior. The difficulty is determining whose criteria of social usefulness to use; society's, the family's, the clinician's, or the head and neck cancer patient's. Moreover, social utility measurements of quality of life do not take into account the patient's perspective, violating one of the central tenets of quality of life assessment. Assessment of returning to work used alone will not adequately capture quality of life in the head and neck cancer population as the desire or ability to return to work may be influenced by a number of other variables, such as the need for frequent follow-up care with medical professionals. Being able to return to work does not necessarily result in good quality of life. Likewise, not being able to return to work does not necessarily result in poor quality of life.

26.3.3 The Ability to Fulfill Personal Goals

The third conceptualization of quality of life focuses on achievement of personal goals. It relates to the congruence between desired and achieved goals. An individual feels satisfied or happy when personal goals which are important to him/her are achieved. The person feels dissatisfaction or unhappiness when he/she fails to achieve desired goals. Fulfillment of personal goals is consistent with an individualist perspective in that it requires input from the individual. Terms like "be all that you can be" reflect its fit with American ideals of individual achievement and advancement. A major strength of this conceptualization when used with head and neck cancer patients is that it requires a personal evaluation of the life's experience

in terms of goal achievement. The head and neck cancer patient is asked to rate the degree to which he/she is able to accomplish their goals. Those who are better able to accomplish goals have a better quality of life. In terms of reliability and validity, however, it is often difficult to develop instruments that adequately measure concepts, such as quality of life, which require self-reported, subjective indicators. For some, these are considered "soft" outcomes because of the relative lack of precise measurement when compared to other objective measures typically included in cancer clinical trials, such as tumor response. Furthermore, goal achievement may not be meaningful to all individuals undergoing treatment for head and neck cancer. This inability to capture quality of life in all people from an achievement of personal goals perspective is considered a weakness of this conceptualization.

26.3.4 Feeling Happy About One's Life

Feelings of happiness represent the fourth conceptualization of quality of life. This conceptualization focuses on the range of affective states from depression to euphoria and represents the balance between positive and negative feeling states. Those who are happier have a better quality of life than those who are unhappy. Like achievement of personal goals, measurement of quality of life from a happiness perspective requires input from the individual. In Western culture, however, happiness implies a more transitory feeling; happy one moment and sad the next. As a result, quality of life from a happiness perspective may be unduly influenced by episodic events that occur throughout the course of a typical day, such as missing a scheduled appointment. Exposure to this type of event may make a head and neck cancer patient feel unhappy but it generally will not change one's overall evaluation of the quality of their life. While the benefits of happiness for head and neck cancer patients cannot be downplayed, evaluating quality of life from a happiness perspective is more likely to capture fleeting, affective states than overall quality of life.

26.3.5 Feeling Satisfied About One's Life

Satisfaction, the final conceptualization of quality of life, is closely related to happiness although they are not synonymous. While happiness implies a short-term affective state, satisfaction with life implies a long-term cognitive evaluation. Ferrans advanced the notion that quality of life is the most appropriate conceptualization for quality of life as life satisfaction requires a long-term, personal, cognitive evaluation regarding life's conditions. When viewed from this perspective, life satisfaction is conceptualized as an assessment of life's experiences based on comparisons between desired and actual conditions of life. Those who have a better quality of life are the ones who are most satisfied with their lives. An example of the differences between

the happiness and life satisfaction conceptualization may be best illustrated with an example. If a head and neck cancer patient is asked, how happy are you with …? He or she most likely will respond with information related to how they are currently feeling? They may have had a particularly trying day and they may be very "unhappy" about it. From this data, knowledge regarding an individual's current affective state is obtained. On the other hand, if a head and neck cancer patient is asked, how satisfied are you with …? They are more likely to make a cognitive judgment going beyond the here and now to consider their total life experience when answering this question. Coupling life satisfaction with relative importance of various aspects of life further enhances measurement of quality of life. Ferrans added the notion of relative importance to her definition of quality of life so that the person's sense of well-being stems from satisfaction or dissatisfaction with the areas of life that are important to him/her [6].

There are similar strengths and weaknesses in terms of using the happiness and satisfaction conceptualizations for assessment and evaluation of quality of life in people with head and neck cancer. Measurement of happiness and satisfaction requires input from the individual, thus, both are consistent with an individualist perspective. While this is a recognized strength, it may also represent a weakness as reliance on self-reported quality of life information makes it more difficult to establish reliability and validity compared to using data obtained from objective measures. Even so, appreciation for the full impact of head and neck cancer on the individual's quality of life can only be obtained with direct input from the individual necessitating the use of self-report measures.

26.3.6 Summary of Quality of Life Conceptualizations

Choosing the appropriate conceptualization for use in use in the head and neck cancer population is dependent upon the reason for the evaluation. In general, all of the conceptualizations provide very useful although different, quality of life information. The life satisfaction conceptualization, however, is the most appropriate to use when evaluating quality of life with head and neck patients as it captures the individual's cognitive evaluation of life's experience. Measurement of quality of life from a life satisfaction perspective promotes the recognition of uniqueness and diversity among individuals (regardless of culture) in terms of perception of quality of life. The satisfaction conceptualization recognizes that quality of life is a dynamic rather than a static concept. Because life's goals are frequently altered following the diagnosis and treatment for head and neck cancer, assessing and evaluating quality of life from a satisfaction conceptualization allows one to capture the patient's changing values. In many situations, however, there is a strong need to determine life satisfaction as well as deviations from normal functioning. In these cases, assessing quality of life from the life satisfaction and ability to lead a normal life conceptualizations provide the most comprehensive approach.

26.4 Conceptual Frameworks

As the concept of quality of life has evolved over the past 40 years, the need for theoretical frameworks to guide the assessment and evaluation of quality of life in research and clinical practice has become increasingly important. Two frequently used models to guide quality of life research and clinical practice in people with cancer include Ferrell and colleagues City of Hope Model [13] and Ferrans and Powers Quality of Life Model [14]. These models define the domains of quality of life that are important for all individuals, including people with cancer, and address specific areas of life that should be addressed when collecting information regarding quality of life. The models are remarkably similar. Both view quality of life from an individualistic perspective and as a multidimensional construct. The Ferrans Model consists of four domains; health and functioning, socioeconomic, psychological/spiritual, and family domain. The Ferrell Model consists of physical well-being and symptoms, psychological well-being, social well-being and spiritual well-being. The aspects of life that are addressed by each model are listed in Table 26.3. The fact that these models were developed simultaneously and independently of one another provides substantial support for the theoretical underpinnings of both models.

When reviewing the literature for guidance on quality of life assessment and evaluation, it becomes readily apparent that a wide range of variables have been used to represent quality of life, particularly in individuals diagnosed with a life-changing disease like cancer. The range of variables includes symptoms, changes in functional status, life satisfaction, etc. For the novice clinician and researcher, this lack of a gold standard for assessing quality of life can be confusing and overwhelming. The Revised Wilson and Cleary Conceptual Model of Patient Outcomes provides a conceptual framework for approaching quality of life assessment [15, 16]. This model is particularly useful for clarifying various health outcomes that have been used to measure quality of life, including those associated with head and neck cancer. This model examines the relationship between constructs, such as symptoms, functional status, and quality of life, and provides conceptual clarity for assessing and evaluating a range of variables that are commonly included under the umbrella term, quality of life.

The Wilson and Cleary Model proposes the dominant, causal relationships between traditional, biological and physiological variables to health-related quality of life [15, 16]. The five types of health outcomes include (a) biological function; (b) symptoms; (c) functional status; (d) general health perceptions; and e) quality of life. While an extensive review of all patient health outcomes associated with head and neck cancer is beyond the scope of this chapter, providing examples within each of the Wilson and Cleary categories is desirable to further illustrate the usefulness of the model. Clarity about how each aspect of the model relates to quality of life in the head and neck cancer population is needed to advance science.

Outcomes measures of biological function is a term that refers to the assessment of cell function, organ function, and organ system function. Examples of biological

Table 26.3 Comparison of Ferrell and Colleagues City of Hope Model [13] and Ferrans and Powers Quality of Life Model [14]

Ferrell model (Multiple adaptations available)	Ferrans model
Physical well-being and associated symptom	Health and functioning domain
Functional ability	Health
Strength/fatigue	Health care
Sleep and rest	Pain
Nausea	Energy (fatigue)
Appetite	Ability to take care of yourself without help
Constipation	Control over life
	Chances for living as long as you would like
	Sex life
	Ability to take care of family responsibilities
	Usefulness to others
	Worries
	Things for fun
	Chances for a happy future
Psychological well-being	Psychological/spiritual subscale
Anxiety	Peace of mind
Depression	Faith in God
Enjoyment/leisure	Achievement of personal goals
Pain distress	Happiness in general
Happiness	Life satisfaction in general
Fear	Personal appearance
Cognition/attention	Self
Social concerns	Social and economic subscale
Roles and relationships	Friends
Affection/sexual function	Emotional support from people other than your family
Appearance	Neighborhood
	Home
	Job/Not having a job
	Education
	Financial needs
Spiritual well-being	Family subscale
Suffering	Family health
Meaning of pain	Children
Religiosity	Family happiness
	Spouse, lover, or partner
	Emotional support from family

function that may be assessed in people with head and neck cancer include blood pressure, heart rate, and liver function tests. *Outcome measures of symptoms* refers to the subjective experience and cognitive evaluation of the individual as a whole to changes in biological function. Fatigue, pain, and dysphagia are examples of symptoms commonly assessed to evaluate the impact of head and neck cancer and associated treatment. *Outcome measures of functional status* assess the individual's ability to objectively perform functional tasks. One primary goal of head and neck cancer therapy is to preserve as much function as possible of nearby nerves, organs, and

tissues; therefore, including tests to assess functional status is of prime importance. Examples of functional outcomes include the ability to speak or swallow. *General health perceptions* refer to the individual's evaluation of functional ability or health status. Examples that may be associated with head and neck cancer include perceived ability to eat, swallow and speak clearly. *Overall quality of life outcomes* refers to the individual's cognitive judgment of well being and life satisfaction. Life satisfaction or satisfaction with health and functioning are examples of overall quality of life outcomes that can be measured in conjunction with an exercise program.

These patient health outcomes range along a continuum of increasing biological, social, and psychological complexity. The biological and physiological outcomes anchor one end of the continuum with the more complex and integrated measures of patient outcomes, such as quality of life, at the other end. As one moves along the continuum, there are an increasing number of individual and environmental contributory influences on patient outcomes that may not be under the control of the health care provider. This model is particularly useful for researchers and clinicians working with head and cancer patients as it provides guidance for examining and predicting relationships among symptoms, functional status and quality of life. Identifying predictors may help patients and providers with health care decisions. If the ultimate outcome of quality cancer care is improvement in quality of life, then understanding these relationships is essential for developing effective interventions.

26.5 Qualify of Life: Relationships Between Symptoms, Functioning, and Life Satisfaction

The relationships among symptomatology, functioning, health status perceptions, and life satisfaction are complex, with individual and environmental factors influencing expectations. People with head and neck cancer are told by their health care providers to expect changes in their health status as a result of the disease itself or treatment of the disease. A timeframe to expect anticipated side effects is generally provided. For example, patients receiving treatment for head and neck cancer are typically informed to expect difficulty with swallowing when receiving radiation to the oropharyngeal area. Problems with quality of life, however, may arise when reality and expectations differ substantially. Consider the hypothetical case of a head and neck cancer patient with dysphasia. During the course of radiation and immediately following treatment, this patient expects to have difficulty swallowing, thus, quality of life (in terms of life satisfaction) may not be impacted as this is an expected side effect. If the patient recovers faster than he or she expected, improvements in life satisfaction may follow. If slower, then the patient may report declines in life satisfaction. Thus, a lag time may exist between experiencing actual changes in health status and assimilating these changes into an appraisal of one's quality of life. Recent literature in other cancer populations support this notion and the same may be true for people with head and neck cancer [17].

26.6 Quality of Life Measurement

26.6.1 Unidimensional Versus Multidimensional

Ideally, the measurement of quality of life should reflect the underlying conceptualization. Early attempts to measure quality of life, however, were often atheoretical and frequently consisted of instruments that measured only one aspect or domain of quality of life. These are referred to as unidimensional quality of life instruments. Examples of unidimensional quality of life instruments used to assess quality of life in head and neck cancer include the Karnofsky's Performance Index and the Kubrod Performance Scale. These two instruments primarily measure functional status or ability to perform activities of daily living. Over the past three to four decades, however, significant progress in QOL research has been made. Quality of life experts now agree that quality of life is a multidimensional concept consisting of at least the physical, psychological, and social domains. Thus, in order to ensure comprehensive assessment of quality of life, the physical, psychological, and social domains must be measured. Sole reliance on a unidimensional instrument to measure quality of life is considered unacceptable. Furthermore, studies that exclusively rely on a unidimensional instrument to measure QOL are deemed inadequate as the instrument may fail to detect QOL changes in other domains that are of central importance to the individual's quality of life appraisal.

The multidimensional nature of quality of life is well supported in the head and neck cancer literature. The most frequently identified domains include the physical/functional, psychological/emotional, social, economical, and family domains. Measuring the multiple domains associated with quality of life allows the clinicians and researchers to pinpoint problematic areas as well as identify areas of strength for the patient. Researcher and clinicians may use a battery of instruments to measure the various quality of life domains or a single instrument that assesses various domains. More commonly, studies use single quality of life instruments that contain items reflecting the various domains or aspects of life. Examples of single, multidimensional instruments frequently used in the head and neck cancer literature include the FACT [18], EORTC-QLQ C-30 [19], and the SF 36 [20]. A listing of single instruments and the domains that are measured are included in Table 26.4. It should be noted, however, that these instruments reflect different conceptualizations of QOL, thereby producing different results even when used in the same group of patients in the same study.

One troublesome area in quality of life research relates to determining the relative importance of specific domains to the overall quality of life appraisal. Are all domains equally important when appraising QOL? It appears, at least, for some people that the importance of each domain will vary from individual to individual. Furthermore, the domains may vary in importance in one individual at different points in time. How to rectify weighting of the domains is a recognized problem in quality of life research. One approach to resolve this issue is to have the individual weight the importance of the various domains or individual aspects of life. Although

Table 26.4 Examples of quality of life instruments

Instrument	Domains measured	Mode of administration
Generic measures		
Cantril's Self-Anchoring Scale [21] (1 item)	Global uni-dimensional	Self-administered
Karnosky Performance Scale [22] (1 item)	Functional status	Observer rated
MOS SF-36 [20]	Physical functioning Role functioning Bodily pain General health Vitality Social functioning Role emotional Mental health	Computer-administered Electronic version IVR-version Interviewer-administered Self-administered Telephone-administered
SLDS [23] (18 items)	18 items related to relationships, health, appearance, leisure time, ability to eat, physical strength, and BMT	Self-administered
SIP [24] (136 items)	Physical dimension Psychosocial dimension Sleep and rest Taking nutrition Usual daily work Household management Leisure Recreation	Interviewer-administered Self-administered
WHOQOL-100 [25] (100 items)	Physical health Psychological health Level of independence Social relations Environment Spirituality/religion/personal beliefs	Self-administered
WHOQOL-BREF [26] (26 items)	Physical health Psychological Social relationships Environment	
Zubrod Performance Scale [27] (1 item)	Functional status	Observer rated
Cancer-specific measures		
CARES [28] (91–132 items)	Global HQOL scale Five summary scales Physical Psychosocial Marital Medical interaction	Self-administered

(continued)

Table 26.4 (continued)

Instrument	Domains measured	Mode of administration
	Sexual	
	31 Subscales measuring everyday functioning	
COH, QOL-CA [29] (28–30 items; different versions)	Physical well-being and symptoms	Self-administered
	Psychological well-being	
	Social well-being	
	Spiritual well-being	
	Single item global measure of QOL	
EORTC QLQ C-30 [19] (30 items)	Five functional scales	Self-administered
	Physical functioning	Telephone interview
	Role functioning	
	Emotional functioning	
	Cognitive functioning	
	Social functioning	
	Multi-item symptom scales	
	Fatigue	
	Pain	
	Nausea and vomiting	
	Global quality of life/health status scale	
	Six single item questions	
FACT-G [18] (28 items)	Physical well-being	Interviewer-administered
	Function well-being	Self-administered
	Social/Family well-being	
	Emotional well-being	
	Satisfaction with doctor/patient relationship	
FLIC [30] (22 items)	Current health	Self-administered
	Role	
	Sociability	
	Emotional	
	Pain	
	Nausea	
	Hardship due to cancer	
QLI [6] (35 items related to satisfaction) (35 corresponding items related to importance)	Health and functioning	Self-administered
	Psychological/spiritual	
	Social and economic	
	Family	
Head and neck cancer-specific		
EORTC QLQ-H&N35 [31] (35 items)	Pain	Self-administered
	Swallowing	
	Senses problems	
	Speech problems	

(continued)

Table 26.4 (continued)

Instrument	Domains measured	Mode of administration
	Trouble with social eating	
	Trouble with social contact	
	Less sexuality	
	10 single item questions	
FACT-HN [32] (11 items)	Head and neck specific module that can used alone (FHNSI) or in conjunction with FACT-G	Interviewer-administered Self-administered
UW-QOL [33] (15 items)	12 items specific to head and neck	Self-administered
	3 general questions	
HNQOQL [34] (20 items)	Pain	Self-administered
	Communication	
	Eating	
	Emotion	
HNRQ [35] (22 items)	Oral cavity	Self-administered
	Throat	
	Skin	
	Digestive function	
	Energy	
	Psychosocial function	
LORQv3 [36] (25 items)	Oral function	Self-administered
	Dentation	

this would appear to solve the problem, weighting the importance of the various domains is a cognitively difficult task. In our work, many individuals find this difficult to do and weight most if not all items equally (unpublished data).

26.6.2 Global Measures

Global measures of quality of life have been used in the head and neck cancer literature. Global ratings of quality of life refer to those measures that result in one score representing overall quality of life. An example of a single item, global measure of quality of life is Cantril's Self-Anchoring Scale [21]. This particular scale asks respondents to rate their quality of life based on a 10 point scale with the endpoints anchored by the best and worst quality of life they can imagine. The advantage to using a global measure is that it takes into account the patient's values. The interactive nature of the various quality of life domains is implicitly understood. The disadvantage to using a global measure relates to its specificity. For clinicians and researchers who plan to test interventions to improve quality of life, it will be important to determine which dimensions of quality of life stay the same, improve, or deteriorate over the course of treatment for head and neck cancer. For this reason, a global measure, used alone, may not be the most suitable approach.

26.6.3 Generic Measures

Generic measures of quality of life attempt to provide a comprehensive measure of all quality of life domains. These instruments have commonly been developed to measure quality of life in the general population. They have also been used in a variety of illness groups including head and neck cancer patients. The SF-36 is an example of a quality of life instrument developed for use in the general population that has been used in head and neck cancer patients. The advantages to using a generic instrument are that it allows one to make quality of life comparisons with the general population as well as across illness groups. This is particularly helpful when trying to evaluate the impact of a cancer therapy. The disadvantages of using a generic tool relates to its sensitivity. Because such a broad approach to measuring quality of life is required, the instrument may not be sensitive enough to detect specific changes in quality of life that are directly impacted by head and neck cancer or the various treatments.

26.6.4 Cancer-Specific Measures

In the head and neck cancer literature, many studies evaluating quality of life rely on cancer-specific quality of life instruments. These instruments generally emphasize quality of life issues that are most pertinent to the diagnosis of cancer, treatment of the malignancy, and potential side effects. Most of these instruments contain items related to the physical, psychological, and social domains, at a minimum. Additional domains, such as the spiritual domain, are tool specific. Because of the focus on cancer, these tools tend to be more sensitive to treatment effects and changes in particular conditions such as fatigue and dysphagia. On the other hand, use of a cancer-specific tool may be so specific that it misses critical aspects of the patient's life, not associated with cancer and/or treatment, that impact quality of life perception. The recommended approach, in terms of choosing a generic versus cancer specific tool in the head and neck cancer population, would depend on the reason for the quality of life assessment, whether for research or clinical practice. In general, the safest approach would be to choose an instrument that is generic enough to cover broad aspects of the patient's life and specific enough to detect changes related to the head and neck cancer and subsequent treatment.

26.6.5 Head and Neck Cancer-Specific Measures

Like most cancers, the clinical manifestations of the malignancy and associated treatment side effects depend on the anatomical location of the disease. Likewise, head and neck cancer-specific quality of life instruments target the unique concerns of head and neck cancer patient that are likely to be affected by the cancer and/or

treatment. For instance, difficulty with swallowing and chewing, are problems that are more likely to occur in someone with head and neck cancer as opposed to an individual with colon cancer. Head and neck cancer-specific instruments will primarily contain items that are unique to head and neck cancer. A number of well-established head and neck cancer-specific quality of life instruments exist, such as the Functional Assessment of Cancer Therapy – Head and Neck (FACT – H & N), and the University of Michigan Head and Neck Quality of Life Questionnaire. The major advantage to using a site specific instrument is the ability to determine the nature and severity of commonly occurring health issues that are specific to head and neck cancer. These issues are unlikely to be address by a more generic instrument. This disadvantage to only using a head and neck cancer-specific instrument is that comparisons to the general public or even other cancer populations will not be possible. Depending on the reason for the quality of life assessment, one approach to ensure a comprehensive assessment would be to include a generic instrument in order to make comparisons to the general public and a head and neck cancer-specific instrument so that the unique concerns of head and neck cancer patients would be adequately captured.

26.6.6 Proxy Measures

There may be times when the head and neck cancer patient is unable to provide quality of life information, yet, judgments regarding the head and neck cancer patient's quality of life are needed. In these cases, information regarding the head and neck cancer patient's quality of life may be sought from other closely related individuals, such as the spouse, treating physician, etc. These "proxy measures" must be used with extreme caution. When considering the use of proxy measures, the question becomes whose values are important to the quality of life evaluation? Is it the patient's, the physician's, or is it the spouse's values that are important? Different people value different things. What is important to one person may or may not be important to another. As the individual is the only appropriate judge of his/her own quality of life, there may be wide discrepancies when a proxy measure is used. Some studies have documented that observers frequently assign lower scores to the patients' quality of life than the patients did themselves. These finding do not mean that the proxy measures are not important or valid [37, 38]. Rather, they are important because they represent the proxy's point of view in terms of the head and neck cancer patient's quality of life. If it is the head and neck cancer patient's point of view that is important, then it is the individual's perspective which should be sought. Unfortunately, there may be times when this is not possible and a proxy assessment of quality of life is the only option. In a study of 116 recurrence free patients with laryngeal, pharyngeal, and oral cavity cancer following radiotherapy or surgical treatment, an observer rater toxicity scale (DAHANCA toxicity score) effectively assessed objective treatment-induced toxicity but severely underestimated patient complaints [39].

26.6.7 Recall or Observation Period

Another important factor to consider when assessing quality of life is the recall or observation period. The recall or observation period should be driven by the purpose of the quality of life assessment in head and neck cancer patients. Treating healthcare providers interested in determining changes in quality of life following an aggressive chemotherapy protocol may require more frequent assessments with shorter recall periods to capture treatment effects. Conversely, a researcher interested in long-term effects of head and neck cancer treatment may opt for less frequent assessment with longer recall periods. While there is no gold standard for recall or observation periods associated with assessing quality of life in people with head and neck cancer, clinicians and researchers must carefully consider the recall period so that the chances of detecting quality of life changes are enhanced.

Retrospective assessments of quality of life are the norm; yet, there are a number of issues associated with recall bias that should be considered. Recall bias occurs when people are asked to recall events or experiences that have occurred in the past. The memory of the event or experience is distorted due to cognitive restructuring [40]. In the head and neck population, cognitive restructuring potentially impacts the ability to provide accurate quality of life information. Multiple factors influence the reconstruction of memories, such as length of time since the event/experience, whether the event/experience was anticipated, and novelty of the event/experience [41, 42]. For example, a head and neck cancer patient who has been relatively pain-free but experiences one short-lived episode of extreme pain is likely to be more heavily influenced by the acute, short-lived episode of pain rather than the relatively pain-free periods. This is particularly true if the short-lived painful episode occurs immediately prior to completing a self-report questionnaire. Individuals simply do not add up the number of painful episodes, incorporate intensity ratings, and then average them over time to produce a summary of the experiences of the past week.

More recently, greater attention has been paid to collecting real-time assessments of patient reported outcomes, such as symptoms and quality of life, to reduce the problems associated with recall biases. Ecological momentary assessment is a methodological approach for capturing repeated real-time data in a naturalistic environment. Because people respond in real time, the problems with recall biases and summarization processes are minimized [43]. The three components of ecological momentary assessment (real-time data collection) include (1) studying people in their natural environment, (2) collecting information regarding the person's immediate or near immediate state, and (3) sampling the phenomena under study multiple times throughout the course of the day. In recent years, advances have been made in methods for collecting information on patient-reported outcomes, such as quality of life. Several studies have demonstrated the feasibility of using computerized programs for the self-report of symptoms during scheduled clinic visits or at home, providing support for this approach [44–46].

26.6.8 Psychometric Properties of Quality of Life Instruments

As quality of life is self-reported construct, there are a number of factors, specifically related to the instrument itself, that impact the interpretability of the results. These psychometric properties are considered essential elements for determining the quality of an instrument. Reliability and validity are generally considered the most important properties for self-reported data. Reliability refers to whether an instrument consistently measures a construct, such as quality of life, over time, as well as across individuals, groups, and/or situations. Validity refers to whether an instrument measures what it is intended to measure. The vast majority of frequently used quality of life instruments employed with the head and neck cancer population are well-established in terms of reliability and validity. For clinicians and researchers developing a new instrument to collect this data, however, these properties must be determined prior to interpreting the results. The Patient Reported Outcome and Quality of Life Instruments (PROQOLID) contains information regarding 700+ quality of life instruments, including information regarding psychometric properties and available translations [47].

26.6.9 Determining the Appropriate Mode of Administration for Assessing Quality of Life

The explosion in technology has broadened the approaches used to assess, collect, and report quality of life outcomes. These advances, such as smart phones, personal digital assistants (PDAs), interactive voice response (IVR) systems, computers and the Internet, have made it possible to collect data from head and neck cancer patients that previously may not have been accessible. Platforms for collecting QOL data now include (1) paper and pencil based instruments; (2) telephone-based; (3) computer-based; or, (4) web/Internet-based platforms [48]. The vast majority of quality of life instruments are paper and pencil based although more and more of these are being converted so that they can be administered via other platforms. Telephone-based technology uses computer applications to gather quality of life information through land-lines or cellular phones. Interactive Voice Response systems are one example of telephone-based technology that can be used to collect quality of life information. Computer-based technology collects quality of life data through computerized applications installed on stand-alone computer devices allowing the individual of interest to directly input their own quality of life information. This can occur in a variety of locations, such as the health care providers' office or a clinic examination room. Web/Internet-based technology collects QOL information directly from the person of interest through a web-based program accessed on an Internet-ready computerized device. This approach offers even wider accessibility as patients are able to input quality of life data from any location that has internet availability, such as the patient's own home or even via a smart telephone.

The various modes of administration (paper and pencil, telephone-based, computer-based, and web/internet-based) share several parallel benefits, such as the ability to choose a language and formatting options for the delivery of questions. The technology-based approaches offer some additional benefits that may be particularly attractive for use in people with head and neck cancer. For example, all of the technology-based approaches have the ability to send medical alerts to the health care providers if programmed to do so. This is particularly helpful if quality of life information is being collected for clinical purposes. A predetermined threshold for notification may be set by the health care providers. Head and neck cancer patients who cross the threshold are able to immediately notify the provider of adverse events and potentially initiate treatment for the problem earlier. For instance, the head and neck cancer patient may be experiencing severe pain. Notifying health care providers in real-time potentially accelerates access to treatment as opposed to waiting for a clinic visit. In addition, each technology-based category has several distinct advantages that are particularly helpful for assessing and evaluating quality of life information in head and neck cancer patients. Telephone services (either land-lines or cellular) have widespread availability making telephone-based technologies highly accessible to almost all people. For those head and neck cancer patients that have difficulty speaking, using the keypad to enter quality of life information further improves accessibility. Computerized devices are manufactured in a variety of shapes and sizes, making this category highly flexible for meeting the needs of broad categories of people. Quality of life outcomes in head and neck patients may be collected and stored on smart phones, tablets, PDA's, or even wrist actigraph devices with subjective event markers. Accessibility of these computerized applications to collect quality of life data is further enhanced when applied to web/internet based approaches. Web/Internet based technology has the capacity to reach diverse populations in a variety of geographic locations. This is particularly helpful for collecting quality of life information from head and neck cancer patients who are engaged in research studies. In addition, computer- and internet-based technologies allow for audio as well as visual cues when collecting quality of life information which may be particularly helpful for head and neck cancer patients who experience functional deficits that impact their ability to hear or see. While these various modes of collecting quality of life information improve the ability to access this data, choosing the appropriate mode of administration primarily depends on the reason for collecting this information in the first place.

26.7 Common Quality of Life Issues in People with Head and Neck Cancer

Head and neck cancer is a relatively uncommon malignancy, yet, attracts a substantial amount of quality of life research interest due to the myriad of structural, functional, and cosmetic sequelae associated with the disease and/or treatment [49]. A recent search of PubMed using the search terms, "quality of life" and

"head and neck cancer" revealed over 3,500 research articles. While significant progress related to understanding quality of life in head and neck cancer patients has been made, a number of issues impede progress and impair our understanding. Small sample sizes, including patients with diverse stages of head and neck cancer as well as disease sites in the same study, cross-sectional as opposed to prospective, longitudinal assessments of quality of life, and lack of a gold standard to measure quality of life hinder interpretation of quality of life findings in head and neck cancer. Even so, general statements regarding changes in quality of life following the diagnosis and treatment of head and neck cancer are possible although these may not be applicable to all patients, across all disease sites and stages. Specific information related to the effects of a particular type of head and neck cancer on quality of life requires an in-depth analysis of the current research findings. More importantly, the impact of head and neck cancer on quality of life is more closely associated with the stage and site of the disease [50]. For example, the effects of a stage 1 laryngeal cancer on quality of life may be substantially different than the effects of a stage 4 anterior floor of mouth cancer. The time immediately following diagnosis can be very stressful as people with head and neck cancer and their families speculate about the potential changes that the diagnosis will make on their lives. Providing specific information regarding expected changes in symptoms and functional status may reduce anxiety and ultimately improve patient satisfaction and overall quality of life [51].

26.7.1 Overall Quality of Life

Like other cancers, a general trajectory of changes in quality of life can be expected following the diagnosis and treatment for head and neck cancer. Overall, quality of life can be expected to decline immediately following the initiation of cancer treatment, whether the treatment includes surgery, radiation therapy, or chemotherapy [49]. This decline is associated with increased symptoms and decreased functional status [52, 53]. Following completion of treatment, however, many symptoms associated with treatment should start to resolve, although not all symptoms will completely disappear and some may become worse [54]. For example, problems with teeth, dry mouth, and sticky saliva became worse over time, between diagnosis and 5 years after diagnosis, in one longitudinal study of people with pharyngeal cancer [55]. While patients with head and neck cancer should expect some improvements in functional status following completion of therapy as a result in improvements in symptoms, many patients face long-term functional problems [56]. Improvements in functional status will primarily depend on the cause of the problem, whether the problem is reversible or irreversible, and availability and implementation of rehabilitative interventions. Even with the expected increase in symptoms and decreases in functional status in the first year following diagnosis, many patients report improvements in quality of life as compared to baseline level 12 months following treatment [57–59]. Again, a word of

caution is necessary as people with head and neck cancer may have been experiencing problems at the time of diagnosis so a return to baseline as measured at the time of diagnosis may not truly reflect a return to normal functioning [60]. Long-term, people with head and neck cancer may continue to experience problems for years following treatment, although this too will depend on the disease site and stage, treatment, and co-morbid conditions [61, 62].

26.7.2 Physical Domain

Changes in health status and physical functioning in patients with head and neck cancer may result from the underlying cancer or from the subsequent treatment with surgery, radiation, chemotherapy and/or the multimodal therapy. The major complications and side effects associated with each therapy are detailed in the respective chapters of this textbook. From a quality of life perspective, the complications and problems that are likely to impact the physical domain include problems with eating, swallowing, speech and communication, taste, breathing particularly if a tracheotomy or laryngectomy is required, skin and mucous membrane integrity, changes in the consistency and amount of saliva and mucous, as well as changes in physical appearance. The relative impact on quality of life is generally associated with severity of symptoms although other factors, such as intrinsic coping mechanism may play a role [63]. In addition to these site specific changes, patients may experience a range of systematic issues, such as fatigue, that further diminish quality of life [64]. While this is not a comprehensive list, items related to these problems will typically be included on a head and neck specific quality of life instrument. The impact that symptoms and other associated problems have on physical functioning has important consequences for quality of life outcomes in head and neck cancer patients. In cross-sectional study of head and neck cancer patients who had received definitive or post-operative radiotherapy +/− chemotherapy for head and neck cancer, treatment modality significantly impacted physical and cognitive functioning, while disease stage significantly affected global quality of life [65]. In addition, pretreatment functioning may be predictive of post treatment physical morbidity as seen in one prospective study of head and neck cancer patient with a variety of disease sites [66]. In this study, pretreatment performance status predicted post treatment morbidity. The ability to accurately predict those at risk for developing adverse outcomes prior to the start of treatment may have important therapeutic implications particularly if rehabilitative efforts are employed early to mitigate some of these effects.

26.7.3 Psychological Domain

There is substantial interest in the psychological impact of head and neck cancer and subsequent treatment. Numerous studies have detailed the prevalence and severity

of psychosocial effects. Psychological issues range from anxiety and depression to changes in body image. It is likely that these psychological factors are inter-related in a wide variety of situations and depend on the disease site and stage as well as the amount of disfigurement associated with the disease and treatment. To illustrate, anticipation of disfiguring facial surgery has been associated with extremely high levels of anxiety [67]. Likewise, successful reintegration of body image following disfiguring surgery is a crucial component of bolstering quality of life. A number of factors, such as gender, may influence the role that psychosocial functioning has on quality of life. Males and females may respond differently to disfiguring surgery. While both men and women with greater levels of disfigurement experience more depression, social support appears to buffer the impact of greater levels of disfigurement on well-being for women but not for men [68]. A thorough review of the psychological impact of head and neck cancer is found in the respective chapter of this textbook.

26.7.4 Social Domain

There are a wide range of potential social implications of head and neck cancer. Issues related to the social domain include role functioning, employment, social functioning, belong to groups, etc. A number of factors associated with head and neck cancer impede social functioning, like the inability to speak or speak clearly. Following treatment, head and neck cancer patients often report impaired social functioning [69]. For example, head and neck cancer or the treatment of cancer may negatively impact employment status. In one study, over 35% of those patients who were employed changed jobs primarily due to the discomfort caused by the head and neck cancer treatment [70]. Others may not be able to return to their line of work due to changes in functional abilities. An individual who relies on verbal communication as a requirement for their job may no longer be able to perform the job duties if their ability to speak has been significantly altered. As people are living and working longer, rehabilitative efforts directed toward employability following head and neck cancer treatment are needed especially for those who are no longer able to continue in their current profession but are cured of the underlying disease. Like the physical and psychological domain, disease site and stage as well as treatment received impact the head and neck cancer patient's social function [61]. People with head and neck cancer often rely on sources of social support during the treatment phase to cope with activities of daily living. At least some patients, however, report that perceived social support decreased from pre to post treatment even though it seems likely that this is the time when the support is most needed [71]. Head and neck cancer can be associated with a high caregiving burden particularly for those that are elderly and/or have more advanced disease. The high caregiving burden may result in high unmet supportive care needs, particularly if sources of social support were strained prior to diagnosis [72].

26.8 Using Quality of Life Information

26.8.1 Using Quality of Life Information in Research

While conducting quality of life assessments for clinical practice is becoming more commonplace, most formal assessments are conducted for research purposes. For this reason, most quality of life information published in the head and neck cancer literature has been gathered from research studies. These studies are significant because they focus on real world concerns of head and neck cancer patients and build knowledge in terms of providing a better understanding of the problems experienced by patients as well as identifying patients who may be at greater risk for problems. In order for society to benefit from knowledge related to quality of life in head and neck cancer patients, the assessments must be conducted in a research setting in order for the knowledge to be generalizable to other like patients.

Quality of life studies in head and neck cancer fall into three broad categories; to describe and/or predict quality of life, compare quality of life outcomes in treatment trials, and/or to test the effectiveness of supportive care interventions. Specifically, information discovered from quality of life studies may be used to (1) compare quality of life outcomes in clinical trials that examine the effectiveness of a new treatment to a standard treatment; (2) compare quality of life outcomes when both treatments are equivalent in terms of survival, and quality of life outcomes may influence decision making; (3) to determine the short- and long-term impact of head and neck cancer and/or specific treatments on quality of life; (4) identify factors that predict quality of life outcomes; (5) to identify quality of life outcomes that predict survival; (6) identify, prioritize, and develop interventions for problems that significantly impact the head and neck cancer patient's ability to comply with planned treatment; and (7) test interventions that enhance supportive care throughout the head and neck cancer care continuum.

Researchers must consider a number of factors when designing a quality of life study for people with head and neck cancer. The first and most important issue is to clearly determine the purpose of the study. All other research design decisions flow directly from the purpose of the study. The second issue to consider is the selection of an instrument to measure quality of life. Table 26.5 lists examples of questions that researchers may consider prior to selecting an instrument. Most importantly, the quality of life instrument must be reliable, valid and able to provide the information that the investigator needs to address the research question. No single quality of life instrument can adequately address all research questions across all head and neck cancer populations. For instance, a instrument that is appropriate for use when studying the long-term consequences of head and neck cancer treatment may not be appropriate for use when examining the short term consequences of head and neck surgery. On the other hand, it may be helpful and even necessary to use the same instrument across all assessment points when conducting a longitudinal study to describe QOL trends post transplant.

Table 26.5 Selecting a quality of life instrument to use in the research setting

Examples of questions to consider when selecting a quality of life instrument for head and neck cancer patients
Research
Should a generic or a cancer-specific, or head and neck cancer-specific instrument be used?
What aspects of life does the instrument address? Head and neck specific issues? Treatment issues?
Does the instrument provide the information needed to address the research questions?
Is there consistency between the research question and underlying conceptualization of the instrument? Is there agreement between the conceptual and operational definitions?
Does the instrument have established psychometric properties? Reliability? Validity?
What type of scores does the instrument provide? Overall quality of life? Domain or subscales scores? Both?
How many items are included in the instrument?
How long does it take to complete the instrument?
How will the instrument be administered? Paper and pencil? Telephone administration? Computer administration? Internet administration?
Given the head and neck cancer patient's expected health status, is it likely that the patient will be able to complete the instrument in a timely manner?
How often will the instrument be administered?
Is the instrument responsive to changes in the head and neck cancer patient's condition?
Is the instrument sensitive enough to reflect true changes in the head and neck cancer patient's condition?
Can clinicians easily interpret the research findings obtained from the instrument?

As illustrated earlier in the chapter, choosing a quality of life instrument has multiple implications related to the interpretability and generalizability of research findings. While designing a perfect study to examine quality of life in head and neck cancer is nearly impossible, researchers must attempt to minimize the limitations. Several research design decisions specifically related to quality of life deserve special mention. There must be a clear link between the research purpose and design. A longitudinal design adds strength to a quality of life study in that it allows changes in the physical, psychological, and social domains to be examined at various important time points, such as the prior to treatment, completion of treatment, 1 year post diagnosis, and so on. In additional, a longitudinal approach as opposed to a cross-sectional design adds power to the study as subjects serve as their own control while controlling for extraneous variables. The primary disadvantage to using a longitudinal approach is that these designs are costly, lengthy, and patient attrition may be a problem. Importantly, subject burden must be minimized to ensure continued participation in the study. Head and neck cancer patients frequently experience a wide range of stressors, particularly during the treatment phase when quality of life outcomes are particularly salient for determining the impact of treatment. Making a conscious effort to collect enough information to address the quality of life research question needs to be balanced against overburdening the subject with unnecessary questionnaires. Finally, careful attention must be paid to sample selection. Because head and neck cancer is relatively rare, there may be a tendency to group patients

together in one quality of study regardless of disease site and/or stage. This is particularly true for single site studies when large numbers of head and neck cancer patients are not available as potential subjects. Given the heterogeneity of potential complications associated with the various head and neck disease sites, the ability to find statistical significant findings may be hampered with a heterogeneous group of head and neck cancer patients. Every attempt should be made to limit the sample to comparable head and neck cancers and/or stages of disease to recruit a more homogeneous sample, thus, improving the likelihood of finding statistical significance.

26.8.2 Using Quality of Life Information in Clinical Practice

Quality of life questionnaires can be used in clinical practice to facilitate communication and identify problems in people with head and neck cancer that otherwise might go undetected. Unfortunately, the criteria to select a quality of life instrument that is appropriate for clinical practice are not as clear. No one quality of life instrument will satisfactorily capture all the necessary information to address all clinical practice needs. Different situations may call for different QOL tools. Clinicians require instruments that can be readily administered, scored, and interpreted. Many instruments, however, may be burdensome, particularly if it contains a large number of items. An alternate approach would be to administer a single-item global rating of quality of life. Unfortunately, this type of assessment would not provide adequate information to identify specific needs of the head and neck.

Table 26.6 lists several examples of questions that may be helpful in the selection process. As in the research setting, the instrument must be able to provide the head and neck health care practitioner with adequate information to assess the patient's quality of life. The clinician must also determine when changes in quality of life ratings reflect clinically meaning changes in quality of life perception that would justify altering treatment. The lack of clarity related to the interpretation of quality of life findings for individual patients in a clinic setting is one of the major barriers to implementing quality of life assessment in clinical practice.

26.8.3 Statistical Significance Versus Clinical Significance

One of the underlying principles for assessing quality of life in people with head and neck cancer is to recognize change, both negative and positive, and then determine whether the change is meaningful enough to have clinical ramifications for patient care. In order to better recognize and interpret quality of life changes in people with head and neck cancer, the significance should be evaluated on two levels, statistical and clinical [73]. Determining the clinical significance of quality of life changes helps bridge the gap between research and clinical practice, thereby,

Table 26.6 Selecting a quality of life instrument to use in the clinical setting

Examples of questions to consider when selecting a quality of life instrument for head and neck cancer patients
Clinical
What purpose does assessment of quality of life serve in the clinical setting?
Who will be responsible for reviewing the findings?
Will the tool be able to provide adequate information to assess the impact of head and neck cancer on quality of life?
What specific aspects of quality of life does the instrument address? Functional status? Symptoms? Global quality of life? Satisfaction?
Is the instrument sensitive enough to detect changed in the head and neck cancer patient's quality of life?
Does the instrument have established psychometric properties? Reliability? Validity?
Can the instrument be easily administered in a clinical setting?
How will the instrument be administered? Paper and pencil? Telephone administration? Computer administration? Internet administration?
How many items are included in the instrument?
How long does it take to complete the instrument?
How frequently will the instrument be administered? Daily? Weekly? At preset times? At each office visit?
Where will the instrument be completed? In the clinic? In the home?
How will information be transmitted from the head and neck cancer patient to the health care provider?
Given the head and neck cancer patient's expected health status, is it likely that the patient will be able to complete the instrument in a timely manner?
Are there guidelines available for determining clinically meaningful changes in quality of life in cancer patients in general or head and neck cancer patients, specifically?
How will the instrument be scored? Who will score it?
Are the findings obtained from the instrument easily interpreted?

improving patient care. Researchers use inferential statistics to test hypotheses, such as comparing quality of life outcomes among head and neck cancer patients who are receiving different types of treatments for their disease. Quality of life outcomes are considered statistically significant if the probability of obtaining the observed outcomes is considered unlikely by chance alone (usually less than 1 in 20 or 5%). Statistically significant changes in quality of life may or may not translate into differences in quality of life that the patient can actually perceive. Likewise, the change may be too small to warrant changes in care. For a change to be clinically significant, it must be large or important enough to have clinical ramifications for patient care. For instance, a small numerical change in quality of life scores may be large enough to be deemed statistically significant, but the change is too small to be considered clinically meaningful or even detectable to individual head and neck cancer patients [74]. In this example, the evidence for incorporating the quality of life research findings into patient care may not be warranted.

Determining the clinical significance of various quality of life instruments is a major focus of quality of life research. This helps those who care for head and neck cancer patients interpret the findings. Different methods for determining the clinical significance

of quality of life scores are available [75–77]. One commonly used method is the anchor-based approach, which uses other clinically relevant indicators as "anchors" for interpretation of the quality of life scores. For instance, mean score changes for the multi-item subscales of the EORTC QLQ-C30 were found to correspond with patients' ratings of change in their perceived health status [78, 79]. As a result, guidelines for interpreting the clinical significance of scores for the EORTC QLQ-C30 are available. Mean score changes of 5–10 points are considered small clinically significant differences; mean score changes of 10–20 points are considered moderate differences; and changes over 20 points indicate large clinically significant differences. Thus, a 21 point difference between two sets of scores on the physical functioning subscale of the EORTC QLQ-C30 would be interpreted as a large, clinically significant change.

Other numeric changes in quality of life scores to determine clinical significance have been established for a variety of quality of life instruments. A difference of two points or more in mean scores is recognized as clinically significant For the Quality of Life Index [80–82]. For the FACT-General and Fact-Head and Neck, a change of 5–10% corresponds to clinically significant differences in quality of life in patients with laryngeal cancer [83].

Another method for determining the clinical significance of quality of life changes in head and neck patients is the distribution-based approach. The ½ standard deviation method [84] and the empirical rule effect size [85] are two of the primary methods used in clinical research. The ½ standard deviation method simply uses a ½ standard deviation to estimate differences in quality of life that are likely to be clinically significant. Quality of life scores that deviate from baseline scores by more than ½ standard deviation are considered to be clinically significant. The empirical rule effect size builds upon the ½ standard deviation method by incorporating effect sizes into the determination of clinical significance. While both of these methods are helpful for determining the clinical significance of quality of life changes in head and neck patients, these ½ standard deviation and the empirical rule effect size were developed primarily for use with group level data and may or may be correspond to clinically significant changes in individual patients. These methods, therefore, must be used with caution when applied to the care of individual head and neck patients.

Finally, determining whether a change in quality of life scores is considered clinically significant is also influenced by the user and the reason for the quality of life assessment. In the head and neck cancer population, there are three primary users of quality of life information; the patients, clinicians and society [86, 87]. The values and standards of each group varies, and the different values and standards influence whether a quality of life outcome is interpreted as clinically significant. A clinical significant change in quality of life for the patient may or may not be interpreted as clinically significant by the health care provider. For example, a head and neck cancer patient may perceive a 10 point increase in oral cavity pain to be clinically significant and question whether it is worth continuing therapy. The head and neck clinician, on the other hand, must weigh the benefits of treatment against increased symptomatology to determine if a change in clinical practice is warranted. A 10 point increase in pain, while concerning for the clinician, may not justify changing a treatment strategy that has a high cure rate. Obviously, the primary intent

of the oncology professional would be to relieve symptoms as best as possible. There are times, however, when complete alleviation of symptoms is not possible. In a case such as this, a clinically significant change in quality of life as perceived by an individual patient may or may not be acted upon by clinicians, depending on the magnitude to change. The important message being that goals of therapy should be thoroughly discussed and agreed upon by patients and clinicians so that there is a clear understanding of the goals of therapy. For further information related to the clinical significance of quality of life, the reader is referred to a series of six articles published by a consensus group of quality of life QOL experts [88–93].

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Chapter 27
Cancer Drugs, Clinical Trials, and Regulatory Agencies

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Contents

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Abstract The treatment of cancer, including Head and Neck, often requires powerful medication which needs to undergo a rigorous development and evaluation process. This complex interaction between basic scientists, clinical investigators and the pharmaceutical industry is largely overseen by the Food and Drug Administration (FDA). The FDA must regulate the medications approved in the United States for the safety and benefit of the patient. Therefore, a comprehensive and detailed approval process has been developed over the last several decades that attempts to assure proper drug evaluation without undue delay in approval of these vital products. The elaborate process begins with preclinical trials where investigational medications are tested in animals to assess whether there is predicted benefit and safety in humans. When the medication is deemed safe enough to evaluate in humans a lengthy process of three phases of clinical trials begins. Each clinical trial phase has specific goals and requirements allowing progression of the drug towards approval. When it comes to testing and utilizing these medications for head and neck cancer patients there are several important ethical issues to consider. These issues include that these medications are usually only tested in patients who have tried and failed already approved treatment regimens, placebos should not be used in this patient population because it is not ethical to give these sick patients no treatment at all and patients that cannot participate in the clinical trial due to the very specific requirements of many trials may be able to access the investigational medication through a protocol process. Investigators in head and neck clinical trials are responsible for looking out for the needs of these very ill patients. It is a delicate balance to maintain proper clinical care and still conduct trials to search for better drug treatment regimens. An investigational review board is used to review and oversee clinical trials to make sure the trials are being completed properly and in the best interest of the patients. In instances where the trials show positive results, the developers of the drug will seek FDA approval to be marketed for specific clinical uses. This entire approval process is followed by surveillance of the drug even after it has reached the clinical use market. Although the FDA is charged with the task of careful consideration of all new potential cancer drugs there is some controversy as to whether this process actually slows clinical use of certain drugs in the United States. Whether a clinician is considering using a new cancer drug or an investigator is looking for the next hopefully better drug, knowledge of the FDA process of trials and drug development is vital to understand.

Keywords Food and drug administration • Clinical trials • Ethics • Drug approval process

Abbreviations

BLA Biologic License Application
DMF Drug Master File
EMA European Medicines Agency
FDA Food and Drug Administration
ICH International Conference of Harmonisation
IND Investigational New Drug Application
IRB Institutional Review Board
NDA New Drug Application

27.1 Why Does the Food and Drug Administration Regulate Medications?

27.1.1 Why Are Head and Neck Cancer Drugs Regulated?

Head and neck cancer drugs, like most medications, are closely regulated both to ensure the safety and the benefit of the patient. The Food and Drug Administration (FDA) oversees the important task of ascertaining three main points about any specific drug. First, the FDA must decide whether the potential benefits of a new treatment outweigh any identifiable risks [1]. Since head and neck cancer drugs can have many potentially harmful side effects, a sponsor needs to show that the benefits of taking these medications is worth it for the patient to be put at risk for these side effects. Second, once a clinical trial has been initiated the FDA is responsible for deciding whether or not these trials should continue [1]. This decision is based on several factors including both the effectiveness of the investigational medication and the side effects that are observed and reported in trials. Third, when clinical trials are completed the FDA must decide whether or not the treatment should be allowed to be sold to the public, what claims the manufacturer can make regarding the medication and what the drug label should say about how to use the medication, anticipated potential side effects as well as warnings [1]. All of these critical elements are decided through the drug approval process when the study sponsors submit the study information to the FDA.

27.1.2 An Overview of How Cancer Drugs Get Approved or Rejected

The FDA regulates medications through their well-documented approval process. Head and neck cancer drugs must go through a rigorous testing process before

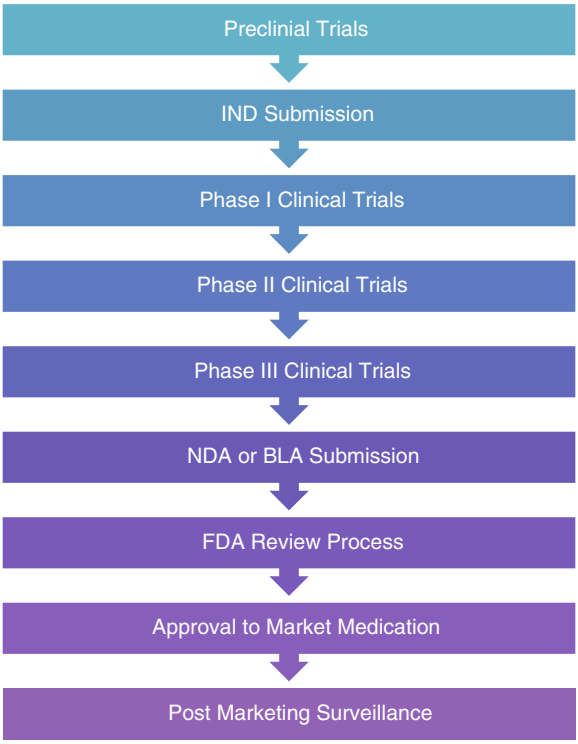

Fig. 27.1 Overview of the process of receiving approval for a new medication

approval for treatment (Fig. 27.1). The process starts with testing the investigational medication in animal subjects to help predict that the medication will be safe enough to test in humans [2]. Subsequently, an application, called an Investigational New Drug Application (IND), is submitted to the FDA. Assuming there is no rejection of the IND the investigational medication next proceeds through three phases of clinical trials, each time testing in more patients to try to generalize the results to the entire patient population that would be receiving the medication [2]. After successful completion of all phases of clinical trials a New Drug Application (NDA) or Biologic License Application (BLA) is submitted to the FDA depending on the type of medication being investigated. The FDA then thoroughly reviews the application and will give either a final approval or report back that more information is needed. Even after approval of the medication post marketing surveillance will be ongoing to see if new side effects develop in a larger population [2].

27.1.3 Brief History of FDA Laws

Food and Drugs Act: In 1906, this first law targeted fraudulent medicines and required that drugs meet certain standards of purity and strength. This law was

expanded to cover false and misleading claims pertaining to ingredients and effectiveness. The Food and Drugs Act was very difficult to enforce [2].

Federal Food, Drug, and Cosmetic Act: In 1937, there was an incident with Elixir Sulfanilamide, which was responsible for the death of over 100 people. During that time Sulfanilamide was found to be easily dissolved in diethylene glycol, a chemical normally used as antifreeze and now known to be a deadly poison. The doctor who made the formulation did not consider this possibility and since no safety testing was required for medications the Elixir was shipped out and caused many deaths. The incidents with Elixir Sulfanilamide lead to the establishment of the Federal Food, Drug and Cosmetic Act (FDC Act) of 1938. This act made manufacturers prove the safety of medications, authorized the inspection of factories, and for the first time established penalties for fraudulent claims and misleading labels [2].

Durham-Humphrey Amendment: In 1951, the first federal law was enacted that required physician's prescription to read "unsafe for self-medication" [2].

Kefauver-Harris Drug Amendments: Another health care related disaster prompted the addition of this law in 1962. Thalidomide was a sedative used during pregnancy in Western Europe during this time. No studies were completed on the effect this drug may have had on reproduction, a developing fetus, or the potential to induce other disease such as cancer. Unfortunately, thousands of babies were born with birth defects such as, phocomelia which resulted in shortened, absent, or flipper-like limbs [2]. The response was the Kefauver-Harris Drug Amendments, where a drug now had to not only been proven to be safe but also effective through adequate and well-controlled studies [2]. This law would be applied to all drugs introduced since the 1938 FDC Act. Pharmaceutical companies were now required to report all adverse events to the FDA and include all information on benefits and adverse events to prescribers. These amendments also required informed consent from all patients that would be participating in investigations of new medications [2].

Orphan Drug Act: An orphan drug is intended to treat rare conditions and disease for which adequate treatment has not yet been developed [2]. Pharmaceutical companies evaded the extensive research and testing of these medications since only a small group of potential patients exists. This law enacted in 1983, gave manufacturers tax benefits for their research in this area and 7 years marketing exclusivity if a company developed one of these drugs [2].

Drug Price Competition and Patent Term Restoration Act: This act gave patent holders the opportunity to extend the terms of patents for drug products by giving them a portion of the patent term lost to the extensive federal regulatory review process. This act also made generic version of medications more easily available [2].

Revision of Regulations for New Drug Application Regulations: In 1985, revisions were made that changed the requirements for manufacturers calling for better organized applications, clearer data, more information on side effects from medications, quicker problem-solving, and in some instances provided for approval based on foreign studies [2].

Treatment Use of Investigational Drugs: In 1987, this regulation was passed which allowed expanded access protocols for promising drugs in clinical trials. This allowed for a better understanding of real-world application of these medications and also provided treatment to some patients where no effective treatment may exist. This regulation was very promising for cancer patients who may not have treatment options left. Under these regulations the medications still need to show reasonable evidence in well-controlled studies before expanded use was allowed [2].

Accelerated Approval: Also in 1987, the accelerated approval process was approved. Prior to 1987, drugs approval was based solely on the effect the drug had on specific illness or a patients' length of survival. Under accelerated approval judgment could be based on a surrogate endpoint, an effect of the drug on a measurable process related to disease [2]. For instance, a surrogate endpoint in a head and neck cancer trial would be how long the treatment is used before there is progression of the disease based on a preapproved measure of disease activity [2].

Procedures for Subpart E Drugs: These procedures added in 1988 apply to studies on drugs and biologics (non-chemical medications such as antibodies, hormones, growth factors, etc.) used to treat life-threatening or severely-debilitating diseases. Under this new legislation sponsors of clinical trials for these products may request FDA officials to review and reach an agreement on the design of preclinical and early clinical trials early in the drug development process [3]. Furthermore, after successful data is available for phase I, sponsors may again request a meeting for the planning of phase II trials, with the goal that successful completion of these trials will lead to approval for marketing of the medication. This is essentially a fast-track status for drugs used for more serious disease state where without intervention the likelihood of death is very high [3].

Parallel Track Mechanism: In 1992, this policy made it possible for patients who could not participate in controlled clinical trials or who had no therapeutic treatment alternative to have access to promising investigational drugs for AIDS and other HIV-related diseases. The medications were available under a "parallel track" protocol, in which, the clinical trials were still being conducted [2].

Generic Drug Enforcement Act: This act in 1992 added stricter convictions for fraudulent and illegal activities when companies applied for new drug applications for generic drugs [2].

Prescription Drug User Fee Act (PDUFA): Starting in 1992 a fee was added to certain new drug applications. The funds produced from this fee have been used to hire more review staff at the FDA to help accelerate review of new medications [2]. Review times were now set at 6 months for priority applications and 12 months for standard. Priority drugs include any drugs for AIDS and all drugs that offer a significant medical advance over the therapies that exist for the disease state [2].

Food and Drug Administration Modernization Act: This act enacted in 1997, decreased the review times for a standard application to 10 months and also extended the Prescription Drug User Fee Act for another 5 years [2].

27.1.4 International Conference on Harmonisation

The International Conference of Harmonisation (ICH) is a joint initiative started in 1990 between Europe, Japan and the United States. ICH involves both regulators and research-based industry representatives of these countries who engage in discussions focusing on assessing and ensuring safety, quality and efficacy of medications [4]. The goal of the ICH is to bring coordination to the interpretation and application of guidelines. A key benefit of ICH includes the prevention of duplication of clinical trials. For instance, according to this cooperation a drug for head and neck cancer may be able to use a trial from Europe to get approved in the United States or Europe. This agreement may also lessen the need for animal testing as test results could be pooled from these different countries to show safety and efficacy in animals. This organization can decrease the amount of time it takes to develop a drug and the amount of resources needed [4].

The ICH cooperates between Europe, Japan and the United States to makes guidelines focusing on four different aspects of drug development [4]. The first of which is quality guidelines. Quality guidelines include many aspects from stability testing, that is used to make sure the drug is stable enough, for example in different temperatures or climate zones, to good manufacturing practices (GMP) that are required when manufacturing pharmaceutical products. Safety guidelines include many areas such as testing the possibility of the drug to cause cancer or the effect the drug will have on the reproductive system of the patient. Another aspect included is efficacy guidelines. Efficacy guidelines include most topics related to how clinical trials are performed including good clinical practices (GCP), which are expectations of how all participants of clinical trials should behave. The final type of guidelines is multidisciplinary including topics that do not fit clearly into any of the other three categories. An example of this is the Medical Dictionary for Regulatory Activities (MedDRA) which was designed by the ICH Steering Committee as a highly standardized medical terminology which is used internationally for registration, documentation and safety monitoring of medicinal products. Over the past two decades, ICH has worked to correspond between different countries, coordinate guidelines, and attempt to accumulate information that will help medicinal products to safely and accurately be approved in a timely manner [2, 4].

27.1.5 Procedures for Parallel Scientific Advice with European Medicines Agency (EMA)

In September 2004, the European Medicines Agency (EMA), the FDA's counterpart in the European Union, and FDA agreed to partake in a pilot program to provide parallel scientific advice (PSA). PSA is the exchange of views on scientific issues during the development of new medications [5]. This pilot program was to focus on breakthrough products. There were a few expected advantages of the program

including increased dialogue between the EMA, FDA and sponsors of the investigational medications from the beginning of the product life-cycle, a deeper understanding of the bases of scientific advice and the opportunity to avoid unnecessary testing duplication or unnecessary diverse testing methodologies while optimizing product development [5].

27.2 The FDA Approval Process

27.2.1 Preclinical Trials

After a new promising compound has been identified, it must be tested first in animals prior to any evaluations in humans. This preclinical testing phase usually lasts approximately 3–4 years. The goal of these trials is to elucidate the proposed degree of safety a drug would have in humans and minimize the risk patients would be put at when agreeing to participate in the next early phase clinical trials [6]. There are many different types of studies performed in these preclinical trials. One type typically performed are safety pharmacology studies, which test the drugs effect on vital organ systems including the cardiovascular system, the respiratory system, the central nervous system and other systems. Additional possible early phase studies include single-dose acute toxicity studies, and repeated-dose toxicity studies which test the indicated dose of the medication for possible toxic effects. Carcinogencitiy tests can be required in preclinical testing but this is usually if a medication is to be used for a chronic or recurrent disease state [6]. Some studies that would fall into the preclinical category can be done alongside clinical trials, such as studies to test the body's effect on the drug and how a potential toxicity would affect the body [6].

An important aspect of preclinical trials includes absorption, distribution, metabolism, elimination and toxicity testing, also known as ADMET [7]. There is complete absorption of intravenous medications because they are administered directly into the bloodstream. Intravenous medications are most commonly used for head and neck cancer therapy. However, in recent times there is a focus on trying to create more convenient oral therapy, where absorption is an important aspect. Oral absorption of any medication is based on many physiochemical characteristics of the drug, such as solubility, that are fairly easy to measure [7]. On the other hand, it is also affected by many factors in the human body such as the acidity of the stomach or the time it takes the medication to reach the site of absorption which need to be accounted for as well and are not easily demonstrated in preclinical trials [7, 8].

The distribution of the medication through the bloodstream to the place of head and neck cancer malignancy is first effected by proteins in the blood [8]. If an investigational medication binds to these compounds it will take longer for the medication to distribute to where it needs to be. Distribution is best studied through

radiolabeled compounds, when an investigational compound is attached to a compound that will show up on radiologic exam and show where in the body it moves to [7]. Most important is the concentration of the compound that reaches the target tumor this can be analyzed in the final analysis of the animal tumor tissue in preclinical trials [7, 8].

An investigational compound can be metabolized in many different sites in the body such as the intestines, liver or even the site of the tumor [7]. The metabolism of a compound was previously studied *in vivo*, meaning in a live organism, but has recently been moving towards *in vitro* studying meaning outside of a live organism. Analysis of metabolism is also being done earlier in the discovery process because if a compound is too quickly metabolized it will not have any action and if it is metabolized too slowly it is likely to have very toxic side effects. If a compound is found to have metabolism issues early in development and they cannot be remedied, the compound will likely not be studied further [7].

The body eliminates most compounds through the kidney [8]. Recently, many studies have been done to help better understand the transporters in the system involved in elimination. Understanding these transporters will help to better identify early on how a drug will be eliminated from the body [7]. Toxicity testing covers a broad range of different aspects of the compound. Drug interactions are of concern especially in head and neck cancer therapy where drugs are commonly used in combination with other therapy. These interactions can cause incorrect amounts of the other medications causing either, less of a therapeutic effect or more toxicity in the patient [7]. Toxicity testing plays a different role in compounds intended for head and neck cancer due to the significant side effects that are commonly associated with medications used to treat such a serious disease state. In these compounds there may be a higher level of acceptable toxicity depending on the positive effect that the drug will have on the body [7]. Overall, ADMET testing is a very important aspect of preclinical trials, and an investigational compound must show a promising ADMET profile in order to be considered for clinical trials.

27.2.2 Pre-investigational New Drug Application (Pre-IND) Meeting

The Pre-IND Meeting is held to review and reach an agreement on the design of animal studies needed to initiate testing of the medication in humans [9]. The Pre-IND meeting is also used to plan for Phase I clinical trials, and to discuss the best approach for presentation and formatting of data in the IND. This process was put into place to foster early communication between sponsors and new drug review divisions in order to better provide guidance on the data necessary to warrant IND submission [9]. Pre-IND meetings are not requested prior to all IND submissions, usually only for novel medications for new or complex areas of research including head and neck cancer [9].

27.2.3 Investigational New Drug Application (IND)

After an investigational medication has completed the pre-clinical testing phase with promising results an Investigational New Drug Application or IND needs to be submitted to the FDA before the drug can be tested in humans. The IND details animal pharmacology and toxicology studies including those on how the drug is absorbed, distributed, metabolized and excreted by the body. They are also designed to show the potential for the drug to be safely used in humans and to look for possible toxicities [9]. Data from any other previous experience with the drug, such as use in other countries, should also be included. Information on how the drug will be manufactured including, the composition, manufacturer, stability and controls used for manufacturing should be submitted; this information will be assessed to ensure that adequate production and supply of consistent batches will be able to be completed [10]. Clinical protocols of planned early phase clinical trials are assessed to assure patients will not be exposed to unnecessary risks. Information is collected on the investigators of the study; including the person who is overseeing the administration of the experimental compound being assessed to confirm they are qualified to fulfill their clinical trial duties [9, 10].

There are three different types of INDs. The first type is an Investigator IND which is submitted by a physician. This physician initiates and conducts the investigation as well as immediately directs the use of the investigational medication [9]. A physician could submit a research IND to try to study an unapproved medication or an approved medication for a new indication or for a different patient population. For example, Erbitux (cetuximab) was first approved for colorectal cancer. However subsequently another physician submitted an IND to study this medication in patients with head and neck cancer, an indication different than for what it was originally approved. The second type of IND is the Emergency Use IND which allows the use of the investigational medication in an emergency situation that would not allow time for submission of an IND in accordance with normal laws and regulations [9]. Emergency Use IND is also used in a situation where patients do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist. The final IND type is a Treatment IND which is submitted for experimental drugs that show promise in clinical testing for serious or immediately life-threatening disease states. With a treatment IND a patient has access to the investigational medication while the final clinical work is conducted and the FDA review is taking place [9].

There are two different main categories of where INDs can originate, commercial and research (non-commercial). Once an IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. In these 30 days, the FDA has the chance to review the IND information to assure patients in clinical trials will not be exposed to unreasonable risk [9].

27.2.4 Drug Master File (DMF)

A Drug Master File (DMF) is a submission that may provide confidential detailed information about facilities, processes or articles used in manufacturing, processing,

Table 27.1 Types of drug master files [11]

Drug master file type	Information included
I	Manufacturing site, facilities, operating procedures and personnel
II	Drug substance, drugs substance intermediate and material used in preparation of drug product
III	Packaging material
IV	Information on excipient, colorant, flavor, essence, or material used in preparation
V	FDA accepted reference information

packaging and storing one or more human medications [11]. A DMF is not a requirement of the FDA and is submitted solely at the discretion of the drug manufacturer. Information within the DMF can be used to support an IND, a New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA). A DMF may not be substituted for any of the above applications and it is never approved or disapproved [11]. It is reviewed alongside the above applications for better understanding of the information the DMF provides. Before the FDA can review a DMF in support of an application, the holder of the DMF must submit a letter of authorization permitting the FDA to reference the DMF [11].

There are five different types of DMFs (Table 27.1). Type I refers to manufacturing site, facilities, operating procedures and personnel. This type of DMF is usually used by manufacturing sites outside the United States. This can assist the FDA in conducing onsite inspections and should describe the site equipment and layout in detail. Facilities within the United States usually do not need type I DMFs unless they are not registered and not routinely inspected [11]. Type II looks at the drug substance, drug substance intermediate, and material used in their preparation or drug product. This type of DMF should be limited to one drug intermediate, drug substance, drug product or type of material used in their preparation. For drug intermediate, drug substance or material used in their preparation all significant steps in manufacturing need to be summarized. The information for the finished drug product should usually be submitted in the IND, NDA, BLA or supplemental application that is being submitted. However, if this information cannot be submitted in the application then a type II DMF should be included [11].

Type III refers to packaging material. Each material used in packaging should be identified by the intended use, components, compositions and controls for its release [11]. Names of the suppliers or fabricators of these components should be given in the type III DMF. A type IV DMF includes information on excipient, colorant, flavor, essence, or material used in their preparation. Each additive used in preparation should be identified and classified by how it is manufactured, release specifications, and testing methods. Toxicity data on these additives should be included in this section if not available in another document as a cross reference [11]. A type V DMF refers to information in FDA accepted reference information. This type should not be used for miscellaneous information, duplicate information or information that could be included in another type of DMF. If information that

does not fit into type I through IV DMF is to be included a letter of intent must be submitted to the Drug Master File Staff and FDA will be in contact with the holder to discuss the proposed submission [11].

27.2.5 Phase I Clinical Trials

After an Investigational New Drug Application (IND) is not rejected by the FDA, the investigational drug can move into phase I clinical trials. The main goal of these trials is to see if the medication is safe in humans [6]. A small number of volunteer patients usually participate in this phase. In a trial, for example, for a blood pressure medication this phase would include approximately 25–50 healthy patients [12]. Alternatively, a trial in this phase for head and neck cancer would include around 15–30 patients who have advanced disease that is not responding to or for another reason cannot be treated with the usual treatment [6]. This phase tests both how the human body responds to the drug and how the drug responds to the human body. The dose of the medication is started at low levels and slowly titrated upward until a maximum dose that can be given safely is reached [12]. This phase can be used as a beginning for documenting side effects or complications as it is the first time the drug is tested in humans. Approximately 70% of drugs that are tested in Phase I clinical trials are safe enough to move on to phase II clinical trials [12].

27.2.6 Phase II Clinical Trials

After successful completion of phase I clinical trials the medication moves to Phase II where the effectiveness of the drug is tested [6]. In the example of a blood pressure medication this would include around 100–300 patients with high blood pressure [12]. The investigational medication will be compared to placebo or an active control medication to compare the effect each has on blood pressure. However, for head and neck cancer this phase would include a more focused group of about 30–50 patients who have head and neck cancer to see if the investigational medication produces a beneficial effect. In this phase, a head and neck cancer drug would not likely be compared to any other medication. This phase also monitors for unexpected and expected side effects and complications [6]. About 33% of medications that enter phase II trials are considered safe and effective enough to be moved to phase III clinical trials [12].

27.2.7 Phase I/II Clinical Trials

Sometimes phases of clinical trials can be combined to allow for faster development of new intervention and to minimize the risk of clinical trial participants [6]. This

practice would be common in head and neck cancer due to the smaller available patient population of the disease state and the serious problems that could occur with many of the medications for this disease state [6].

27.2.8 Phase III Clinical Trials

After Phase II clinical trials are completed with promising results, Phase III trials will commence. Phase III clinical trials are designed to test the efficacy of the new intervention as compared with standard therapy, if possible [6]. In the blood pressure medication example this phase would include 1,000–5,000 patients or possibly even more [12]. The studies would test against a placebo or an active control, usually in a double-blind design, meaning neither the patient nor the investigator knows which medication the patient is receiving until the completion of the study. On the other hand, a head and neck cancer medication would include several hundred to possibly thousands of patients. The studies would test against the current standard therapy for the specific type of head and neck cancer. Phase III trials compare not only the beneficial effects of the investigational medication to current therapy but also the quantity and severity of side effects. Optimally, all Phase III trials should be randomized, requiring that patients are randomly assigned which treatment group that they will be in. Randomization is usually done by a computer and is used to help keep characteristics of the groups receiving the different medications similar [12]. If Phase III trials are completed with promising results, the investigator may file a New Drug Application (NDA) with the FDA.

27.2.9 New Drug Application (NDA)

After the manufacturer completes enough clinical trials to clearly show the safety and effectiveness of the investigational medication, all the information is combined to form the New Drug Application, or NDA. After the FDC Act of 1938, every new drug has to submit an NDA in order to legally be marketed in the United States [2]. This application will combine data gathered during pre-clinical studies used to submit the IND through all clinical trials completed or on-going [10]. The NDA seeks to prove whether the drug is safe and effective, and for its use if the benefits of the drug outweigh any risks. Proposed labeling, such as the package insert, is assessed for appropriateness and to make sure all information of importance is included [10]. Manufacturing methods are evaluated for quality measures used to maintain the drug's identity, strength, quality and purity. The NDA is designed to reveal the drug's "whole story" from animal studies, ingredients and how the drug behaves in the body to clinical tests, manufacturing, processing and packaging [10].

27.2.9.1 Biologics License Application (BLA)

A biologics license application or BLA is used similarly to an NDA but instead for biologic medications such as blood products or gene therapies [13]. The BLA would include most of the same information as an NDA would, including pre-clinical data, clinical studies, proposed labeling and information on the applicant, the product, the manufacturer and manufacturing process [13].

27.2.9.2 Supplemental Applications

Supplemental Applications can be used to add information to the labeling of already approved products. Supplemental New Drug Applications (sNDA) and Supplemental Biologics License Applications (sBLA) can be used for drugs and biologics, respectively to add a new indication for medications [14]. For instance, Erbitux (cetuximab), originally approved for colorectal cancer showed benefit for patients with head and neck cancer in clinical trials. These trials can be submitted in a sBLA to supplement the information already known about the medication for approval of the new indication [14].

27.2.10 Data Review/Expert Panel Review

The official review of the medication by the FDA does not begin until after the NDA has been submitted. The review team consists of many different types of people who come together to make a final decision on whether or not the drug is safe and effective [15]. It is important to remember that safe in this context means that the benefits of the drug outweigh the risks, as there are no drugs completely void of side effects. Medical doctors will assess how the medication could best be used in the clinical setting. Chemists, microbiologists and pharmacologists focus on the make-up of the medication and how it will work with the human body. The statistics from the studies will closely be looked at by statisticians for accuracy and significance [15]. The review team looks closely at the clinical trials to look for possible weaknesses in any part of the study. For instance, these weaknesses could include testing a drug in the wrong patient population; such as, testing a drug in patients with breast cancer and then trying to get the drug approved for patients with head and neck cancer off of that specific trial. Another weakness could be if an incorrect trial endpoint is used [15]. For example, accelerated approval applications use surrogate endpoints as a marker; a surrogate endpoint in a head and neck cancer trial would be how long the treatment is used before there is progression of the disease based a preapproved measure of disease activity versus a regular approval which may use survival as an endpoint [16].

Reviewers all receive specialized training in order to enforce good review practices as well as consistency in drug review. The reviewers are required to

interpret all the results the investigators have submitted and determine whether they agree or disagree with the conclusions drawn and also notice where more information may be useful [15]. Each reviewer then prepares their own written evaluation containing conclusions they have drawn from the information submitted and places where more information is needed. These written reviews are submitted to team leaders, division directors, or office directors for further consideration [15].

Advisory Committees are used by the FDA to protect and promote the public health. These committees can help the FDA obtain independent expert advice on scientific, technical, and policy matters [15]. Membership on these committees ranges from academic/practitioner to industry representatives or even consumer or patient representatives. However, the representative must be a qualified expert in their field and be able to analyze complex scientific data and understand the significance from a public health standpoint [15]. There are many procedures in place by the FDA to also determine a committee members financial interest as well as conflict of interest in order to try to keep the advisory committee as unbiased as possible and to note where any conflict of interest may come from [15].

27.2.11 Post Marketing Surveillance

After the NDA has been approved by the FDA the drug may be marketed. Post Marketing Surveillance also known as phase IV, is conducted while the drug is on the market [6]. It is used to look for toxicities that may occur infrequently and therefore may not have been seen in the small groups of people tested in the first three phases of clinical trials. This phase can be used to study the long-term safety and efficacy data of a medication that may not have been seen in the shorter clinical trials [6, 12].

27.2.12 Endpoints of Head and Neck Cancer Trials

Endpoints used for clinical trials focusing on head and neck cancer are different as compared to an endpoint for other medications, for instance a blood pressure medication. A medication used to lower blood pressure could use the amount the medication decreases the blood pressure as the endpoint of the trial. On the other hand, a drug for head and neck cancer would have endpoints based on areas such as survival and tumor progression. The latest drug approved for recurrent or metastatic head and neck cancer is Erbitux (cetuximab) and the main efficacy outcome for the trial for approval of this medication is overall survival [17]. Overall survival (OS) is defined as the time from randomization until death from any cause [16]. It is measured in the intent-to-treat population, which includes any patient who is randomized to a study group even if they are not adherent or don't correctly follow the protocol or procedure agreed on for the study. Survival is the preferred endpoint of a cancer medication trial and is considered the most reliable when studies are

Table 27.2 Summary of endpoints used in head and neck cancer clinical trials [16]

Endpoint	Use	Necessary study design	Advantages	Disadvantages
Overall survival	Clinical benefit for regular approval	Randomized	Direct measure of benefit, easily measured, precise	Need larger studies, affected by crossover and sequential therapy, includes non-cancer death
Objective response rate	Surrogate for accelerated or regular approval	Single-arm or randomized, blinding preferred	Assessed earlier and in smaller studies, effect attributable to drug not natural history	No direct measure of benefit, not comprehensive measure of drug activity, only subset of patients benefit
Complete response	Surrogate for accelerated or regular approval	Single-arm or randomized, blinding preferred	Durable complete response can represent clinical benefit, assessed earlier and in smaller studies	No direct measure of benefit, not comprehensive measure of drug activity, only subset of patients benefit
Progression free survival	Surrogate for accelerated or regular approval	Randomized, blinding preferred	Smaller sample size with shorter follow-up, measure of stable disease included, not affected by crossover or subsequent therapy, based on objective and quantitative assessment	Not always statistically validated, not precise, subject to assessment bias, frequent radiological or other assessments, involves balanced timing of assessments among treatment arms

accurately conducted [16]. This endpoint is considered precise and therefore easier to measure. OS is documented by the date of death therefore making bias not a factor. Clinically meaningful results can be achieved when there is a statistically significant improvement in overall survival and the toxicity profile is acceptable, including no dramatically worse side effects or worsening of other diseases. Some disadvantages of OS include that any factor leading to death is considered a negative outcome, and a large trial with a long follow-up period is needed to follow many patients until death (Table 27.2) [16, 17].

Another outcome measure used in the supplemental Erbitux (cetuximab) approval is progression free survival (PFS), which is similar to OS [17]. PFS defined as the time from randomization until objective tumor progression or death [16]. For this endpoint, the definition of tumor progression should be detailed in the protocol of the study. There are no standards for defining progression. PFS can be used in shorter trials because tumor progression can be assessed before the determination of survival benefit [16]. Unlike when using OS as an endpoint and exact date of death is known, the exact date of progression in PFS is unknown. When this endpoint is used a progression date must be defined by the protocol. A progression date (PDate) is assigned to either a time when progression can first be declared or the date of the visit immediately following the radiological assessments which document the progression [16, 17].

Objective response rate (ORR) was a final outcome used in the supplemental Erbitux (cetuximab) approval [17]. ORR is the proportion of patients with tumor size reduction of a predefined amount in a certain period of time [16]. Response duration is usually measured from the time of initial response to documented tumor progression. ORR is a direct measure of drug antitumor activity, which can be evaluated in a single arm study. The response criteria should be defined in the protocol before the start of the study. ORR's significance is assessed by its extent, duration and the percentage of complete responses, when there is no detectable evidence of tumor [16, 17].

27.3 Ethics of Head and Neck Cancer Clinical Trials

27.3.1 Patients of Head and Neck Cancer Trials

Clinical trials for head and neck cancer enroll patients with the disease state. Unlike, clinical trials for a medication that may be used to lower blood pressure where early phase trials include healthy volunteers, head and neck cancer trials will include only patients with the current disease state. With the vast amount of serious side effects associated with the medications used to treat such a serious disease state it would be completely unethical to submit a healthy volunteer to taking such a medication. Patients that are eligible for head and neck cancer clinical trials are based on the type and stage of cancer and the cancer treatments already received in order to make the patients as similar as possible to ensure the outcome of the trial is due to the intervention being tested and not other factors [18, 19].

Patients who will participate in these trials need to complete an informed consent process. The patient must be fully informed of their alternatives to participating in the clinical trial. One of the problems with informed consent is patients' full understanding of the information they are given due to health literacy issues or the forms being too complicated for the patient to fully understand [20]. In these situations the patients may be just giving consent even though they are not sure of all the information regarding the trial. Early phase trials are usually conducted in patients with no other therapeutic option. The properties of the investigational medications in humans are usually not fully known in the initial phase trials therefore patients often may have very advanced disease with few if any established regimens likely to provide benefit. Unfortunately, for most of these patients Phase I trials will not show any benefit, as these phase I trials are conducted primarily to find an acceptable dose of the medication in humans for future trials. Patients that consent to Phase I trials may have expectations that exceed the data for benefit from trials in this early of a stage. Ethically these patients need to be well informed of the likelihood of benefit in these trials which may not always occur [18–20].

27.3.2 Placebo Controlled Trials

A placebo is an inactive substance or treatment that looks the same as, and is given the same way as, an active drug or treatment that is being tested. In a placebo controlled trial the effects of the active investigational medication are compared to the effects of a placebo medication [21]. This type of trial is usually done to first see if taking the investigational medication is better than taking nothing at all before comparing it to other marketed products. Placebo controlled trials are rare in trials for head and neck cancer medications. The only time that placebos are really used in these types of trial is if a new medication would be added to a currently used regimen and the trial is looking to test whether or not the addition of the investigational medicine would be an advantage over the current regimen [21]. Placebos are avoided in these types of cancer trials as it would be unethical to give a patient with head and neck cancer no treatment at all if an approved treatment exists. For this reason investigational medications are usually compared to the standard of care for head and neck cancer. However, if for a certain type of head and neck cancer no approved, effective therapy exists a placebo controlled trial may be considered ethical as long as the patient is receiving best supportive or palliative care as opposed to no treatment at all [21].

27.3.3 Open-Label Trials

Open-label trials are those that allow the patient to know which treatment they are receiving. The problem with open-label studies is they can introduce bias in many ways. The patient may have heard about a certain side effect of a particular medication

and be more likely to notice it if they are aware that they are receiving that medication. Another potential bias is that if the investigator knows what medication the patient is receiving they may be more likely to perceive an improvement on any marker that is being measured for their investigational medication [16]. The best types of trial are often double-blind where both the investigator and the patient do not know which medication the patient is receiving. However, some patients with head and neck cancer may not feel comfortable not knowing which kind of medication they are receiving [16].

27.3.4 Randomized Trials

When a trial is randomized that means that each study person is assigned by chance, usually done by a computer program, to a group either receiving the current standard of care or the group which will be receiving the experimental medication. Randomization is important to assure that the two groups are as similar as possible [22]. This similarity between the groups is important because only if these study groups are similar can the results be adequately compared between them. Randomization is an ethically acceptable practice in head and neck cancer clinical trials because at the point of starting the trials the doctors really do not know whether or not the new approach represents an advance over the current conventional therapy. However, this must be shown through scientific data. Patients in randomized clinical trials are afforded additional benefits not usually given to patients completing therapy outside of a trial such as close monitoring by the investigators [22].

27.3.5 Access to Investigational Drugs

There are four legal ways for patients who need investigational medications to access them. In general, there should be no charge for these unapproved medications and all known effective life prolonging therapy should already have been attempted [23]. The primary and preferred method of access to investigational medications is enrollment in controlled clinical trials as has been previously discussed. Advantages of this method include that the study is usually closely monitored, drug supply should be assured and results can be made available for review and analysis. On the other hand, these trials are very tightly regulated and the patient may not fit the eligibility requirement or have access to the study site geographically [23].

The second mechanism for accessing investigational medications is closely related to the first. It involves enrollment as a special exception to a clinical trial. This requires approval from the principal investigator and the sponsor for inclusion. Again, with the strict requirements the patient may most likely not meet only one or two eligibility requirements and location is still an issue. Also, review and analysis of the results is likely not available [23].

A third mechanism is through a single patient IND. After receiving authorization from the drug manufacturer, an individual practitioner can apply to the FDA for an IND to place a single patient in a study with an enrollment of one. This relies on the agreement from the manufacturer to make the drug available. This method bypasses the eligibility and geographic location problems. However, there will be more inconsistence than in a controlled clinical trial in safety monitoring, investigational medication supply and analysis of outcomes [23].

The final mechanism is the treatment IND. This mechanism is used when there is preliminary efficacy data on an investigational medication and it is under review by the FDA for approval for marketing. A treatment IND is only available later in the development process and the patient or their third party payer may be charged for the cost of the drug, but not the planned market price. Although, since there is fast turnover of an approval for oncology drugs the treatment IND is rarely observed in this patient population [23].

27.4 The Roles of the Clinical Trial Participants

27.4.1 Obligations of Investigators in Clinical Trials

The investigator is a critical part of the clinical trial process. Investigators are responsible for enrolling subjects, collecting the data, and providing management and training to site personnel. The investigator must agree to follow the protocol or process set in place by the study, as well as all applicable regulations [6]. Other responsibilities include protecting the welfare of patients and their rights. Informed consent must be obtained from each study participant, which is a form that must be signed or an oral agreement depending on the phase of the study that lays out all the foreseeable risks and benefits of the trial and gives the patient the choice of participating in the trial or not, after interpreting this information. It is the responsibility of the investigator to make sure that only the correct patients, who have given their informed consent, receive the investigational medication and do so following the protocol [6]. Adequate records must be maintained of the study drug disposition, and case histories of all patients participating in the trial; these records must be retained for a required length of time of 2 years after the NDA is approved or if an NDA is not to be filed or is not approved until 2 years after the discontinuation of the investigation and the FDA is notified [24]. The investigator must submit progress reports, adverse event reports as well as financial disclosure reports to the sponsor in a timely manner. The investigator must seek approval from an Institutional Review Board (IRB) and ensure that they are responsible for initial and continual review of the study. The investigator must report all changes to the trial and any unanticipated problems promptly to the IRB. Finally, FDA officers must be allowed to inspect study records upon request [6, 24].

27.4.2 Who Sponsors Clinical Trials?

Contract research organizations (CRO) are used when additional resources or therapeutic expertise is needed to assist with the clinical trials. The CRO would acquire the same obligations and be held to the same standards as any other investigator for the transferred duty. Some of the duties that may be transferred to the CRO include site monitoring, project management, shipping of clinical trial supplies, data management and statistical analysis [6].

The National Cancer Institute (NCI) is part of the National Institutes of Health (NIH), which is an agency funded by taxpayer dollars. The NCI sponsors studies conducted by cancer cooperative groups, which are networks comprised of doctors and institutions that specialize in certain aspects of cancer. There are currently 10 major cooperative groups conducting studies all throughout the United States. Some other sponsors of cancer clinical trials include parts of the Department of Veterans Affairs and the Department of Defense [25].

When a pharmaceutical or biotechnology company seeks to market a medication they must first prove that it is safe and effective. For this reason, these companies are among some of the main sponsors of clinical trials. The company will either completely sponsor the trial or they could just donate the investigational medication that is to be used [25].

Some non-profit organizations also sponsor clinical trials. Organizations such as the American Cancer Society will put forth money they have raised towards trials to support the investigation of newer therapies [25].

27.4.3 Institutional Review Board (IRB)

An Institutional Review Board or IRB is a critical participant in the research process [6]. An IRB is a group designated to review and monitor research involving human subjects [26]. The IRB has specific membership regulation. It must include at least five members with differing backgrounds. It is stated in the code of federal regulations that: "The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects" [26]. Members should have a respectable awareness of laws, regulations and professional conduct and practice. An IRB must contain at least one member whose primary concern is in scientific areas and at least one whose primary concern is in nonscientific areas. At least one member must be a person who has no affiliation with the institution including having no one in their immediate family affiliated with the institution of which the review board is a part of. A member may not participate in decisions on specific research if they have any related conflict of interest. The IRB may invite individuals with a specific expertise to weigh their opinions in a specific area of research, however this individual may not vote with the IRB on the research [26].

The group may approve, require modifications or disapprove research proposals in accordance with the FDA [27]. This review is done in order to help protect the welfare and rights of human subjects that will be enrolled in the clinical trials [6]. The IRB conducts a review before the trial is allowed to begin and also periodically throughout the trial, in order to make sure the patients' rights are protected at all times. The group must try to assure that risks are minimized and reasonable in relation to potential benefits [27]. Selection of patients for the trial should be unbiased, proper informed consent should be obtained and confidentiality of all data must be maintained throughout the study. The IRB is also responsible for reviewing and guaranteeing that that the investigators obtain informed consent from all patients [27].

27.5 FDA Controversies on Cancer Drug Approvals/Rejections

27.5.1 United States Vs. Europe on Drug Approvals

Many articles have been published stating that specific medications are being approved much quicker in other countries as compared to the United States [28–30]. Contrary to what many of these sources have suggested, in a direct drug-to-drug comparison of cancer drugs approved in the United States and Europe, the United States typically has shorter review times for oncology medications and in fact often has the drugs approved first [31]. In a study that looked at review times for the initial approval of oncology drugs from 2003 through 2010 in the United States, the submission date was the date of the first NDA or BLA and review time counted up until final approval by the FDA. In Europe, however, there is a two-step process in place before a drug can be marketed. First of which is the EMA Committee for Medicinal Products for Human Use must express a positive opinion on the marketing authorization. Second, the European Commission must adopt that opinion. The submission date was when the first Marketing Authorization Application submission in the first step of the process and the review time was counted up until the EMA's positive opinion and marketing authorization [31]. A "delay to market" was calculated as the number of calendar days between the FDA final approval date and the European Commission adoption date [31].

The study identified 35 new oncology drugs that were approved in either the United States or Europe over the 2003–2010 time period. This study found that all the drugs that were approved by both regulatory authorities were available to patients in the United States first and more oncology drugs and biologics in the periods were approved by the FDA than the EMA [31]. Pharmaceutical companies usually submit their findings from clinical trials to the FDA before the EMA. The study also found that the FDA consistently took less time to review a new oncology medicine than the EMA. For instance, Erbitux (cetuximab) submitted data to the FDA on August 14, 2003 and to the EMA July 1, 2003. This was one of the exceptions where the data was submitted first in Europe; however, the FDA

approved the drug quicker, in 182 days, after the submission compared to the EMA's 267 days. The drug was still authorized for marketing 138 days earlier in the United States than in Europe [31]. This data is for the initial approval of Erbitux (cetuximab) for colorectal cancer, and does not include data for the supplemental approval of head and neck cancer. The FDA approved the supplemental application of Erbitux (cetuximab) for head and neck cancer on March 1, 2006 and the EMA approved it February 23, 2006, representing less than a week between the two approvals [31].

Unlike many of the other articles that suggest the FDA of being slower than other countries at approving oncology medications this study looked at specifics and directly compared the two regulatory agencies [31].

27.5.2 Off-Label Use

The use of a medication off-label refers to using a medication for any purpose for which it is not specifically indicated. Off-label uses may include a different disease state, dose, frequency or patient population than what the medication is approved for [32]. The use of chemotherapy agents off-label is common in treating patients with cancer. This is due to many factors, one of which being that some cancer medications are targeted therapy. For instance, Herceptin (trastuzumab) is a humanized monocloncal antibody that recognizes the human epithelial growth factor receptor 2 (C-erb-B2 also known as HER2/neu) protein specifically [33]. This drug is only indicated for specific types of breast and gastric cancer based on labeling. However, C-erb-B2 (HER2/neu) expression has been seen in some patients with head and neck cancer. A study that tested synovial sarcomas of 3 head and neck, 1 chest wall, and also 7 extremity sites of sarcoma found strongly positive results for C-erb-B2 (HER2/neu) expression in all 3 head and neck patients and none in any of the other sites [33]. These results show that the C-erb-B2 (HER2/neu) protein can be found in head and neck cancer and that the off-label use of Herceptin can be supported as long as the cancer has been tested for its expression [33].

Another factor leading to the large degree of off-label use of cancer medications is that chemotherapy involves the use of multiple drugs. Multidrug regimens are usually not approved by the FDA [32]. This is due to the abundant amount of chemotherapy combinations and the fact that would be impractical for the FDA to have separate approvals of each one. Also, cancer treatment is a dynamic field that is always changing. At any time, researchers are conducting studies on already approved medications to see if they can be used for a different type of cancer than indicated or in a new combination [34]. However, with all the testing of different regimens and different therapies it is important to remember that if a drug has not shown promise for a specific indication and there is no reason to believe that it may be helpful in a specific situation it should not be used [34]. For example, Herceptin can be used in a head and neck cancer that has expressed the C-erb-B2 (HER2/neu) protein, but if the patient is not expressing that gene specifically it

may well have no benefit to the patient. In the situation without the gene the patient is not likely to have promising results and is being put at risk of serious side effects [33].

27.5.3 Sodium Dichloroacetate

A current controversy related to the treatment of head and neck cancer surrounds the use of sodium dichloroacetate (DCA). This drug has been studied in Canada to show remarkable anticancer properties [35]. When DCA is used in cancer patients it seems to leave normal, healthy cells untouched. This medication can be taken orally and because it is a very small molecule can penetrate into the tissue easily and reach the cancerous cells [36, 37]. Even though this drug has been around for many years, there are no human clinical trials completed in the United States currently with this medication in cancer patients. A Canadian study was completed in 5 patients with brain tumors using DCA in combination with surgery, temozolomide and radiation [38]. Four out of the five patients in the study showed promising clinical results. However, most of the results came from *ex vivo,* or outside of the body, analysis of the tumor tissue removed from the patient before and after DCA therapy [38]. An issue with this medication is that it is difficult to show the anti-tumor effects *in vitro* [39]. DCA targets tumor metabolism which is hard to create when tumor cells are treated in a dish. Usually these *in vitro* tests are used to determine the possible effectiveness of drug *in vivo.* A current issue for this medication is how to best test this drug *in vitro* [39]. Another problem with this medication is it has been around for many years used in disorders of mitochondrial function, and is now a generic medication. Due to the vast majority of resources needed to develop a drug especially for a cancer drug, pharmaceutical companies do not have enough of these resources to spend on clinical trials for a medication that they will be given no exclusivity to market [36]. Stanford University is currently in the recruiting phase of a phase I and phase II trial for this medication in head and neck cancer patients (NCT01163487 and NCT01386632). These trials have the possibility of leading to a breakthrough in current treatment for head and neck cancer.

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Chapter 28
Drugs to Treat Head and Neck Cancers: Mechanisms of Action

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Contents

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Abstract This chapter presents the anticancer agents used for the treatment of head and neck squamous cell carcinomas (HNSCC), emphasizing the mechanisms of action of the various drug classes. Current therapies for HNSCC can be broadly divided into four categories: (1) DNA damaging agents, (2) Antimetabolites that interfere with DNA synthesis, (3) Antimitotic agents that interfere with cell division, (4) Agents that target pathways whose dysregulation are critical for tumorigenesis, including apoptosis and angiogenesis. Agents from the first three groups interfere with cell division and are therefore fundamentally non-selective. Most of their significant adverse effects result from the damage they inflict on normal cells that divide or remodel rapidly. Targeted therapies in contrast have greater potential to selectively inhibit transformed cells while sparing normal tissues. All HNSCC therapies are affected by resistance mechanisms that decrease drug efficacy. Typical mechanisms of tumor resistance include reduced drug uptake, increased drug efflux, rapid metabolism, and overexpression/mutation of target enzymes and receptors. Resistance can be pre-empted using combination chemotherapy regimens in which several anticancer agents are given simultaneously. These agents are also used in multimodal therapies, i.e. as a complement to surgery and/or radiation. Indeed, most HNSCC is treated with multimodal therapy and combination chemotherapy. Intravenous injection is the typical route of administration, however a few can be given orally. We also discuss several compounds in various stages of investigation.

Keywords Antitumor activity • Biochemical target • Microtubules • Antimitotic agents • Antimetabolites • Folate pathway • Alkylating agent • Signal transduction • Toxicity • Resistance

Abbreviations

5-FU	5-Fluorouracil
5HT	5 hydroxytryptamine
Ala	Alanine
Arg	Arginine
Asn	Asparagine
Asp	Aspartate
ATP	adenosine triphosphate
Bcl-2	B cell lymphoma-2
BCR-ABL	Break point cluster region-abelson
BLM	Bleomycin
BP-I	Back pocket I
BP-II	Back pocket II
BP-III	Back pocket III
BP-IV	Back pocket IV
CDK	Cyclin-dependent kinase
c-Kit	stem cell factor

CML	Chronic myeloid leukemia
CNS	Central nervous system
CTR1	Copper Transport Receptor −1
Cu^{++}	Copper (II)
Cys	Cysteine
DCA	Dichloroacetate
DFG	Aspartate-Phenylalanine-Glycine
DHF	Dihydrofolate
DHFR	Dihydrofolate Reductase
DNA	Deoxyribonucleic acid
DTX	Docetaxel
EGCG	Epigallocatechin
EGF	Epidermal growth factor
EGFR	Epidermal Growth Factor Receptor
ERB	Eukaryotic ribosome biogenesis protein
FADD	Fas-associated protein with death domain
FAK	Focal adhesion kinase
FBP	Folate Binding Protein
FGFR	Fibroblast growth factor receptor
Flk-1	Fetal liver tyrosine kinase 1
Flt-1	Fms-like tyrosine kinase
FPGS	Folypoly-γ-glutamate synthetase
FR	Folate Receptor
GARFT	Glycine Amide Ribonucleotide Transformylase
GIST	Gastrointestinal stromal tumors
Gln	Glutamine
Glu	Glutamate
Gly	Glycine
HeLa	Henrietta Lacks (cervical cell variety named for deceased patient)
HER	Human Epidermal Receptor
HGF	Hepatocyte growth factor
HNSCC	Head and Neck Squamous Cell Carcinoma
IGF	Insulin-like growth factor
IGF-I-R	Insulin-like growth factor I receptor
Ile	Isoleucine
IM	Intramuscularly
IR	Insulin receptor
IRK	Insulin receptor kinase
IV	Intravenously
kDa	KiloDalton
KDR	Kinase insert domain-containing receptor
Leu	Leucine
Lys	Lysine
MDR	Multi-drug resistance
MET	Receptor for hepatocyte growth factor

MMR	Mismatch repair (DNA repair mechanism)
MT	Microtubules
MTA	Multi targeted antifolate
mTOR	Mammalian Target of Rapamycin (a serine/threonine protein kinase)
MTX	Methotrexate
N^5,N^{10}-CH_2THF	N^5,N^{10}-methylenetetrahydrofolate
NSCLC	Non-small cell lung cancer
PDH	Pyruvate Dehydrogenase
Pgp	P-glycoprotein
PI3K	Phosphoinositol 3-Kinase
PKC	Protein kinase C
PORT	Post Operative Radiation Therapy
Pt	Platinum
PTX	Paclitaxel
RFC	Reduced Folate Carrier
RTK	Receptor Tyrosine Kinase
THF	Tetrahydrofolate
TNF-α	Tumor necrosis factor–alpha
TPF therapy	Three-drug regimen: docetaxel (Taxotere)/cisplatin (Platinol)/5-fluorouracil (5-FU)
TS	Thymidylate Synthase
VEGFR	Vascular Endothelial Cell Growth Factor Receptor
VFL	Vinflunine
VBN	Vinorelbine

28.1 Introduction

Head and neck cancer usually refers to cancers that arise from the mucosal linings of the cavities of the head and neck. The NCI lists eight subtypes of head and neck cancer based on the area of origin: (1) hypopharyngeal cancer, (2) laryngeal cancer, (3) cancer of the lip and oral cavity, (4) metastatic squamous neck cancer with occult primary, (5) nasopharyngeal cancer, (6) oropharyngeal cancer, (7) paranasal sinus and nasal cavity cancer, and (8) salivary gland cancer. In all but salivary gland cancer, the neoplasm usually begins with deranged squamous epithelial cells, hence the generalized descriptive designation "Head and Neck Squamous Cell Carcinoma" (HNSCC) is commonly used to describe all these cancers. Cancers of the salivary gland can arise from a large number of different cell types. However salivary gland cancers are rare and account for no more than 5% of head and neck cancers. It should also be pointed out that metastatic squamous neck cancer with occult primary refers to squamous cell metastasis to cervical lymph nodes in the absence of a discernible primary tumor.

This chapter is largely focused on the various drugs used to treat HNSCC and their detailed mechanisms of action. We also discuss toxicities and mechanisms

of resistance for these agents, and pharmacokinetic and pharmacodynamic considerations for developing individualized chemotherapeutic regimens.

28.2 Cancer Chemotherapy

Cancer can arise when any of a number of cellular growth control mechanisms becomes abnormal. For example, cancer cells can develop capabilities that confer self-sufficiency in growth signals (e.g. proliferation of autocratic growth signals that lead to excessive cell division) or insensitivity to inhibitory signals (which reduces the tendency of a cancer cell to enter a resting cellular phase). Alternatively, cancer cells can develop mechanisms to evade apoptosis (i.e. programmed cell death), leading to limitless replicative potential. Cancer cells can also secrete factors that stimulate angiogenesis, which is needed to increase the supply of nutrients and oxygen to a rapidly proliferating neoplasm, or to express enzymes and processes that enhance tissue invasion and metastatic dissemination [1]. These physiological changes transform normal human cells into malignant cells, leading to tumor development and progression of disease. Chemotherapeutic agents are designed to alter or inhibit any of these innate tumorigenic processes, thereby inhibiting tumor proliferation, progression and metastasis.

Some anticancer agents target normal cell division at the level of deoxyribonucleic acid (DNA) or microtubule (MT) cytoskeleton. Other agents target cellular proliferation and differentiation by affecting cell surface receptor ligand binding and signal transduction functions, or by disrupting intracellular signaling pathways or transcriptional regulation. Agents that affect angiogenesis or tissue microenvironment structure can not only slow down tumor growth, but also reduce tumor metastasis by inhibiting tissue invasion by cancer cells and the spread of the tumor to sites distal. Based on their biochemical targets and anticancer potential, agents used to treat HNSCC can generally be divided into four basic categories:

1. Drugs that directly damage DNA.
2. Antimetabolite drugs that interfere with DNA synthesis. These agents inhibit three intracellular enzymes: dihydrofolate reductase, thymidylate synthase, and ribonucleotide reductase.
3. Antimitotic drugs that interfere with cell division by disrupting the microtubule assembly.
4. Targeted therapies, so-called because they are capable of comparatively selective inhibition of transformed cells. Kinase inhibitors and growth receptors antagonists exemplify this relatively new category. Some of these agents are small molecules, while others are monoclonal antibodies.

Agents from the first three groups are fundamentally non-selective. Their effect on any cell type relies on their ability to interfere with cell division. Hence, many have significant adverse effects that result directly from the damage they inflict on non-cancer cells that normally divide or remodel rapidly. In contrast, drugs that

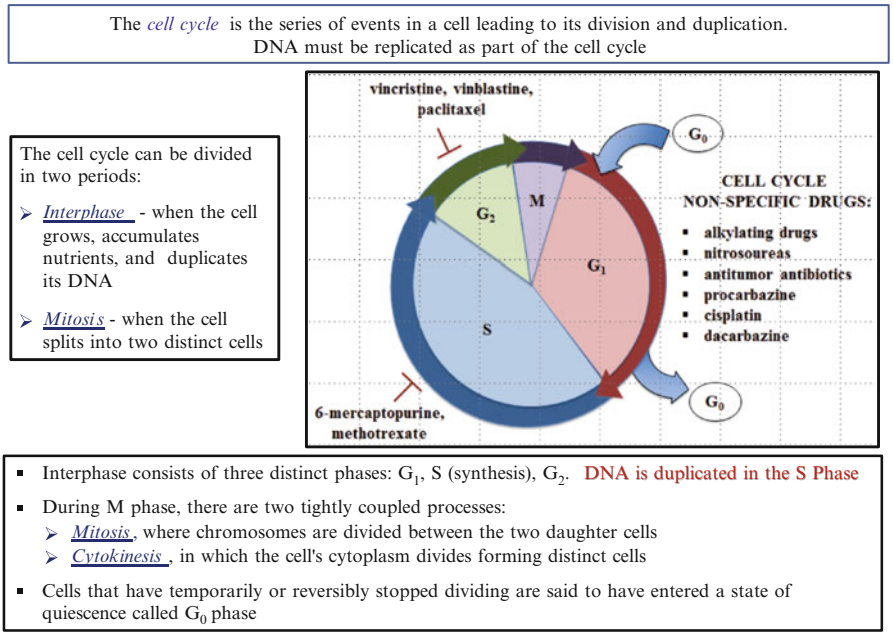

Fig. 28.1 The cell cycle

target kinases and growth receptors are representative of a new era in chemotherapy, one in which anticancer drugs can, in theory at least, selectively kill or inhibit transformed cells while sparing normal tissues.

It should be emphasized that two or more chemotherapy agents are often administered simultaneously in what is called combination therapy. Also, chemotherapeutics are often combined with surgical and/or radiation therapy in what is termed multimodal therapy. In most every case of HNSCC, treatment will be either combination chemotherapy or multimodal therapy. Specifically for HNSCC, preferred cytotoxic agents used alone or in combination regimens include alkylating agents such as the platinum compound, cisplatin, the antitumor antibiotic, bleomycin (BLM) [2–4], antimetabolites such as 5-fluorouracil (5-FU) and methotrexate (MTX), and antimitotic agents such as paclitaxel (PTX) and vinorelbine (VBN).

The choice of a chemotherapeutic agent depends on the life cycle of a tumor cell [5, 6]. Figure 28.1 reviews the basic phases of the cell cycle and the phases where different cytotoxic agents have their primary effect. Cytotoxic agents that act by damaging DNA are most effective during the S, or DNA synthesis phase of the cell cycle. Antimitotic agents such as the vinca alkaloids and taxanes inhibit mitosis and work best for cells entering the M phase.

Targeted therapies are unique in that they modulate specific processes critical to cancer progression [7, 8]. Kinase inhibitors such as imatinib [9], sunitinib [10] and gefitinib [11] are examples of clinically approved targeted therapies. Imatinib has proven very

successful in the management of chronic myeloid leukemia and gastrointestinal stromal tumors. Sunitinib, a multi-targeted kinase inhibitor, inhibits the biochemical signaling pathways stimulated by both Vascular Endothelial Cell Growth Factor Receptor (VEGFR) and Epidermal Growth Factor Receptor (EGFR), and is very useful in metastatic renal carcinomas and pancreatic cancers. These agents are cytostatic, i.e. they do not kill the tumor cell but rather slow its proliferation and growth. Because cytostatic agents do not directly abolish tumor cells, they are generally given in combination with agents that are more directly cytotoxic.

Other targeted therapies that are clinically approved for HNSCC include biologically engineered proteins such as bevacizumab [8, 12], a monoclonal antibody that binds to and blocks the function of VEGFR-2, and cetuximab [8, 13], a monoclonal antibody that binds to and blocks the function of EGFR. To maximize therapeutic benefit, bevacizumab and cetuximab are also routinely used in combination with chemical cytotoxic agents for HNSCC [2].

The efficacy of both cytostatic and cytotoxic chemotherapeutic agents is often compromised by the development of resistance – the process by which tumor cells become refractory to the action or potency of an anticancer agent [14, 15]. Resistance can develop by mechanisms such as reduced uptake of drug into cells, rapid inactivation of the drug *in vivo*, overexpression of efflux pumps which function to remove drugs from the cytoplasm of the tumor cell, and overexpression of target enzymes or receptors. The use of combination and/or multimodal regimens reduces the incidence of resistance and improves survival rates.

Chemotherapeutic agents produce severe toxicities that are responsible for the morbidity associated with HNSCC therapy [1]. DNA interactive agents, antimetabolites and antimitotic agents demonstrate anticancer effects due to their ability to interfere with cell division. These agents could be expected to inhibit any cell and are fundamentally nonselective. However, rapidly proliferating cells show a greater susceptibility to chemotherapeutic agents, consequently greater cellular inhibition is seen for tumor cells. Rapidly proliferating tissues such as bone marrow, hair follicles, and intestinal epithelium are particularly susceptible to damage from cytotoxic drugs [6, 16]. Adverse effects such as nausea and vomiting (affecting the GI tract), alopecia (affecting hair follicles), and myelosuppression (affecting bone marrow) are commonly associated with use of chemotherapeutic agents. Additional toxicities include pulmonary fibrosis, organ infections, cardiotoxicities and nephrotoxicities. The "new era" targeted therapies, owing to their ability to inhibit specific processes involved in cancer progression, should manifest fewer toxicities compared to the more non-specific cytotoxic agents.

In choosing combination therapies, consideration must be given to using different drugs that act by distinct mechanisms of action. Not only will such an approach weaken a cancer cell at multiple points of its growth phases, but the incidence of adverse reactions and toxicities can be lowered by using lower doses of each individual agents compared to single agent therapy [5]. While this scenario improves tumor response rates in some cases, additional toxicities have been noted in certain cases using chemoradiation regimens [17].

New combination chemotherapy regimens continue to be studied to both reduce the incidence of resistance and improve survival rates of afflicted patients. Newer genera-

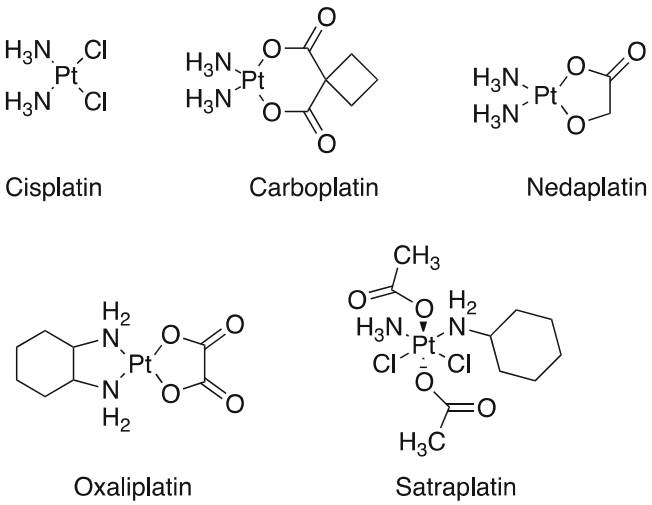

Fig. 28.2 Organoplatinum compounds – agents that interact with and damage DNA

tions of cytotoxic agents such as organoplatinum complexes [18] and taxane analogs [19] are being evaluated both alone and in combination. For HNSCC, specific molecular markers such as mTOR kinases, p53, and Bcl-2 mediated signaling pathways are being investigated as specific therapeutic targets [20]. Small molecule inhibitors of EGFR, VEGFR-2 kinases, and Bcl-2 are also under investigation as targeted therapies [21]. Combination chemotherapeutic regimens that integrate novel agents, improve tumor response, preserve organ function and reduce toxicities are being explored [22].

In the next sections, we will describe the specific mechanisms of action of the predominant chemotherapies of each of the four drug classes used to treat HNSCC and will also describe newer agents under investigation.

28.3 Agents Interacting with DNA

28.3.1 Organoplatinum Complexes

Several organometallic compounds containing platinum (Pt) play a role in cancer chemotherapy (Fig. 28.2). Most notable and widely used to treat HNSCC is cisplatin, a Pt (II) complex [23]. Barnett Rosenberg's discovery of cisplatin as an anticancer agent must be appreciated as one of the marvelous instances of serendipity in modern science. "Fascinated", in his own words, by the mitotic imagery of polarized centrioles and migrating chromosomes, Rosenberg perceived a magnetic phenomenon at work. To test this hypothesis he subjected dividing bacteria to an electric field. The result was an interrupted mitosis, which produced sausage-like, filamentous bacterial strands hundreds of micrometers in length. A biophysicist by training, Rosenberg had selected platinum electrodes precisely because, "Platinum of course,

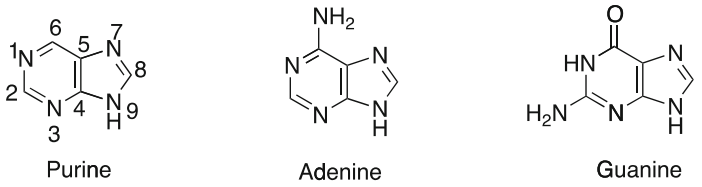

Fig. 28.3 Purine bases in DNA showing the numbering convention

is known to be quite inert in a biologic environment." Subsequent experiments revealed that, far from any magnetic effect, the investigators had quite inadvertently realized the anti-neoplastic potential of "Peyrone's Chloride" (now known as cisplatin), which had been first synthesized in 1845. The episode is recounted engagingly and with much modesty by Rosenberg himself [24].

Organoplatinum agents are weakly electrophilic and are thus susceptible to attack by "soft" nucleophiles such as thiol (–SH) moieties on proteins or amines (–NH) from proteins or DNA bases. The primary anticancer effect of organoplatinum drugs results from their capacity to form a complex with purine bases, and alkylate DNA.

Systemically administered cisplatin localizes to and enters the tumor cell using the copper (Cu^{2+}) transporter protein called CTR1 [25]. Intracellular cisplatin is activated by a chemical reaction involving nucleophilic attack by a water molecule, using a process termed aquation. One of the two chloride atoms in cisplatin is displaced during aquation. This process renders cisplatin activated and now susceptible to attack by nucleophiles, most specifically by the N7 amine of purine bases (e.g. adenine or guanine) in DNA (see Fig. 28.3).

The reaction between the DNA purine base and the hydrated organoplatinum molecule results in a cross-linked DNA-Pt complex. In an initial step, Pt binds to the major groove of DNA [23], where it localizes to and aligns with the DNA bases with which it will coordinate. The Pt then coordinates with N7 of purine bases, and the drug-DNA complex is further stabilized by electrostatic interactions between the two amine ligands of cisplatin and the anionic phosphate residues on the DNA polyribose backbone. The organoplatinum compound forms a cross link with two purine bases. While the predominant cross-linking occurs between adjacent guanine residues or between adjacent guanine and adenine residues on the same strand of DNA (intra-strand or a *"cis"* configuration), inter-strand cross links (between guanine and adenine bases across the individual strands of double stranded DNA) also occur. The DNA-Pt cross-linked complexes can no longer properly form hydrogen bonds, which changes the overall conformation of DNA and results in a bent or "kinked" molecule. The bent DNA structure can no longer separate and duplicate; furthermore the bent structure binds nuclear proteins that prevent DNA repair, rendering the drug-complexed DNA unable to participate in cell division [23, 25] (Fig. 28.4).

All these processes lead to the triggering of programmed cell death pathways (i.e. apoptotic signaling cascades). In addition to binding proteins that prevent DNA repair, DNA-Pt complexes may also bind to and modulate the activities of protein kinases, caspases and E-cadherin.

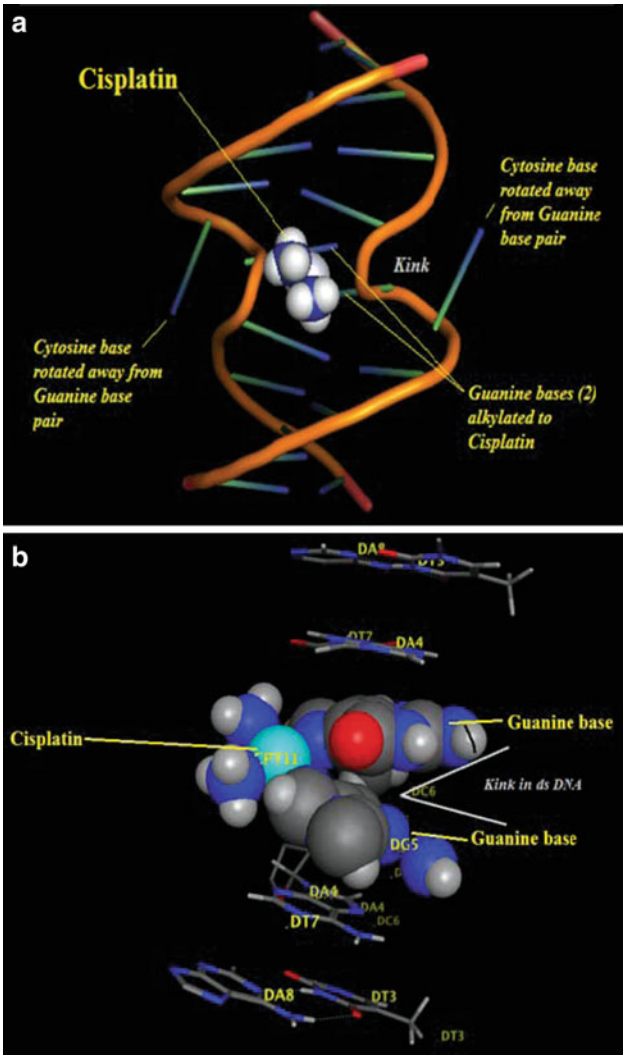

Fig. 28.4 Cisplatin interaction with DNA. *Panel A*: Image of the cross-linked dsDNA-organoplatinum complex. Figure shows cisplatin in space filling spheres cross-linking two guanine bases on antiparallel strands of DNA. Cross strand cytosine bases are shown rotating away from and extending off the deoxyribophosphodiester backbone. Cisplatin kinks (*bends*) the DNA backbone such that GC base pairs cannot properly form inter-strand hydrogen bonds. *Panel B*: A space-filling model showing the molecular orientation of cisplatin cross-linked to two purine bases demonstrating the "bent" or "kinked" conformation this chemotherapeutic agent confers on DNA. Modified using Molecular Operating Environment (MOE) from [26]; PDB code: 1DDP

Cisplatin must be administered IV. In blood, it demonstrates significant plasma protein binding (90%) and is absorbed into cells by both passive and active diffusion. Its initial plasma half-life is less than 1 h. The initial phase is succeeded by a longer secondary phase with an elimination half-life of 58–73 h [27]. Cisplatin accumulates

in the kidneys, testes, liver and intestines, but does not readily cross the blood–brain barrier. Excretion is predominantly renal, and slow, with only a small amount of administered dose recovered in the urine even after several days. Accumulation of cisplatin in the kidneys is highly nephrotoxic and can cause significant damage to the renal tubules, especially in patients with compromised renal function. Hence, patients with kidney disease may not tolerate a standard dose of cisplatin. Chloride-containing solutions, saline, mannitol diuretics or sodium thiosulfate solutions are sometimes co-administered to promote drug excretion and reduce kidney damage [23]. Bone marrow depression, facial edema, bronchoconstriction, ototoxicity, nausea and vomiting are additional toxicities associated with cisplatin chemotherapy.

Cisplatin is a powerful emetic, one so reliable that cisplatin-treated ferrets are a standard rodent model for evaluating anti-emetic candidates [28]. Cisplatin and other Pt agents stimulate gut enterochromaffin cells to release 5-HT and substance P [29]. These signaling molecules engage vagal afferents that relay to emetic centers in the central nervous system. In the absence of preventative measures, cisplatin therapy causes nausea and vomiting in nearly all patients, sometimes to a degree that can be dose-limiting. Nausea and vomiting usually appear within 2 h and persist intermittently over several days after administration. 5-HT_3 blockers with dexamethasone, and more recently combined with the neurokinin-1 antagonist aprepitant, are very effective in controlling nausea and vomiting, and should be administered prior to cisplatin therapy [30].

With improved control of nephrotoxicity and emesis, neuropathy has become the major dose-limiting side effect of cisplatin therapy. The mechanism for this remains uncertain, however cisplatin appears to preferentially accumulate in and damage neurons of the dorsal root ganglion [31–33]. Neuropathy is dependent on cumulative dose, appearing above 300 mg/mm^2. Large sensory fibers are primarily affected, with primary symptoms of numbness or tingling in the limbs progressing to impaired proprioception and sensory ataxia. In more severe cases, gait and ambulation are frankly impaired. Motor functions, as well as pain and temperature perception, are preserved. Neuropathic sequelae are often delayed, with symptoms appearing and worsening months after cisplatin therapy has ended. Many patients enjoy partial improvement and debilitation is rare, but sensory deprivation obvious to the patient may last for many years.

Cisplatin causes hearing loss in a dose-dependent and cumulative fashion. Hearing deficit first occurs in higher frequencies and can progress to affect more functional ranges. Tinnitus is the initial symptom and may occur within a few days, and one or both ears may be affected. Particularly susceptible are young children, and perhaps individuals with glutathione-S-transferase polymorphisms. When possible other ototoxic agents such as aminoglycoside antibiotics should not be co-administered with cisplatin. The mechanism of cisplatin ototoxicity is unclear, but appears to involve reactive oxygen species and oxidative damage to hair cells [34].

Several mechanisms account for resistance to cisplatin. These include reduced uptake of the drug, increased inactivation by glutathione-S-transferase or metallothioneins (which use sulfhydryl groups as nucleophiles to bind cisplatin and reduce the amount available to react with DNA bases), and an expressed deficiency in DNA mismatch repair (MMR) [35–37]. The MMR process involves several

DNA-associated enzymes that bind to cisplatin-DNA adducts and activate apoptotic signaling cascades and cell cycle arrest. A functioning MMR pathway will increase the cytotoxic potency and effectiveness of cisplatin. Conversely, a deficiency in MMR enzymes will thus render cisplatin less effective. In ovarian cancers, cisplatin resistance has been attributed to the overexpression of efflux transporters ATP7A and ATP7B, which pump drug out of the cell, thus lowering intracellular concentrations and reducing drug effectiveness. This mechanism of resistance has not yet been demonstrated in specific instances of HNSCC.

In combination therapy regimens, cisplatin is often used with radiation. It is a potent radiosensitizer, which ultimately improves overall response rates [22]. Additionally, improved tumor response rates have been observed for cisplatin/docetaxol (DTX), cisplatin/bevacizumab, cisplatin/cetuximab and cisplatin/5-fluorouracil/cetuximab combination regimens [38, 39]. Carboplatin (see Fig. 28.2) works by the same mechanism as cisplatin, however carboplatin is slightly less potent on a mole-to-mole basis [40]. Carboplatin is a more convenient agent because it does not require hydration, and is less nephrotoxic, less ototoxic, and less neurotoxic. However it is associated with higher levels of myelosuppression. Despite carboplatin's potential advantages and conveniences, cisplatin remains the choice agent for HNSCC, because of superior efficacy [41].

A second generation platinum complex, nedaplatin (see Fig. 28.2) has shown improved antitumor effects in combination with DTX [42]. Nedaplatin is approved for the treatment of HNSCC in Japan. A third generation Pt complex, oxaliplatin (see Fig. 28.2) is also under investigation for HNSCC in combination with PTX or PTX/cetuximab [43]. Oxaliplatin is effective against cisplatin-resistant tumors, in particular for MMR-deficient tumors [44]. Oxaliplatin's cytotoxicity is independent of MMR because oxaliplatin-DNA adducts themselves do not bind to MMR. This is attributed to a greater bend in DNA with cisplatin compared to oxaliplatin, which provides a better conformation so that MMR enzymes can bind to and repair the DNA.

Satraplatin (see Fig. 28.2) is a Pt (IV) complex that is considered a prodrug. One of the two primary amine cross-linking foci (which normally carries a positive charge) is temporarily neutralized, requiring activation *in vivo* [18]. By virtue of its reduced charge, the prodrug is better able to cross intestinal membranes and is the only Pt complex that can be given orally. It is currently being explored for ovarian and prostate cancers, but has not yet been investigated for HNSCC. Myelosuppression, neutropenia and thrombocytopenia are side effects that have been observed with satraplatin.

28.3.2 Bleomycin

The glycopeptide antibiotic bleomycin (BLM) has been used as an anticancer agent for more than 40 years and is commonly employed in HNSCC. BLM refers to a family of congeners isolated from the bacterium *Streptomyces verticillus*. The prescribed anticancer agent often includes a mixture of several congeners (Blenoxane®) comprising predominantly BLM A2, B2 and A5. The basic structure of all BLM congeners has four domains as shown in Fig. 28.5. These include a metal binding

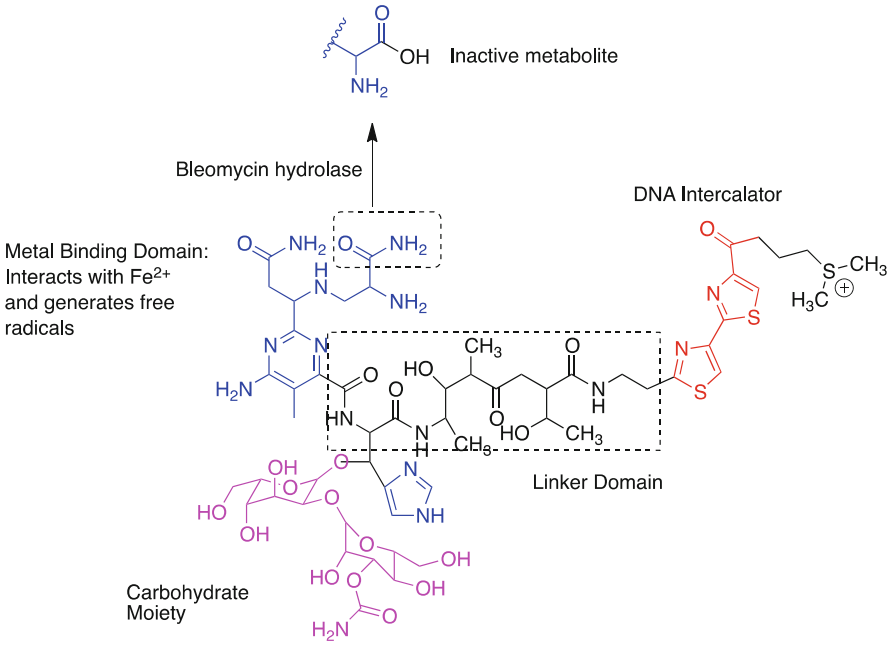

Fig. 28.5 The structure of Bleomycin A2 (BLM-A2). The metal (iron II) binding domain is the site that is activated by oxygen to form free radicals. The imidazole residue directly beneath the linker domain box is also part of the metal binding domain. Also shown are associated carbohydrate structures and a reactive bithiazole DNA intercalation site

domain, a DNA intercalation domain, a linker domain and a carbohydrate domain [45]. The different congeners (i.e. A2, B2, A5) are defined by unique substituted, positively charged side chains that extend off the R-group as shown in the figure.

The mechanism of action for BLM involves DNA strand breaks. Its unique structure enables BLM to first bind to selective DNA sequences and then cleave the DNA molecule near this binding site using oxidative power elicited by the actions of a juxtaposed iron II ion on oxygen (O_2) molecules [45, 46]. BLM can cause both single DNA strand breaks (ssDNA) and double DNA strand breaks (dsDNA). The different congeners of BLM all contain side chains with strong positive charges, which help BLM interact with the negatively charged phosphate backbone of a DNA polymer. Different parts of the antibiotic interact with high specificity and selectively with DNA bases, and importantly to dsDNA-base-pair "hot spots" that are rich in guanine-cytosine and guanine-thymine sequences [47].

The DNA binding domain of BLM (shown in red) involves two aromatic thiazole rings (i.e. bithiazole). These groups partially intercalate between DNA base pairs to help orient the drug to specific DNA sequences. The thiazole groups help provide both hydrogen- and pi-bonding energy to bind this part of BLM to nucleotide bases and orient the other parts of the molecule for anticancer, DNA-cleaving activity.

The metal binding domain of BLM chelates intracellular iron (Fe^{2+}) using each of the imidazole, pyrimidine and polyamine moieties that make up this domain (shown in blue). In the three dimensional structure of BLM, the imidazole group (shown below the linker domain highlighted by the dashed box) is brought into juxtaposition with the pyrimidine and polyamine moieties to form a multi-coordinated binding pocket for the iron II atom. This metal chelation site binds oxygen (O_2) and abstracts protons from atoms in the DNA molecule to generate highly reactive oxygen free radicals. The free radicals are localized at the site of BLM binding and subsequently cleave the deoxyribose backbone, leading to single-strand breaks. The selectivity of BLM for G-C or G-T rich sequences of DNA has been attributed to slight variations in structure, which allow for facilitated abstraction of protons to generate the bond-breaking toxic oxygen species. Further anticancer activity of BLM is elicited by the cleaved cyclic deoxyribose sugar, which further forms a highly reactive (electrophilic) aldehyde called propenal that inactivates essential cellular proteins by alkylating nucleophilic cysteine (Cys) residues.

The other two domains of BLM include the linker and carbohydrate (shown in pink) regions. The linker region plays a role in DNA cleavage, although the mechanism is poorly understood. The carbohydrate moieties are necessary for cellular recognition, uptake, and metal coordination, and contribute to the solubility of BLM in aqueous solutions.

BLM also cleaves all cellular RNAs, however the clinical relevance of RNA cleavage is yet uncertain [45]. Medicinal chemists continue to generate synthetic BLM analogs and conjugates which facilitate an improved understanding of the structural features necessary for differentially targeting of DNA and RNA, and also for facilitating cellular uptake [48–51].

Because its oral bioavailability is less than 5%, BLM must be given by injection (parenterally) either intravenously (IV), intrapleurally, intramuscularly (IM) or subcutaneously (sub Q) [16, 52]. Intravenous BLM is given in a metal-free form; in blood, however, it rapidly binds plasma copper (i.e. Cu(II)). While its mechanism of uptake into cells is unclear, BLM is both relatively large and hydrophilic, and therefore is probably imported into the cell via receptor-mediated uptake. Its copper substituted complex is thought to facilitate transport into cells. However, BLM uptake does not use the same copper transporter protein (CTR1) used for cisplatin [53]. Inside the cell, the copper ion can be exchanged for an iron ion that establishes a more highly reactive site for making reactive oxygen species.

BLM's plasma half-life is about 2–4 h, and excretion is ~60% renal. In patients with impaired renal function (which is a more likely scenario in patients who have previously received cisplatin), BLM's plasma half-life is extended to ~20 h. Impaired kidney function, arising either as a primary cause or a secondary side effect of alternative therapies, is a key parameter to monitor when devising any chemotherapeutic strategy. BLM does not cross the blood–brain barrier. It is patently teratogenic (i.e. causing malformations in fetuses or embryos) in rats and its use is associated with high incidence of human fetal abnormalities.

In the clinical setting, a powerful advantage of BLM is its relatively low rate of myelosuppression and immunosuppression relative to other chemotherapeutics. BLM therapy, however, is dose-limited by interstitial pneumonitis, which occurs in

about half of all patients, and deteriorates to fatal fibrosis in ~3% of cases. Tetrathiomolybdate, an experimental agent used to selectively chelate copper ions, may lower the risk of BLM-induced fibrosis by inhibiting the action of copper-dependent inflammatory cytokines. Its use has a favorable effect on mouse models of HNSCC metastasis [54]. Erythema is also observed after 2–3 weeks of BLM therapy. Rarely, an erythema patient presents with flagellate whip-marks that later becomes hyperpigmented [55]. Erythema is generally not a major problem that, when persistent, responds well to glucocorticoids. Raynaud's Phenomenon may also result from BLM.

The action of BLM is regulated by the action of BLM hydrolase, a Cys protease that hydrolyzes the terminal amide moiety to the corresponding carboxylate. Tumor resistance to BLM is associated with high concentrations of BLM hydrolase, while low levels in the lungs and skin may explain preferential toxicity [56]. HNSCC display lower concentrations of BLM hydrolase and respond well to BLM. Enhanced repair of BLM-induced DNA strand cleavage and reduced cellular uptake of BLM might also explain poor response rates [57, 58].

28.4 Antimetabolites: Agents That Interfere with DNA Synthesis

Antimetabolites are structural analogs of purine and pyrimidine bases or of their nucleosides. These agents interfere with specific metabolic reactions involved in the synthesis of DNA. Antimetabolites such as 6-mercaptopurine, 6-thioguanine, allopurinol and acyclovir have been approved for treatment of cancer, and also infectious diseases, gout, and other autoimmune diseases.

Methotrexate (MTX), pemetrexed, and 5-fluorouracil (5-FU) are the most common antimetabolite agents used to treat HNSCC. They specifically target the enzymes thymidylate synthase (TS) and dihydrofolate reductase (DHFR). These two enzymes participate in the pathways that make nucleotide bases from precursor building blocks, and then prepare (activate) nucleotide precursors so they can be incorporated into duplicating DNA strands [59, 60]. TS is an absolute requirement for the synthesis of thymidine nucleotides needed for DNA replication. TS takes deoxyuridine monophosphate (dUMP), and transfers a one carbon (methyl) moiety to the uracil ring of the uridine nucleotide using the folic acid precursor, N^5, N^{10}-methylenetetrahydrofolate (N^5, N^{10}-CH_2THF), forming deoxythymidine monophosphate (dTMP, see Fig. 28.6). Folate is a critical cofactor in this and many other reactions. Its specific function in the synthesis of DNA resides in its capacity to transfer one-carbon units in various redox states during the synthesis of both purine and pyrimidine bases. Inhibiting folate reactivity results in the inability to synthesize necessary building blocks for DNA synthesis, thereby preventing cell division. DHFR is the key enzyme that makes the activated form of folate required for TS activity. The antimetabolites methotrexate and pemetrexed are structural analogs of folate; they compete for the active site of DHFR and reduce the chance for successful production of the N^5, N^{10}-CH_2-THF co-factor [61]. 5-FU is a structural analog of

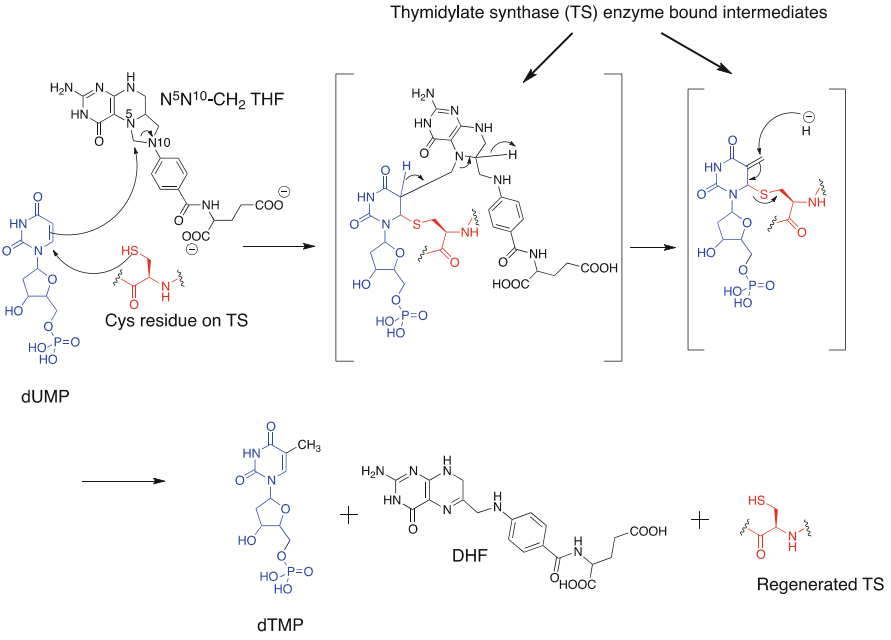

Fig. 28.6 Biosynthesis pathway of thymidine nucleotides and the role of folate derivatives in this process. TS catalyzes the synthesis of 2′-deoxythymidine-5′–monophosphate (dTMP) from 2′-deoxyuridine-5′-monophosphate (dUMP) and 5,10-methylenetetrahydrofolate (N^5,N^{10}-CH_2THF). A key Cys residue in TS provides an anchoring point for the uridine base of dUMP to accept a one carbon transfer from N^5, N^{10}-CH_2THF which is further reduced to a methyl group to form thymidine base needed for DNA synthesis

dTMP; it competes for the active site of TS and reduces the chance that necessary nucleotide building blocks will be available for DNA duplication in dividing cells.

The TS reaction shown above details how an activated, high-energy methylene group-containing tetrahydro form of folic acid (N^5, N^{10}-CH_2-THF) transfers its high energy bonds to dUMP. In the process, the folic acid loses two electrons to form low-energy dihydrofolic acid (DHF). DHF must be re-reduced back into tetrahydrofolate (THF) to be available for additional cycles of TS activity and for the synthesis of purine bases. This important reaction is catalyzed by DHFR and uses 2 NADPH cofactors to add reducing equivalents to DHF. Figure 28.7 Panel A shows the structural similarity between MTX and THF. Panel B shows the biochemical reaction catalyzed by DHFR and inhibited by the antimetabolite agent, methotrexate.

TS inhibition leads to an inhibition of dTMP synthesis and a “thymine-less cell death.” Since thymidine is not part of RNA, inhibitors of TS selectivity inhibit DNA synthesis. The direct inhibition of DHFR causes an increase in cellular levels of 7,8-DHF resulting in feedback inhibition of TS, further inhibiting cell growth and contributing to the anticancer effect of these agents.

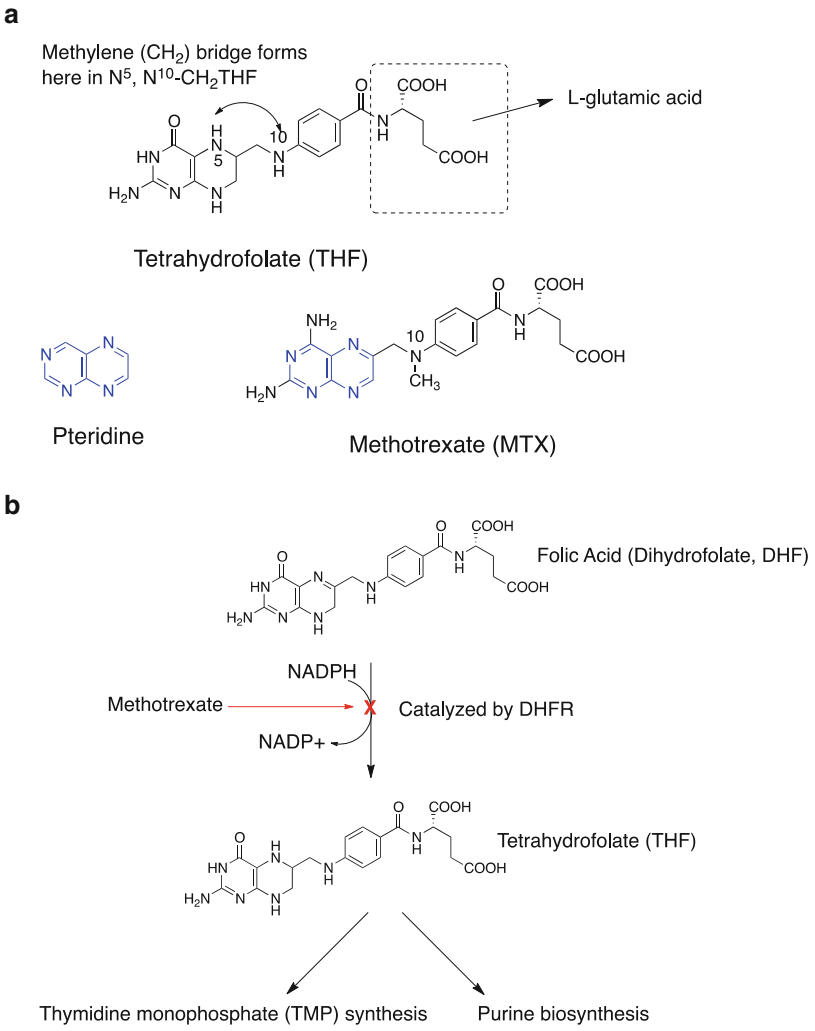

Fig. 28.7 Methotrexate (MTX) and tetrahydrofolate (THF). *Panel A*: Structural similarities of MTX and THF. *Panel B*: Dihydrofolate reductase (DHFR)-catalyzed conversion of folic acid (i.e. dihydrofolate, DHF) to tetrahydrofolate (THF), a reaction that is inhibited by MTX

28.4.1 Thymidylate Synthase (TS) Inhibitors

5-FU is among the very first chemotherapeutic agents to result from a rational design process. Observing that tumor cells had metabolized greater quantities of uracil compared to non-malignant cells, Heidelberg and colleagues synthesized and tested a series of fluorinated pyrimidines from which 5-FU emerged as the most useful in a clinical setting [62, 63]. For over four decades, it has been used as an anticancer agent, most successfully for colorectal cancer, but also for breast, ovarian,

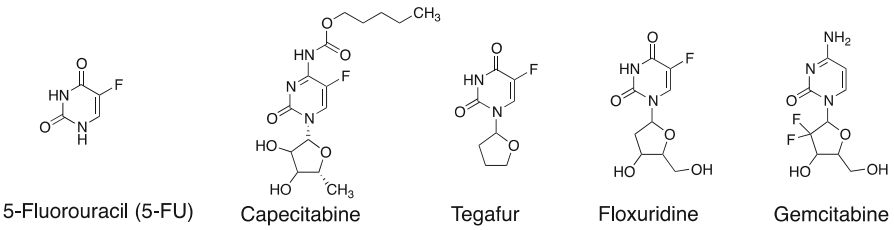

Fig. 28.8 5-Fluorouracil (5-FU) and similar pyrimidine nucleoside analogs drugs

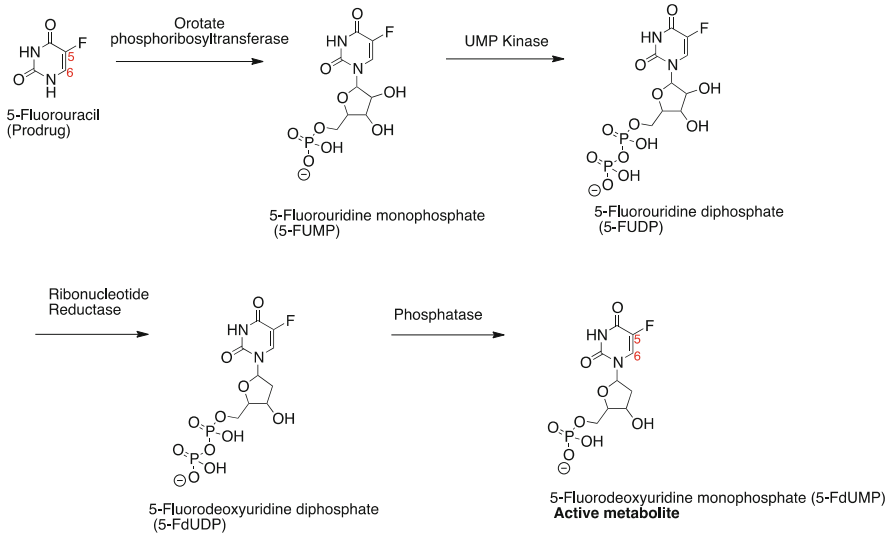

Fig. 28.9 5-Fluorouracil (5-FU) prodrug activation into the deoxynucleotide that binds TS

and head and neck cancers. However, as a single agent in any application, 5-FU offers only modest improvement in response rates and survival. Therefore, 5-FU is usually administered in combination therapy, with, for example, cisplatin, methotrexate, and rifutuximab. 5-FU is also used with radiation in multimodal therapy.

5-FU is a structural analog of uracil that inhibits the conversion of uridine to thymidine in the reaction catalyzed by TS [64]. The anticancer activity of 5-FU resides in its structural mimicry to the normal pyrimidine building block (thymidine) needed for DNA synthesis. It thus competes for the enzyme active site and prevents the proper building blocks from binding. Other structural analogs of pyrimidine bases found in DNA include capecitabine, tegafur, floxuridine and gemcitabine (see Fig. 28.8). All these agents are classified as inhibitors of TS. 5-FU is actually a prodrug that is activated *in vivo* by the intracellular enzymes orotate phosphoribosyltransferase, UMP kinase, and ribonucleotide reductase. These enzymes activate 5-FU first into the ribonucleotide 5-fluorouridine-5′-diphosphate (5-FUDP). 5-FUDP is then further modified to a deoxyribose derivative (for inclusion in DNA synthesis pathways) by ribonucleotide reductase and phosphatase, culminating in the inhibitory molecule 5-fluoro-2′-deoxyuridine-5′-monophosphate (5-FdUMP) (see Fig. 28.9).

5-FdUMP binds covalently to TS and forms a ternary complex with TS and tetrahydrofolate. 5-FdUMP differs from the endogenous substrate dUMP by the presence of a 5-fluoro group and serves as a pseudosubstrate for TS. The fluorine atom substituted at the C5 position of 5-FU is very electronegative. It draws electrons from nearby bonds (i.e. the C5-C6 bond) into its nucleus, making the C6 position of the 5-FdUMP more electrophilic than is typical of the natural dUMP substrate. This electron deficient carbon is more easily attacked by the juxtaposed Cys 195 nucleophile in TS, resulting in the formation of an irreversible covalent bond in the active site. In the presence of dUMP, the THF cofactor of TS normally removes the C5-hydrogen; however the C5-fluorine bond of the antimetabolite is stable to cleavage. Because the ternary complex cannot break down, the enzyme is irreversibly inhibited. And since dTMP is a key component in DNA biosynthesis and cell replication, irreversible TS inhibition leads to an inhibition of dTMP synthesis and, similar to methotrexate, a "thymine-less cell death." Uridine is the pyrimidine also used in RNA, so 5-FU metabolites can also be incorporated into RNA, preventing RNA synthesis and thereby exerting additional cytotoxicity.

Various pharmacological strategies have been used to enhance the killing power of 5-FU. The most common co-administers leucovorin with 5-FU. Leucovorin is a structural analog of folic acid that increases the efficacy of 5-FU by stabilizing the ternary complex with TS [65]. Lower doses of leucovorin are well absorbed from the GI and may be administered orally, however larger doses are by IV or IM. Activity is confined to the S enantiomer, which is available as the enantiopure levofolinic acid. The elimination half-life of leucovorin ranges from about 3–6 h, somewhat dependent on route of administration.

5-FU must be given IV; it can be absorbed from the gut but that process is highly erratic (for reviews see [66]). Its half-life is short but variable, ranging from several minutes to about a half-hour, and it is metabolized by two major pathways (see Fig. 28.10). The so-called anabolic route produces phosphorylated pyrimidines, i.e. the compounds that are mainly responsible for anti-neoplastic effects. In an alternative catabolic pathway, 5-FU is instead inactivated by the enzyme dihydropyrimidine dehydrogenase (DPD), via a reaction that produces dihydrofluorouracil. Subsequent steps yield metabolites that are excreted in the urine, although some products appear in the bile. In standard bolus dosing schedules, as much as 80% of the 5-FU is metabolized in the catabolic arm. Plasma levels rise to several hundred micromolar and then subside quickly, but variably, based mostly on individual differences in DPD activity, which differs by as much as six-fold between individuals. The comparatively severe toxicities experienced by some females are thought to result from a sex-related DPD polymorphism. In any case, the bolus administration is wasteful and less efficacious, because kill concentrations are not maintained for sufficient length of time. Simultaneously, it is probably more toxic to healthy tissues exposed to acutely high concentrations.

Continuous infusion (CI; or PVI, prolonged venous infusion) methods try to address these shortcomings by providing a slow and steady delivery of drug over several days or longer. However the need for infusion pumps and central catheters adds considerable complexity, expense, and opportunity for infection and other medical mishap. These difficulties notwithstanding, continuous infusion with 5-FU and other agents have been effective in HNSCC.

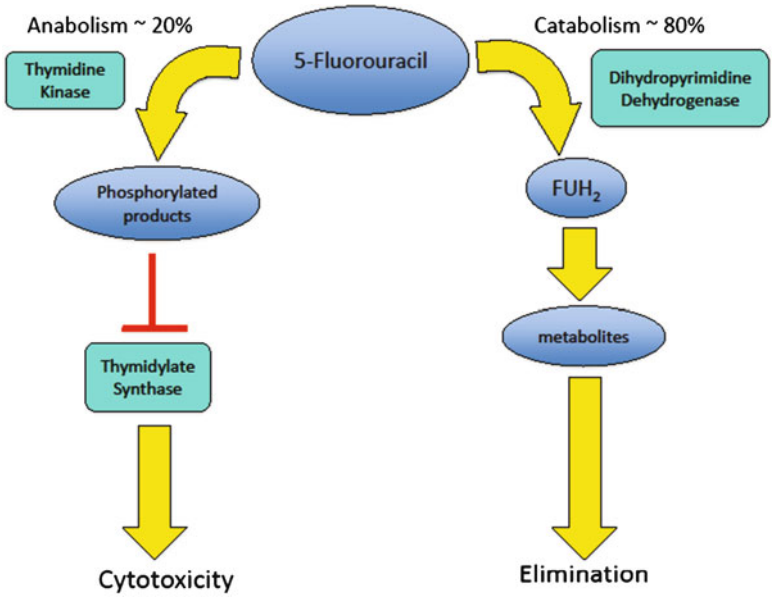

Fig. 28.10 5-Fluorouracil metabolic pathways involved in chemotherapy-induced cellular toxicity. 5-fluorouracil (5-FU) is metabolized via two pathways. With bolus injections, the majority is catabolized by dihydropyrimidine dehydrogenase (DPD) into dihydrofluorouracil (FUH2). Through the anabolic pathway, 5-FU is phosphorylated into products that form a stable intermediary complex with thymidylate synthase. This mechanism leads to thymidine starvation

Some 5-FU and other chemotherapy dosing schedules are further optimized according to circadian patterns. Such "chronomodulation" is based on the observation that DPD activity is generally highest in the late evening and lowest in the late morning. Conveniently, thymidine kinase activity fluctuates in a complementary pattern, with activity highest when DPD is low. The upshot is a window of opportunity to give the drug when the metabolism profile is most favorable for 5-FU's activation via the anabolic pathway. In considering these and other patterns, the best predicted time for 5-FU administration is 4 am, and thus tolerability is improved when the drug is administered between 10 am and 10 pm.

Attempts to produce an orally active version of 5-FU have met with varying success. Doxifluridine (deoxy-5-fluoridine, DFUR) and its carbamate derivative capecitabine were developed as different prodrugs of 5-FU to lessen the chance of degradation. These agents are nucleoside analogs that are absorbed through the intestine and metabolized to 5-FU. One activation step requires the enzyme thymidine phosphorylase, which is overexpressed in tumor cells compared to normal cells. This favors prodrug activation and accumulation at the site of the growing tumor, thus biasing cytotoxicity against tumor cells. Capecitabine is used in the management of HNSCC as a single agent, in combination with the DNA-damaging platinum complexes cisplatin and oxaliplatin, and with antimitotic agents docetaxel (DTX) and paclitaxel

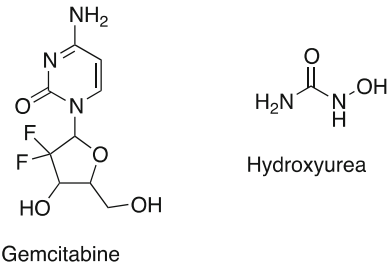

Fig. 28.11 Inhibitors of ribonucleotide reductase

(PTX, see ahead) [67–70]. Owing to the promising results of these studies, evaluations for capecitabine as a component of additional combination regimens are underway.

An oral third-generation fluoropyrimidine derivative tegafur, a tetrahydrofuran 5-FU derivative and uracil (see Fig. 28.8), was intended to overcome reduced efficacy of 5-FU in certain tumor models [71]. Tegafur is metabolically converted to 5-FU and confers anticancer activity by inhibition of TS. However due to CNS toxicity without improvement over 5-FU, tegafur has been discontinued in the US.

The adverse effects of 5-FU and related agents include myelosuppression, stomatitis/esophagopharyngitis, potential GI ulceration, and nausea and vomiting [72]. These are more severe in bolus compared to infusion therapies. Hand-foot syndrome, characterized first by numbness and tingling that progresses to painful erythema, touch sensitivity, and desquamination, is more common with capecitabine.

28.4.2 Inhibitors of Ribonucleotide Reductase

Gemcitabine (see Fig. 28.11) is a cytosine (pyrimidine) analog and includes 2′-fluoro substitutions on the deoxyribose moiety [16]. It is a nucleoside analog that is phosphorylated *in vivo* to a triphosphate (nucleotide) derivative that inhibits ribonucleotide reductase. Ribonucleotide reductase converts ribonucleotides into deoxyribonucleotides necessary for DNA synthesis. Gemcitabine binds to the enzyme active site and competes with 2′-deoxycytidine triphosphate for incorporation into DNA.

Hydroxyurea (see Fig. 28.11) also inhibits ribonucleotide reductase. Its mechanism of action involves scavenging for and neutralizing a tyrosyl free radical species at the enzyme catalytic site [73]. This high-energy free radical is required for the dehydration of ribosugars into deoxyribosugars. By destroying the tyrosyl free radical, hydroxyurea treatment results in a reduced pool of deoxyribonucleotide substrates available for DNA synthesis, thereby slowing cell division. Both hydroxyurea and gemcitabine are potent radiosensitizers that increase cisplatin cytotoxicity [22]. Gemcitabine is under investigation as part of combination regimens with cisplatin and cisplatin/DTX for HNSCC [2]. Hydroxyurea has single agent activity and is currently used as an adjuvant therapy for HNSCC. Resistance has been reported due to overexpression of ribonucleotide reductase.

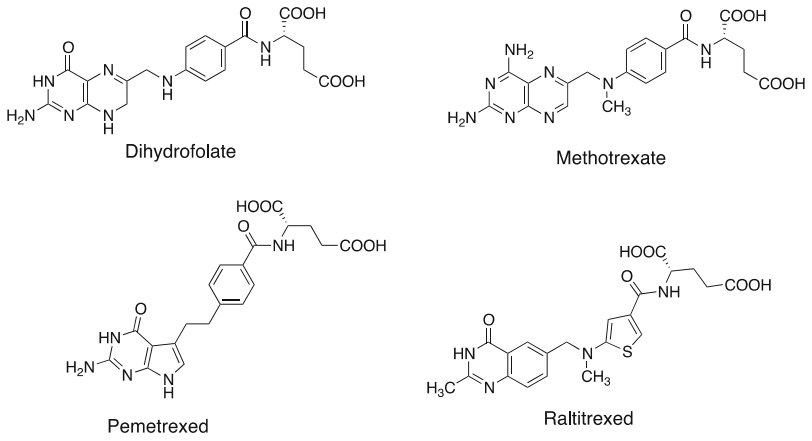

Fig. 28.12 Antifolates interfere with THF metabolic pathways

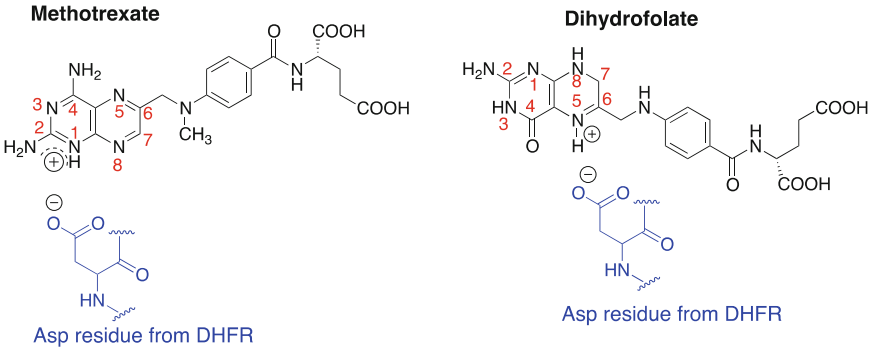

Fig. 28.13 Comparison of the binding modes of the drug methotrexate (MTX) and the cofactor dihydrofolate (DHF) to dihydrofolate reductase (DHFR) (Modified from [74])

28.4.3 Antifolates

Antifolates are agents that interfere with metabolic processes involving tetrahydrofolate as either a substrate or product (Fig. 28.12). As a structural analog of folate, MTX is the classic example of an antifolate drug. Structurally, the different substitutions off the pteridinyl double ring structure of methotrexate (compared to dihydrofolate) alters the protonation sites of the drug, and results in different amine residues of the molecule forming a salt bridge with an aspartic acid residue in the enzyme's active site. MTX is "flipped" in the enzyme site using a primary amine salt bridge off of its C2 position compared to the secondary amine salt bridge off of the N5 position of DHF (see Fig. 28.13).

In a productive interaction between DHF and its enzyme, there are additional interactions driven by hydrogen bonding and van der Waals interactions in the active site.

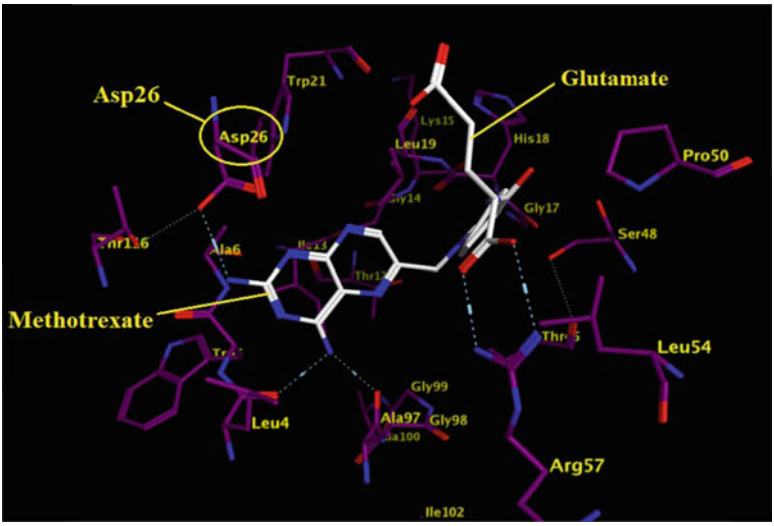

Fig. 28.14 Molecular model showing methotrexate (MTX) with its glutamate side chain bound to Dihydrofolate Reductase (DHFR) (Modified using Molecular Operating Environment (MOE) from [78]; PDB code: 3DFR)

The N5, C6-double bond is so positioned that it comes close to the NADPH cofactor that participates in hydride transfer reactions. When MTX binds, however, the primary amine that is substituted off the C4 position enriches electron density at N1 promoting protonation at N1 instead of N5. Thus, the protonated N1 interacts with the Asp26 residue in DHFR through an electrostatic bond thereby positioning the 5,6-double bond of MTX away from the bound NADPH cofactor [74]. The methylene activated N^5,N^{10}-THF cofactor that is required for the one carbon transfer reaction in the synthesis of purine bases cannot be formed, thereby inhibiting the synthesis of dTMP. The inhibition of DHFR increases cellular levels of 7,8-DHF resulting in feedback inhibition of TS [75–77]. MTX also inhibits the enzyme Glycine Amide Ribonucleotide transformylase (GARFT), which is involved in the synthesis of purine nucleotides. Figure 28.14 shows the interactions of MTX and with various residues including Asp26 in the DHFR active site [78].

MTX can be given orally in the treatment of HNSCC. It is also useful in the treatment of breast, lung cancers and non-Hodgkin's lymphoma. The sodium salt is available for IV, IM, intra-arterial, or intrathecal injection.

MTX is termed a classical antifolate due to the presence of a monoglutamate tail. The monoglutamate tail of MTX permits carrier-mediated transport into cells [79–81]. Two distinct carrier-mediated active transport systems have been identified for antifolate uptake in mammalian cells. These include RFC (Reduced Folate Carrier) and the membrane associated Folate Binding Protein (FBP), also called the Folate Receptor (FR) system. RFC is a low affinity transporter of MTX, while FR is a high affinity transporter with binding affinities in the nanomolar range. Once inside the cell, MTX undergoes a polyglutamylation reaction that adds several

anionic carboxylate groups. Compared to the monoglutamates, polyglutamylation of folates and antifolates offers several benefits: (1) They are polyanionic species that are more readily ion-trapped within the cell. (2) They are utilized much more efficiently by enzymes of the reduced folate pathway, particularly TS. (3) They more strongly inhibit the target enzymes of the folate pathway, especially TS.

MTX-induced nephrotoxicity can occur with high doses, that allow drug to accumulate, and when renal excretion is impaired by kidney disease [59]. At high doses, MTX and its 7-hydroxymetabolite precipitate in the renal tubule, causing damaging crystalluria. Other serious toxicities include lung disease, ulcerative stomatitis and hemorrhagic enteritis, and fatal skin reactions. MTX-induced toxicities can be reduced with IV hydration, urinary alkalinization, and leucovorin rescue. Increased volumes of more alkaline urine enhance the solubility of MTX. Leucovorin generates the folate cofactors needed by DHFR and GARFT to ensure the continued synthesis of pyrimidine and purine nucleotides in healthy cells. It is often used prophylactically after high dose MTX therapy. More recently, the enzyme glucarpidase has been utilized to alleviate MTX-induced nephrotoxicity [82, 83]. In the blood, glucarpidase rapidly hydrolyzes MTX into glutamate and 4-deoxy-4-amino-N^{10}-methylpteroic acid (DAMPA). Glucarpidase cannot cross the blood–brain barrier or cellular membranes; hence it is prudent to also use leucovorin for at least 48 h to overcome the intracellular effects of MTX. Glucarpidase also breaks down leucovorin.

Resistance to MTX develops via several mechanisms including decreased uptake via the reduced folate carrier (RFC)-mediated membrane transport, increase in DHFR activity due to DHFR gene amplification, specific transcription-translational modifications, and decreased polyglutamylation of MTX due to altered or low levels of folylpoly-γ-glutamate synthetase (FPGS) [84, 85].

N^{10}-propargyl-5,8-dideazafolate (PDDF) was identified as a potent inhibitor of TS. However, its clinical usefulness is limited due to unpredictable renal toxicity that can be life threatening in myelosuppressed patients. The low water solubility of PDDF in the renal tubules has led to the development of the structural analog raltitrexed (see Fig. 28.12). Raltitrexed is more water-soluble than PDDF due to the presence of an added methyl group [86]. It utilizes the RFC system more efficiently and is a better substrate for FPGS than PDDF. Raltitrexed is currently under investigation as an adjuvant to combination regimens with carboplatin [87].

Pemetrexed (see Fig. 28.12) is a pyrrolo[2,3-*d*]pyrimidine-based inhibitor of TS whose activity depends on FPGS [88, 89]. Pemetrexed is a multi-targeted antifolate that inhibits DHFR, GARFT and carboxamide ribosyl-5-phosphate formyltransferase (AICARFT). The antitumor activity of pemetrexed is however primarily attributed to its TS inhibition. Pemetrexed is currently used for the treatment of malignant pleural or peritoneal mesothelioma in combination with cisplatin, and as a single-agent for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC). It is under investigation for its use in HNSCC in combination chemotherapeutic regimens with 5-FU and, separately with bevacizumab [90].

Extensive studies have focused on the design and synthesis of several classical and nonclassical antifolates as potential inhibitors of TS and DHFR. These agents

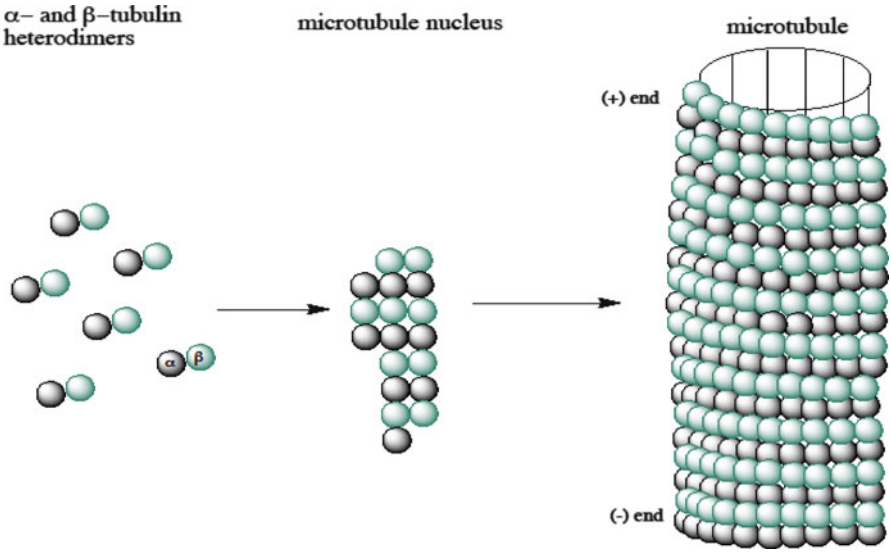

Fig. 28.15 Microtubules form when alpha-beta heterodimer subunit dimers polymerize in a directional manner (Adapted from [105])

demonstrate improved resistance and toxicity profiles *in vitro* and in mouse tumor models [91, 92]. It will be interesting to determine if these results translate to clinical models of HNSCC. Combination regimens under investigation include the multi-targeted antifolate, pemetrexed/gemcitabine/radiation [93]; raltitrexed/5-FU/leucovorin [94]; pemetrexed/cetuximab/radiation [90].

28.5 Antimitotics: Drugs That Interfere with Cell Division by Disrupting the Cytoskeleton

Mitosis is a process during cell division in which replicated genetic material is divided equally between two daughter cells in the form of chromosomes. During mitosis, a bipolar spindle-shaped array of microtubules (MTs) is assembled outwards from the duplicated centrosomes. MTs are filamentous fibers comprising of α- and β-tubulin heterodimers that polymerize end to end to form protofilaments, where the α subunit of one dimer joins with the β subunit of the next. The protofilaments are further arranged in parallel to form hollow cylindrical structures [95]. As the head-to-tail assembly of tubulin dimers occurs in the same direction, MTs have a distinct sidedness, described as plus and minus ends. Within the protofilament bundles, only α subunits are exposed on the (−) end. In contrast, only β subunits are exposed on the (+) end, which is typically considered the growing end of the microtubule (Fig. 28.15).

During cell division, a network of protein fibers aggregate to form thread-like polymers called spindles. MTs are key proteins of spindles, whose function is to attach to the duplicated chromosomes and move them to the two spindle poles on opposite ends of a cell. The dynamic process by which microtubules polymerize allows for both lengthening and shortening of the microtubule network, which thus influences chromosomal segregation and distribution between the two daughter cells. The asymmetrical sidedness of MTs helps drive bound chromosomes to opposite ends of a dividing cell. More specifically, it is the dynamic elongation and shrinking of the (+) end that allows for chromosome segregation during cell division.

Biochemical processes driving MT polymerization are regulated by hydrolysis of GTP and are facilitated by other microtubule-associated proteins. Within the tubulin heterodimer, the α-tubulin subunit is always bound to GTP, which prevents unwinding of the protofilaments [96]. GTP is also associated with the β-tubulin subunit; this GTP, however, is exchangeable. Tubulin with bound GTP is added to the plus microtubule end and polymerizes, forming long tubes. Once hydrolyzed, GDP-tubulin is vulnerable to depolymerization and dissociation from the complex. However, to prevent depolymerization of the (+) end, there is a GTP-tubulin cap. The binding and utilization of GTP contributes to the dynamic structural changes in MTs, described as dynamic instability and treadmilling [97–99]. During dynamic instability, the ends of the MTs switch between long phases of lengthening, brief phases of shortening, and phases of pause, when the microtubules neither grow nor shorten. The two ends of a microtubule are not equivalent during the different phases of dynamic instability, and furthermore depend on the presence of microtubule-associated proteins. Treadmilling dynamics involves growth at one microtubule end and simultaneous and balanced shortening at the opposite end. This process relies on the concentration of available tubulin monomers, which is unique for the (+) and (−) ends. This accounts for the variability in treadmilling speed on either end of the MT. As cancer cells are in a heightened state of active division, the biochemical factors and processes involved in MT dynamics and mitosis are key targets for chemotherapeutic drugs.

In actively dividing cells, the rate of lengthening and shortening of MTs increases from 20 to 100-fold. Agents that disrupt microtubule assembly and function will stop cell division at the mitotic (M) phase of the cell cycle and hence have anticancer activity. Such agents are called antimitotic agents [1]. Natural products such as taxol, vinca alkaloids and colchicine (see Fig. 28.16) have been identified as antimitotic agents. The effects of vinca alkaloids (from extracts of the Madagascar periwinkle plant) were described in natural medicine. In the class of taxanes, the compound paclitaxel was first isolated from the Western yew tree. Colchicine was extracted from the meadow saffron plant. The newer group of epithilones were discovered from a myxobacterium in southern Africa.

The vinca alkaloids and taxanes have a broad spectrum of activity and have been widely used both as single agents and in combination therapies for breast cancer, ovarian cancer, non small cell lung cancer, and Kaposi`s sarcoma. Colchicine, in contrast, has been extensively investigated but is not used to treat cancer due to potent toxicity. The taxanes, paclitaxel (PTX) and docetaxel (DTX), and the vinca alkaloid, vinorelbine (VBN) have improved overall survival in locally advanced and metastatic/recurrent HNSCC [2, 4, 100]. PTX, DTX and VBN are effective as

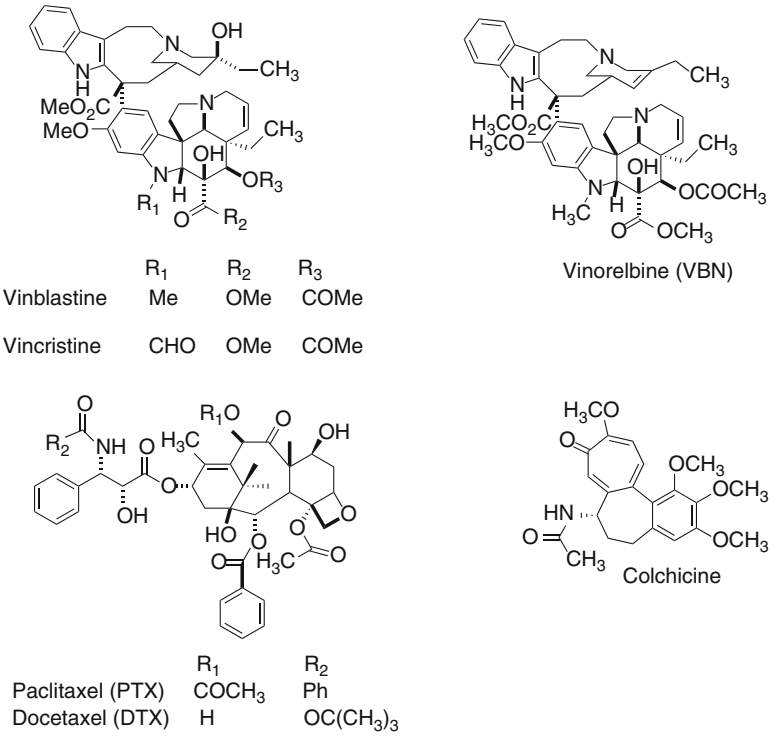

Fig. 28.16 Natural product antimitotic agents

single agents for asymptomatic patients while doublet therapy with cisplatin/DTX, cisplatin/PTX or carboplatin/DTX is used for aggressive disease.

Antimitotic agents have been classified on the basis of their mechanism of action and effect on microtubule polymer mass (a measurement of the degree of MT polymerization). MT-destabilizing agents are identified as those drugs that inhibit MT polymerization at high concentrations. These include the vinca alkaloids (vinblastine, vincristine, vinorelbine, vindesine and vinflunine), colchicine and combretastatin. High-dose vinblastine causes tubulin to assemble into paracrystals that by virtue of their large polymer mass can be detected by light scattering. Initially, these effects on microtubule polymer mass were thought to be the primary mechanism of antimitotic drug activity. However, using 10–100-fold lower concentrations, these agents still block mitosis, and also trigger apoptosis. At concentrations of 10–100 nM in HeLa cells, vinca alkaloids depolymerize microtubules and destroy mitotic spindles [101]. When used at only 0.8 nM however, (the IC_{50} for HeLa cells), vinblastine does not depolymerize microtubules, yet potently blocks mitosis. Similarly, the IC_{50} for PTX-mediated increases in microtubule polymer mass is 80 nM, while inhibition of mitosis occurs with an IC_{50} is 8 nM. Hence, the mechanism of inhibition for antimitotics is more accurately attributed to their inhibition of polymer dynamics rather in alterations in polymer mass.

Microtubule inhibitors are further classified based on the site where they bind to tubulin proteins [102]. Three distinct binding sites on β-tubulin have been identified: (1) the colchicine binding site, (2) the taxol binding site, and (3) the vinca alkaloid binding site [103]. The binding of vinblastine to soluble tubulin induces a conformational change in tubulin, which affects its ability to self-associate into protofilaments. Vinblastine binds with high affinity to the end of the polymerized microtubules but binds poorly to tubulin that is buried in the tubulin lattice. The end result is that vinblastine prevents tubulin polymerization and arrests cells in mitosis. In addition to inhibiting microtubule dynamics, vinca alkaloids may have a second mechanism of action – that of inhibiting the overall assembly of the mitotic network by preventing the binding of microtubule associated proteins. Other antimitotics such as cryptophycins, halichondrins and dolastatins bind at the tubulin vinca site and are under investigation as new anticancer agents.

In contrast to the vinca alkaloids, taxanes inhibit mitosis by stabilizing microtubules. These molecules bind poorly to soluble tubulin, but diffuse through small openings in the lattice and bind tightly to β-tubulin on the internal surface of the microtubule. This binding has been confirmed by the crystal structure of the PTX-tubulin complex. Taxane binding induces a conformational change in the tubulin, thereby increasing binding affinity for neighboring tubulin molecules. The resulting formation of excessive MT bundles perturbs and consequently arrests mitosis. Antimitotic agents such as epothilones and discodermolide also promote microtubule polymerization by binding to the same site as PTX.

Colchicine initially binds to soluble tubulin at the colchicine-binding site, and forms a poorly reversible tubulin–colchicine complex. This complex copolymerizes along with the free tubulin molecules into the microtubule ends. The ends continue to grow but their dynamic interactions and reactivities are suppressed [104]. The conformation of the tubulin–colchicine complex has been suggested to retard new tubulin addition, reduce dissociation of tubulin, and promote loss of the stabilizing GTP, leading to cell death. The binding of compounds such as combretastatin and flavonols to the colchicine site are structurally less complex compared to compounds that bind to the vinca or taxol domains.

Antimitotic agents such as laulimalide and estramustine also show potent microtubule inhibitory effects and bind to novel or unknown binding sites on tubulin. Based on the importance of the non-exchangeable GTP and microtubule associated proteins in regulating microtubule dynamics, nucleoside analogs that bind the GTP site of β tubulin, and ligands that bind to microtubule associated proteins, are also being studied as antimitotics.

Most antimitotic agents have been associated with problems of toxicity, bioavailability and resistance [105]. Neurotoxicity and myelosuppression are the principal side effects. The causes of neurotoxicity may involve effects on microtubule dynamics and assembly in neurons. Myelosuppression is caused by inhibition of mitosis in rapidly dividing bone marrow cells.

Multidrug resistance (MDR) is a major drawback to the use of antimitotics [14, 106]. A major mechanism of MDR involves the overexpression of the permeability glycoprotein (P-glycoprotein or Pgp) efflux pump. (By a recently codified naming

system that imitates the naming system for cytochrome P450, Pgp is formally known as ABCB1 membrane transporter. Here we refer to it as Pgp). Pgp is a membrane transport protein that binds drugs within the cell and uses ATP-derived energy to actively pump drugs into the extracellular space. Drug concentrations are decreased in the cellular compartments where they are needed, leading to reduced anticancer activity. Tumor cells pre-exposed to cytotoxic compounds often overexpress Pgp and related pumps. Pgp possesses a unique architecture in which the single polypeptide chain is arranged in two halves each containing six α-helical transmembrane segments and a cytoplasmic nucleotide-binding domain. On binding ATP, the protein reorganizes into three compact domains that form a central pore, allowing access of hydrophobic drugs from the membrane bilayer to the central pore of the protein. Binding studies have suggested that the protein displays multiple binding sites for its substrates and inhibitors. However, in the absence of detailed structural information on Pgp, a clear pharmacophore for Pgp binding agents is not available. Additional sources of resistance include expression of tubulin isotypes, tubulin mutations and microtubule-regulatory proteins.

Newer analogs of taxane and vinca alkaloids are being developed to overcome problems of toxicity and resistance [107, 108]. Initial modification of PTX has yielded docetaxel (DTX), which demonstrates improved solubility and greater potency *in vitro* compared to PTX. Novel compounds with simpler structures have been identified that bind to the taxol binding site, however the minimal structural elements that confer such specific binding are not yet described. More recently, conjugates of taxane derivatives have been developed for targeted tumor therapy, improved solubility, lower resistance and fewer side effects [109–111]. Vinflunine (VFL), a newer member of the vinca alkaloid family demonstrates lower toxicities and greater antitumor activity than other vinca alkaloids. Its tubulin affinity is several-fold lower than that of vinblastine or vincristine, however VFL is a better inhibitor of the calcium-binding protein calmodulin. Calmodulin binds to and influences the structure and activities of microtubules and other cytoskeletal proteins. The dual effect of VFL on both microtubules and calmodulin has been suggested as a possible mechanism for the superior efficacy and lower toxicity of VFL compared to other vinca alkaloids. VFL inhibits HNSCC cell lines at nanomolar concentrations. The microtubule stabilizing epothilones are not Pgp substrates. Accordingly, they demonstrate equivalent inhibition of drug-sensitive and multidrug-resistant human cancer cells. Ixabepilone, a member of the epothilone family was recently approved for metastatic breast cancer and is under investigation for use in HNSCC [112]. Newer scaffolds with microtubule inhibitory potential and Pgp inhibitory effects have also been developed. Combretastatin and combretastatin analogs are being investigated as colchicine site binders with potent antitumor effects.

Taxane and vinca alkaloids are often used in combination regimens with other antimitotics and additional anticancer agents to afford a synergistic or additive anticancer effect. Use of multiple drugs in treatment protocols allows for lower doses of each anticancer agent to be used, thus reducing the potential for toxicities. Several combination regimens for taxanes are being investigated clinically, some notable examples include doublet therapy DTX/cisplatin [113] and as part of triple therapy DTX/carboplatin/5-FU [40].

28.6 Targeted Therapies: Agents That Inhibit Specific Enzymes, Receptors or Processes That Are Involved in Tumor Growth and Invasion into Tissues

Targeted therapies are so-called because they are capable of selectively inhibiting aberrantly growing cells while sparing normal tissues. One targeted approach involves specifically inhibiting cell surface growth factor receptors whose normal function is to signal a cell to begin dividing. Another approach targets the intracellular, second messenger pathways, that are triggered when such receptors are activated. These signaling pathways transmit instructions to the nucleus to turn on transcriptional mechanisms that regulate cell growth and differentiation. Many of these signaling molecules are protein kinase enzymes; their selective inhibition provides a targeted anticancer effect by repressing cell proliferation. A third approach stimulates apoptotic signaling cascades such as those associated with mitochondrial release of Bcl proteins and cytochrome c. Cancer cells often suppress apoptosis, and therefore, therapeutic override of this suppression can return a cell to its normal life cycle and allow it to die "naturally". Finally, certain targeted therapies limit nutrient and oxygen delivery to the tumor by inhibiting angiogenesis. The expansion of vascular supply is thought to be especially critical for cancer metastasis. Some targeted therapy agents are small molecules, while others are monoclonal antibodies or fusion proteins (biotherapies). Targeted therapies represent a new era in chemotherapy, one in which anticancer drugs can, in theory at least, selectively kill or inhibit transformed cells. Several targets are under investigation in the treatment of HNSCC [21].

28.6.1 Receptor Tyrosine Kinases (RTKs)

The human genome encodes 518 protein kinase genes. Tyrosine kinases are of two basic types: receptor tyrosine kinases (RTKs), which are transmembrane protein receptors; and non-receptor tyrosine kinases, which are cytoplasmic enzymes that are associated with, but distinct from, membrane receptor proteins. Of the 90 unique human tyrosine kinase genes, 58 are RTKs and 32 are cytoplasmic (non-receptor tyrosine kinase) genes [114]. All tyrosine kinase enzymes catalyze the transfer of the γ-phosphoryl group from ATP to the phenolic hydroxyl group of selected tyrosine residues (see Fig. 28.17) [115]. Phosphorylation reactions in general are key signaling events throughout cell biology. Accordingly, tyrosine phosphorylation modulates a wide range of cellular processes including development, differentiation, proliferation, survival, growth, migration, apoptosis, and angiogenesis [116].

28.6.1.1 Pathological Role of RTKs

RTK dysfunction has been implicated in numerous human disorders such as psoriasis, renal disease, and neurological disorders [117]. Most germane to this chapter is the role played by overactive RTKs in several stages of cancer progression including, in particular,

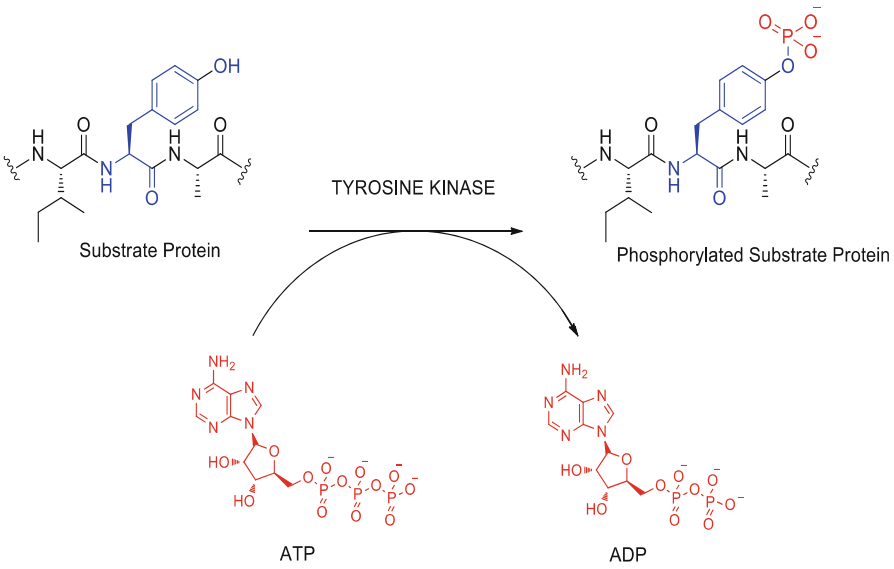

Fig. 28.17 The phosphorylation reaction catalyzed by a tyrosine kinase

the growth of new blood vessels, or angiogenesis [115, 118]. Early in tumor growth, tumor cells stimulate processes that exploit their interactions with the local tissue environment, and provide a means to supply the tumor with abundant nutrients and oxygen. One of the more prominent manipulations depends on the overexpression of vascular endothelial growth factor receptors (VEGFR), which are RTKs that increase endothelial cell proliferation and promote the budding of new blood vessels (i.e. angiogenesis) toward the growing tumor mass. The nascent vessels are generally disorganized, and are mainly comprised of immature, proliferating endothelial cells. These cells further contribute to tumor expansion by releasing other growth factors including platelet-derived growth factor (PDGF) and Type I insulin growth factor (IGF-1). Oversecretion of these and other ligands activates different families of RTKs, facilitating tumor cell growth.

Angiogenesis is in fact critical for the growth of solid tumors, which can expand to only a few cubic millimeters before diffusion processes are insufficient to meet nutrient and oxygen demand [119, 120]. Several current therapies use monoclonal antibodies to block angiogenesis signals by antagonizing growth receptors. Two different types of receptor-specific monoclonals can be made: (i) those that specifically block the ligand binding site of the receptor (i.e. a blocking mAbs); or (ii) those that prevent receptor dimerization by binding to alternative epitopes, so that the autophosphorylation and signaling cascade cannot proceed. Other agents bind to and neutralize the secreted factors themselves (e.g. peptides or small molecule blocking agents such as PDGF and IGF-1) to achieve specific anti-neoplastic effects. In principle, any agent that can bind to the growth factors and/or their receptors, whether monoclonal antibody, fusion protein, or small molecule analog, has the potential to interrupt signaling necessary for cancer progression [119, 120]. Table 28.1 lists some of the properties of the various RTKs and ligands implicated in tumor growth.

Table 28.1 Classification of growth factor receptors

Receptor	Receptor subtype	Ligands	Physiological function	Anticancer therapeutics
EGFR	EGFR ErbB-1 HER1	EGF TGFα Heparin	Cell migration, adhesion & proliferation	Gefitinib Erotinib Cetuximab Lapatinib
IR	IR-A IR-B	Insulin IGF-I IGF-II	Glucose uptake, glycogen synthesis	NVP-AEW541[a]
PDGFR	PDGFRα PDGFRβ	PDGF A PDGF B PDGF C PDGF D	Angiogenesis, VEGF release	Imatinib Sorafenib Sunitinib
VEGFR	VEGFR 1-3	VEGF	Angiogenesis, vascular permeability	Sorafenib Sunitinib

[a]Under investigation [121]

RTK structure is organized in three major domains: an extracellular ligand binding domain, a transmembrane domain, and an intracellular kinase catalytic domain [120] (see Fig. 28.18). Tyrosine kinase activity is common to all RTKs; these receptors are classified into different families based upon the distinguishing characteristics of their extracellular and non-catalytic domains. Different families of RTKs include the epidermal growth factor receptor (EGFR) family, insulin receptor (IR) family, platelet-derived growth factor receptor (PDGFR) family, and vascular endothelial growth factor receptor (VEGFR) family [116]. These families respond to different ligands, and they further differ in their physiological functions and their tissue distributions. However all RTKs operate by a common mechanism: ligand binding to the extracellular domain results in receptor dimerization, which then triggers autophosphorylation of key tyrosine residues on the intracellular domain. This in turn activates additional cytoplasmic kinases (e.g. PI3K, RAS, AKT, MAPK) and propagates a signal that eventually leads to transcriptional activation of DNA and production of proteins that carry out the cellular response related to the initial ligand-binding event.

While one strategy for slowing or stopping tumor cell growth is to block growth factor binding to the extracellular RTK domain, an alternative strategy focuses not on extracellular domain, but on the intracellular, tyrosine kinase enzymatic domain of RTK [115, 122]. All enzymes have active site pockets where substrates and cofactors bind, orient, and become activated so that the specific enzyme reaction can occur. Since tyrosine kinases function to transfer a phosphate from ATP to a specific tyrosine residue, tyrosine kinase enzymes must have a catalytic site that binds ATP. Small molecule anticancer agents have been developed that specifically bind this catalytic site and block normal phosphorylation. Agents in clinical use include imatinib [9, 10, 12, 123–125], gefitinib [12], erlotinib [123], lapatinib [124], sorafenib [125] and sunitinib [10] (see Fig. 28.19). To date, tyrosine kinase inhibitors are generally

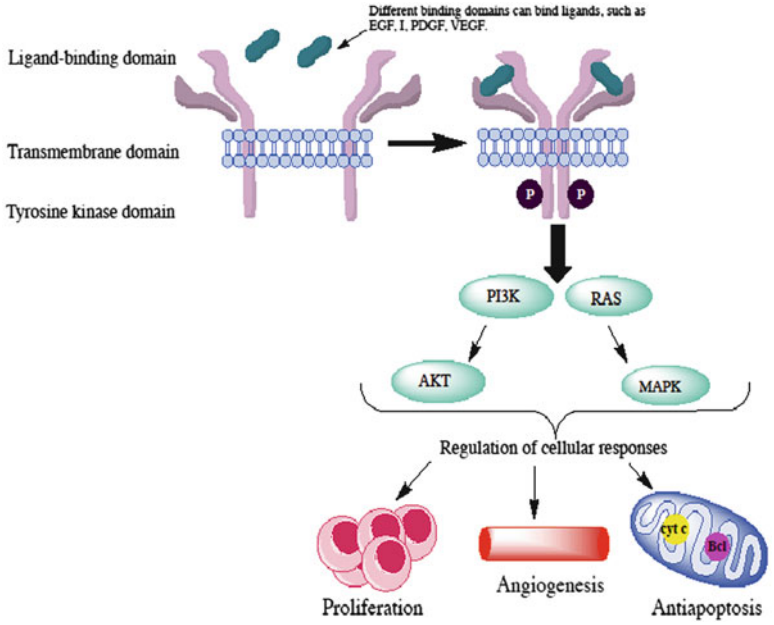

Fig. 28.18 Transmembrane receptors with intracellular kinase domains. Ligand binding stimulates phosphorylation reactions that regulate proliferation, angiogenesis and apoptosis. Families of RTKs include the epidermal growth factor receptor (EGFR), Insulin R (IR), platelet derived growth factor receptor (PDGFR) and vascular endothelial growth factor receptor (VEGFR)

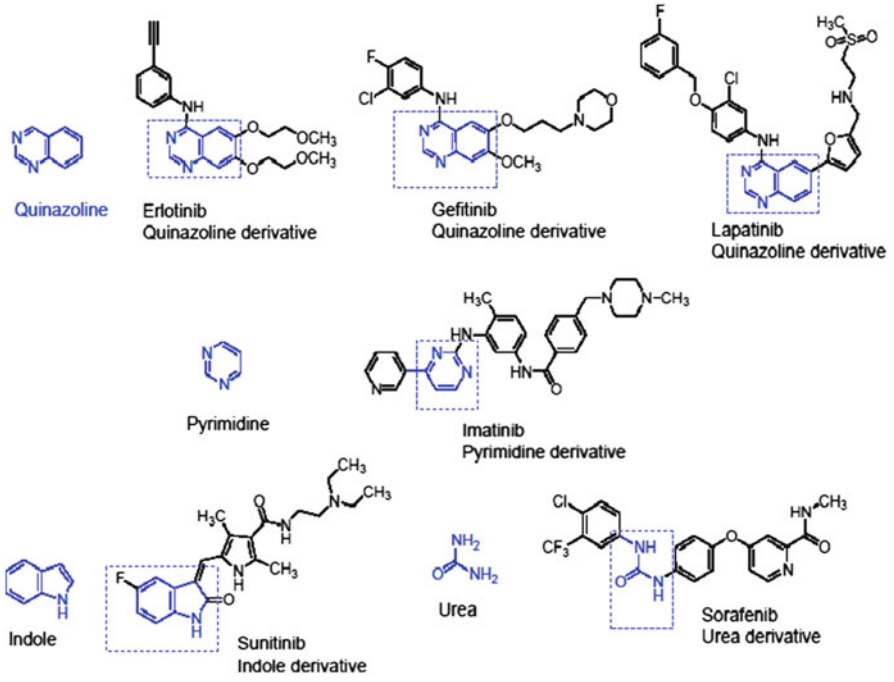

Fig. 28.19 Kinase enzyme inhibitors that target the ATP binding catalytic domain. The *dashed boxes* show the core scaffolds within each molecule that contribute to drug binding within the enzyme active site

cytostatic agents that curtail excessive growth, but do not necessarily kill a tumor cell. Often, they are co-administered with agents that are directly cytotoxic [122].

Our understanding of the RTK catalytic site (which contains the ATP binding site and the tyrosine substrate site and regulatory elements that control access and orientation of multiple factors) has become much clearer with advances in protein crystallization and molecular modeling. Such methods have enabled comparative analyses of how tyrosine kinase binding pockets change between the active and inactive states, and how various RTK inhibitors bind to such binding pockets with enough energy to elicit an inhibitory therapeutic response [126, 127]. The following section focuses on the binding interactions between small molecule inhibitors and the RTK catalytic domain.

28.6.1.2 The Catalytic Cleft of RTKs

The RTK catalytic site consists of two protein regions referred to as the front cleft and the back cleft. Within this cleft, the substrate protein containing the phosphorylatable tyrosine residue and an ATP molecule must bind and orient so that the kinase-mediated phosphorylation can proceed. The ATP binding site occupies the front cleft of the catalytic domain, while the back cleft comprises elements responsible for the regulation of kinase catalysis [130]. These two regions share a border, which includes the tri-peptide aspartate (D)-phenylalanine (F)-glycine (G) (i.e. the DFG motif) and the β3 segment. A gate between the front and back cleft is formed by an amino acid called a gatekeeper residue and an additional lysine (K) residue [129]. If the gatekeeper residue is a small amino acid residue such as threonine (T) or alanine (A), access to the back pocket is allowed. If the gatekeeper is a bulky residue such as phenylalanine (F), leucine (L) or methionine (M), entry to the back pocket is blocked. The lysine residue associated with the gatekeeper residue is conserved in all kinase enzymes and can adopt various conformations. When the enzyme is in an active state, the positively charged lysine residue helps to anchor the negatively charged α- and β- phosphates of ATP.

In a fully active state, the protein kinase adopts a "DFG-in" conformation where the side chain of the DFG aspartate is directed into the ATP binding site, and the aromatic ring of the phenylalanine is positioned in the back cleft. In the active DFG-in conformation, the aspartate residue is required to chelate Mg^{2+} ions, which in turn interact with and orient the γ-phosphate group of ATP for phosphate transfer.

28.6.1.3 The Front Cleft

The front cleft is broadly divided into four regions, each of which can be targeted by effective anticancer agents (see Fig. 28.20) [130].

1. The Adenine Region: This pocket is predominantly hydrophobic, and is involved in binding inhibitor scaffolds. This region is bordered by the gatekeeper residue and the **Hinge Region**. Two key hydrogen bonds are formed by the interaction of

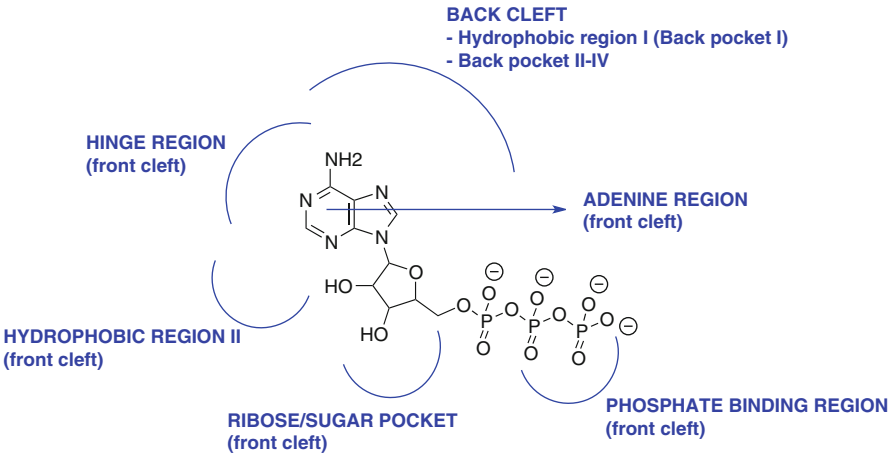

Fig. 28.20 The ATP binding site of kinases

the N^1 and N^6 amino moiety of the adenine ring with the NH and carbonyl groups of the peptide backbone of the hinge region residues of the RTKs. Many potent inhibitors use at least one of these hydrogen bonds. Although not used by ATP, some of the backbone carbonyl residues in the hinge region can also serve as a third hydrogen bond acceptor for inhibitor binding.

2. Ribose Pocket/Sugar Binding Region: The ribose pocket includes three hydrophobic residues (isoleucine (I), valine (V) and leucine (L)). EGFR and other kinase inhibitors including endogenous signalers such as CDK2 target these hydrophobic residues. The ribose pocket is adjacent to a hydrophilic, solvent-exposed region.
3. Phosphate Binding Region: This region includes aspartate (D), lysine (K) and asparagine (N) residues and the DFG tri-peptide motif. This region is highly flexible, hydrophilic, and solvent-exposed, and is considered less important for inhibitor affinity and potency.
4. Hydrophobic Region II: This pocket is not used by ATP but serves as an entrance for ligand binding. The residues and conformation of this pocket vary importantly between different kinases, and is therefore used to improve selectivity between kinase inhibitors.

28.6.1.4 The Back Cleft

The back cleft contains a hydrophobic pocket and is adjacent to the adenine pocket of the front cleft. The back cleft is called **Hydrophobic region I** or Back pocket I (BP-I). ATP does not bind in the back cleft pockets. BP-I has been explored in the design of inhibitors to gain selectivity for kinase targets with small gatekeeper residues [126, 127]. Additional pockets in the back cleft are further denoted as BP-II, the second hydrophobic binding pocket in the back cleft; BP-III, the third hydrophobic

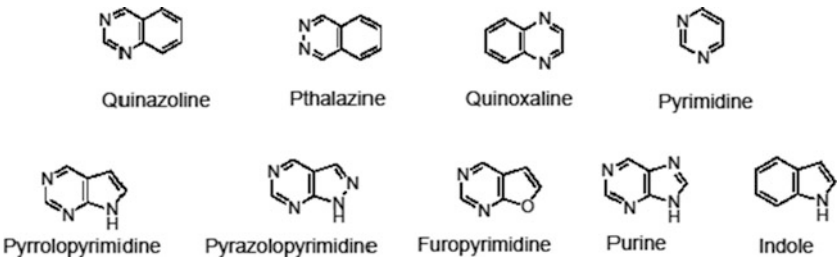

Fig. 28.21 Heterocyclic fused rings commonly found in small molecule kinase inhibitors

binding pocket in the back cleft; and BP-IV, the fourth hydrophobic binding pocket in the back cleft.

The front catalytic cleft of all kinase enzymes is accessible for ligand binding. The small-molecule inhibitors that target the front cleft use a core scaffold to recognize the adenine pocket. The core scaffold can then be substituted optimally to extend into the different pockets of the ATP binding site for improved binding affinity and selectivity for RTKs. Thus, RTK inhibitors can be classified based on their core scaffolds. Scaffolds that use heterocyclic fused ring structures with each ring having six carbons include quinazolines, quinoxalines, pthalazines. Heterocyclic fused ring structures comprised of a 6-membered ring and a 5-membered ring include purines (including adenine), pyrazolopyrimidines, furopyrimidines, benzoisoxazoles, pyrrolotriazenes and pyrrolopyrimidines [126–128]. Monocyclic compounds such as pyrimidine and its derivatives, and its related structure urea, can also bind to the adenine site of the RTK binding cleft. Several of these scaffolds are incorporated in compounds shown in Fig. 28.21. The phosphorylatable substrate binding region is a shallow groove and not a well-defined pocket, hence inhibitor design for the substrate binding region has been particularly challenging.

In the crystal structure of EGFR (active conformation) complexed with erlotinib [131], the back pocket I of hydrophobic region I accommodates the acetylene moiety of the phenyl ring as seen in Fig. 28.22 (Panel A). Lapatinib, in contrast, binds to the inactive (DFG-out) conformation of EGFR, occupying both back pocket I and II [122]. The quinazoline heterocyclic ring in both erlotinib and lapatinib binds to the adenine region of the front cleft in relatively similar orientation. Kinase inhibitory potency and selectivity can be modulated by exploiting different pockets of the ATP binding site as exemplified by erlotinib and lapatinib.

Resistance to small molecule tyrosine kinase inhibitors was first observed in chronic myeloid leukemia (CML) patients treated with imatinib, and has expanded into a significant clinical problem. Imatinib resistance arose due to a threonine-to-isoleucine point mutation at residue 315 of the Bcr-Abl kinase domain (i.e. T315I) [126]. Similar mutations in the kinase domains of PDGFRα (T674I) and c-Kit (T670I) contribute to imatinib resistance in gastrointestinal stromal cell tumors (GIST) as well. Luckily, other kinase inhibitors such as sunitinib, a multi-targeted tyrosine kinase inhibitor that blocks c-Kit, VEGFR, Flt3, and PDGFR, remain effective in patients with imatinib-resistant GIST [10].

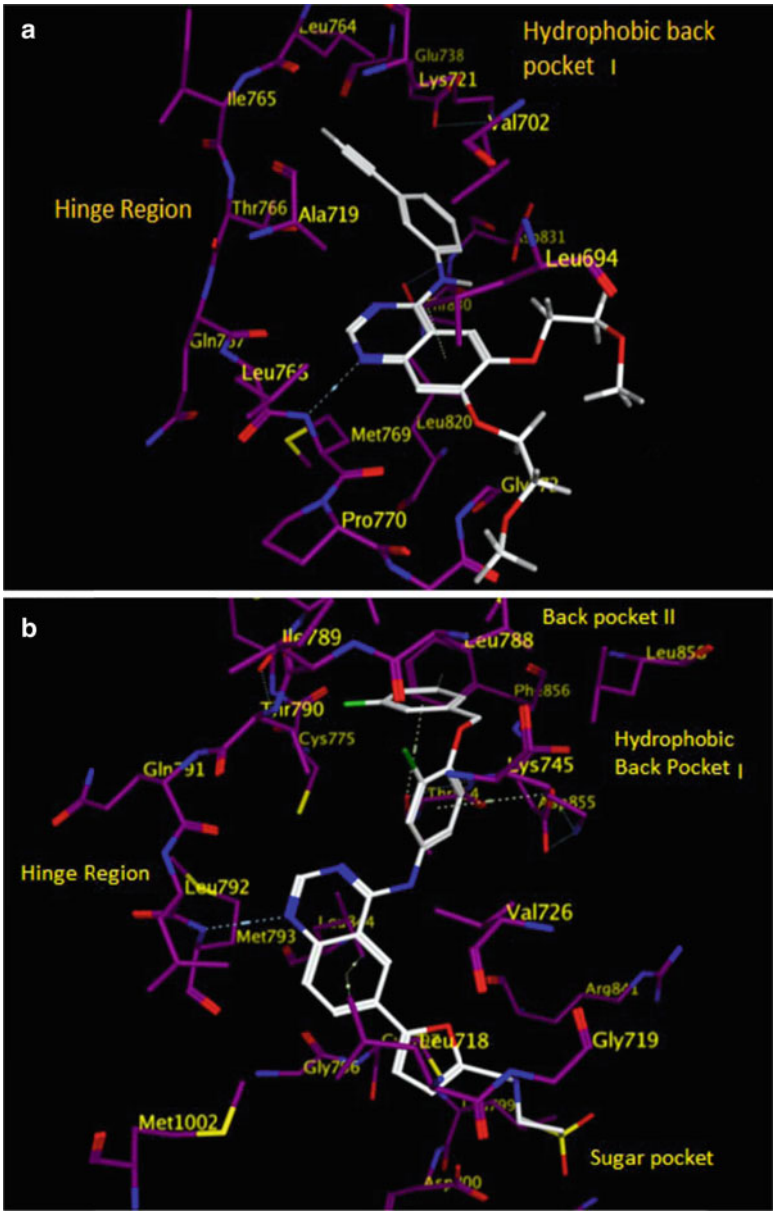

Fig. 28.22 Diagram showing interactions of Erlotinib (*Panel A*) bound to EGFR in its active conformation (PDB code 1M17) (Modified from [131]), and Lapatinib (*Panel B*) bound to EGFR in its inactive conformation (PDB code 1XKK) (Modified from [128])

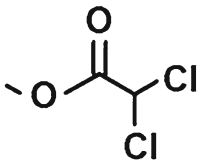

Fig. 28.23 The structure of dicholoracetate (DCA)

Dasatinib is a second-line multi-tyrosine kinase inhibitor that is effective against imatinib-resistant CML [132].

Although aberrant EGFR signaling is associated with HNSCC, and can be successfully modulated by monoclonal antibodies to EGF, ATP-competitive EGFR inhibitors have not shown an improvement in survival rates of HNSCC either as monotherapy or in combination with cisplatin or PTX. Phase II studies using sunitinib, sorafenib (an inhibitor of VEGFR, PDGFR and Raf-1 kinase) and dasatinib have not yet demonstrated improved response rate in HNSCC.

Additional ATP-competitive kinase inhibitors (ARQ197 (Phase I/II), JNJ38877605 (Phase I), XL880 (Phase I/II), PF02341066 (Phase I/II) and lapatinib) are under investigation [133, 134]. Lapatinib has shown promising results with cisplatin and PTX in HNSCC. On a related note, protein kinase C ε (PKC ε), a serine/threonine kinase enzyme, has been suggested to potentiate the aggressive nature of HNSCC [135]. An inhibitory peptide that blocks the catalytic cleft of PKC ε is also under investigation as a targeted therapy for HNSCC. The peptide demonstrates selectivity for cultured HNSCC cells, and inhibits cell invasion, proliferation, and overall tumor growth in mouse models.

28.6.2 Investigational Therapies Targeting Apoptosis

Apoptosis, or programmed cell death, is the natural process by which cells stop growing and become recycled. Evasion of apoptosis is a hallmark of cancer and a crucial step in tumorigenesis [1]. There are two broad pathways that regulate cellular apoptosis. The extrinsic apoptosis pathway is initiated by extracellular forces such as ligand-mediated receptor activation and is known to involve proteins such as tumor necrosis factor-alpha (TNF-α), Fas ligand, and Fas associated protein with death domain (FADD). The intrinsic pathway, which is also known as the mitochondrial pathway, is initiated by intracellular signals such as oxidative stress or DNA damage. Both pathways converge to activate a family of intracellular enzymes known as caspases, which begin the proteolytic degradation and removal of the dying cell.

28.6.2.1 Dichloroacetate (DCA) – Targeting Tumor Cell Glucose Utilization and Mitochondrial (Intrinsic Apoptosis Pathway) Function

Dichloroacetate (DCA, see Fig. 28.23) is a compound that is found in high concentrations in municipal water supplies as a byproduct of water chlorination procedures [136, 137]. It is a small, highly soluble analog of the centrally reactive metabolic end

product of aerobic glycolysis – acetyl CoA. In aerobic glycolysis, acetyl CoA is produced from pyruvate by the action of the pyruvate dehydrogenase (PDH) complex – a tightly associated multi-enzyme complex that transforms the 3-carbon pyruvate into an oxidized, thioester-activated 2-carbon acetyl group. The PDH complex contains important cofactors in addition to three key enzymes. All these factors contribute to the chemical restructuring of pyruvate into a molecule that can drive the production of ATP energy, or drive the storage of energy equivalents as fatty acids and lipids. To produce energy, acetyl CoA combines with oxaloacetate, forming citric acid inside the mitochondrial matrix. Citric acid gets chemically modified and restructured as part of the citric acid cycle (also known as the Tricarboxylic acid (TCA) cycle or the Krebs cycle), and electrons extracted during the process are passed sequentially down the mitochondrial electron transport chain, producing a proton gradient that drives ATP synthase activity. The PDH reactions result in the release of a CO_2 gas molecule, which renders this reaction an irreversible step of the aerobic glycolytic pathway.

PDH complex bioactivity is tightly regulated by phosphorylation and dephosphorylation reactions. When phosphorylated, PDH is inactive. To activate PDH so it can produce acetyl CoA, a PDH phosphatase enzyme must remove a phosphate residue. Conversely, to inactivate an active PDH complex, a PDH kinase enzyme must add a phosphate group to PDH. Cofactors known to regulate the bioactivities of either the PDH kinase or PDH phosphatase enzymes, therefore, can control a cell's capacity to aerobically produce energy.

PDH phosphatase is allosterically activated by calcium, which keeps PDH in its active conformation and promotes the production of acetyl CoA and oxygen-dependent metabolism. In contrast, PDH kinase is allosterically activated by high levels of acetyl CoA, NADH, pyruvate, and ADP. These molecules feedback inhibit production of acetyl CoA and NADH and shut down ATP production. Since DCA is a structural analog of the acetyl group, it was first studied in the early 1970s as a compound that could regulate pyruvate dehydrogenase activity as a competitive inhibitor of acetyl CoA binding to PDH kinase (see Fig. 28.24). More recently however, because of the unique way a tumor cell utilizes glucose and oxygen to produce energy, DCA is being evaluated as an anticancer chemotherapeutic agent against a variety of cancers, including HNSCC.

Cancer cells grow extremely fast and often cannot sustain the demands of oxidative metabolism. To compensate for the high-energy demands associated with rapid growth, tumor cells upregulate glucose transporters on their cell surface to increase glucose uptake and increase the rate of glycolysis. Increased glycolysis results in an increase in the amount of the pyruvate end product, which is inefficiently converted into acetyl CoA in rapidly growing cancer cells. Pyruvate builds up and is shunted into its anaerobic end product – lactic acid, which results in an acidification of the tissues involved with cancer. In essence, a cancer cell shifts metabolic energy production away from mitochondrial oxidative pathways into anaerobic metabolic pathways, even in the presence of sufficient oxygen. This is generally known as the **Warburg effect** in recognition of Nobel laureate Otto Warburg, who in 1956 hypothesized that one cause of cancer was related to this alteration in the way glucose is used [138].

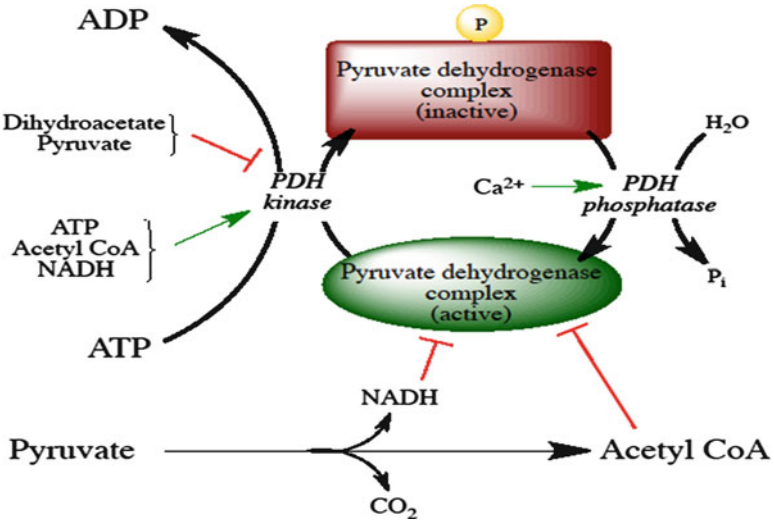

Fig. 28.24 The pathways regulating the activity of the Pyruvate Dehydrogenase complex (PDH)

The "pseudo-anaerobic" metabolism in cancer cells limits mitochondrial production of electron donors like NADH and $FADH_2$. This results in reduced flux of electrons across the mitochondrial membrane and reduced membrane potential, and diminished production of ATP. Equally as important to the tumor cell, however, is that certain mediators of programmed cell death, which are found in the inner spaces of the mitochondria, remain trapped. These mediators, which include the Bcl family of proteins and cytochrome c, must be released from the mitochondria to promote the apoptotic process and drive tumor cell death. When mitochondrial function is suppressed by the Warburg effect, these apoptotic factors are not released, leading to prolonged cellular growth [139].

The lactic acid that is produced is not used by the tumor cells, but is dumped into the surrounding tissues, causing the microenvironment around the tumors to become acidic (i.e. with a pH of ~6.0). Tumor cells try to "catch up" on their perceived oxygen deficit by promoting angiogenesis and removing waste products. This scenario explains in a consolidated way, why alterations in the metabolism of a cancer cell can lead to changes in how the cancer cell interacts with and influences its microenvironment. It is easy to rationalize combination therapies using agents that attack different targets as the preferred method to attack a growing tumor. Anti-angiogenesis therapeutics such as Avastin (bevacizumab), a monoclonal antibody that inhibits VEGFR, renders it unable to bind to its true ligand and thus inhibits the angiogenic process. Of note, Avastin is often used in combination with antimetabolites such as 5-FU, or antimitotic agents such as taxol [140].

As mentioned above, the high rate of tumor glycolysis leads to accumulation of pyruvate, which inhibits PDH kinase (as shown in Fig. 28.24). The net result is more pyruvate converted into acetyl CoA and greater ATP production. If ATP levels rise sufficiently, the entire glycolytic pathway shuts down, reducing the rate of glucose

metabolism, theoretically slowing the growth of the tumor cell. Hence, any additional inhibition of PDH kinase may have therapeutic advantage. DCA is believed to exert such inhibition and hence is being investigated as a novel anti-tumor agent.

DCA is orally available. It is a small, hydrophilic compound of 150 Da molecular weight that easily penetrates most tissues, including the brain (where glucose utilization for energy production is of critical importance). Once inside a cell, DCA distributes to the mitochondria (where its target enzyme is localized), alters the way a cell utilizes glucose (which can be measured by positron emission tomography (PET) imaging) [139], shunts more pyruvate into the mitochondria, and normalizes mitochondrial oxidative metabolism. With production of reducing equivalents and proton pumping restored, the mitochondrial membrane potential returns to levels typical of non-cancer cells. Once membrane potential is normalized, pro-apoptotic factors (Bcl proteins and cytochrome c) are more readily released from the mitochondria leading to tumor cell apoptosis (a good thing). Importantly, DCA has minimal effect on non-cancer cells. The increased use of oxygen by tumor cells is associated with slowed tumor growth [141], and increases the efficacy of cytotoxic co-therapies that require enhanced oxygen levels [142].

DCA has also been studied as a treatment for lactic acidosis. To date, however, the FDA has not approved it for any use, including as a cancer treatment. Some nerve toxicity [139] and liver toxicity [136], often seen before any discernible clinical improvement has been reliably measured, have been associated with DCA.

Mutations in mitochondrial DNA affecting the expression and function of pyruvate dehydrogenase and pyruvate kinase have been noted in HNSCC cells [143]. The studied mutations do affect tumor cell growth in relation to both how glucose is utilized and oxygen is consumed. DCA reversed these effects, suggesting that a coordinated clinical examination of DCA in HNSCC is warranted. Combination therapy approaches, both individually or as fusion molecules (e.g. Mitaplatin – a fusion of cisplatin and DCA) [144], needs further study.

28.6.2.2 Bcl-2 Family of Proteins: Targeting Regulators of Apoptosis Pathways

Bcl-2 proteins represent a family of proteins that can both up-regulate or down-regulate the intrinsic apoptotic pathway [145]. Bcl-2 proteins are associated with the inter mitochondrial membrane space. They are released along with important mitochondrial proteins such as cytochrome c as mitochondria become permeabilized and die. The released factors then help activate the caspase enzymes that carry out cell–destroying processes.

In the Bcl-2 protein family, some proteins (e.g. Bcl-2 and Bcl-XL) are anti-apoptotic or pro-survival. In contrast, other Bcl proteins such as Bcl-2 homologous antagonist killer (Bak or Bax) and Bcl-2 associated death promoter (Bad) are pro-apoptotic [145, 146]. The significance of these findings is that cells overexpressing Bcl-2, including cells involved in HNSCC, demonstrate greater evasion of apoptosis. In addition, cells overexpressing Bcl-2 and Bcl-XL demonstrate greater resistance to platinum compounds and fluoropyrimidines, shifting the balance even further toward rapid tumor cell growth. Further significance for the role the Bcl proteins in apoptosis is seen in studies

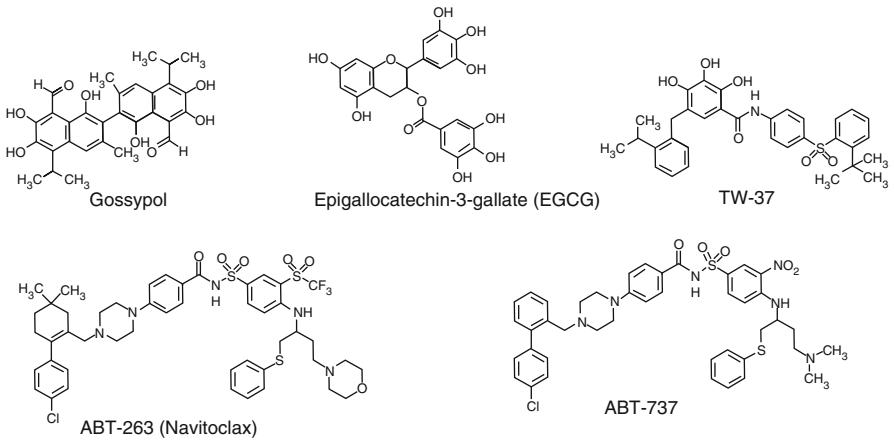

Fig. 28.25 Compounds under study as agents affecting Bcl protein activities

where pro-apoptotic Bak/Bax is downregulated or overexpressed. In HNSCC tumor models, a deficiency in Bak/Bax is associated with tumor progression while overexpression may correlate with a better response to therapy.

Several agents are under investigation as inhibitors of anti-apoptotic Bcl-2 and Bcl-XL, and as potentiators of pro-apoptotic protein Bak/Bax. Certain of these Bcl-binding proteins are isolated from natural products. For example, the green tea derivative, epigallocatechin-3 gallate (EGCG, see Fig. 28.22) can influence both pro- and anti-apoptotic Bcl proteins [145].

Gossypol (see Fig. 28.25) is another natural product inhibitor of Bcl-2 and Bcl-XL [145]. The mechanism by which this polyhydroxylated compound interacts with Bcl-2 led to structure-based design of other novel small molecule inhibitors of Bcl-2 such as TW-37 [147]. Submicromolar TW-37 has been shown to inhibit the growth of head and neck cancer cells [148]. NMR-based screening, parallel synthesis, and structure-based design led to synthesis of another Bcl-2 and Bcl-XL inhibitor, ABT-263 (Navitoclax) and ABT-737 [149]. ABT-737 demonstrated synergistic effects with cisplatin in tumor models inhibiting HNSCC cell growth. Several fragment-based screening initiatives are in use for the discovery of newer small molecule Bcl-2 inhibitors [150], including short peptides possessing anti-apoptotic effects [151].

Several Bcl-2 inhibitors are currently in clinical trials for various cancers [152]. For example, ABT-263 (Navitoclax) is in clinical trials for chronic lymphocytic leukemia, both as a single agent, and in combination with platinum compounds and fluoropyrimidines. Gossypol is in clinical trials for glioblastoma multiforme. An antisense oligonucleotide, Oblimersen is also in clinical trials for breast cancer and lymphocytic leukemia. EGCG is the only agent under investigation for HNSCC in clinical trials.

Figure 28.26 presents a summary overview of cellular targets for anticancer drugs. Each has a different mechanism of action. Some are target-specific factors overexpressed on or by tumor cells, while others are non-specific therapies that target rapid cell growth and division. Some agents target tyrosine kinase enzymes and the signaling pathways in ways that will inhibit tumor growth, proliferation and

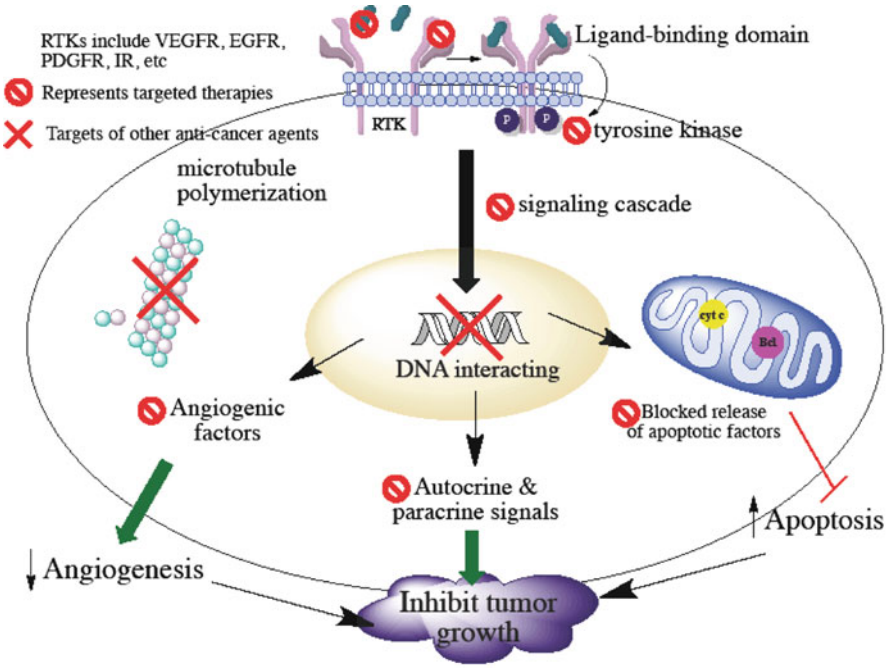

Fig. 28.26 Summary overview of cellular targets for chemotherapeutic drug activity. The family of receptor tyrosine kinases (RTKs) includes the vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), insulin receptor (IR), among others. Upon binding ligands, the monomeric receptor subunits dimerize and autophosphorylate. The activated receptor also functions as a tyrosine kinase, capable of phosphorylating other downstream enzymes and proteins. This signaling cascade bears important consequences on the processes of angiogenesis, proliferation and apoptosis for the survival of cancer cells. Specifically, RTKs promote blood vessel formation and tumor growth, but inhibit the release of pro-apoptotic factors. Targeted therapies for cancer include monoclonal antibodies that may prevent RTK activation, inhibitors of tyrosine kinase enzymes, or agents that promote apoptotic signaling. Other targets for antineoplastic agents shown include those that interfere with DNA functions and microtubule inhibitors

metastasis. While each anticancer drug by itself has anticancer properties, combination or multimodal therapy is the most widely used and preferred approach to achieve a favorable anticancer response and so reduce the likelihood that individual toxicities and adverse effects will be therapeutically limiting.

28.7 Clinical Considerations for Choosing Chemotherapeutic Agent(s)

Deciding on appropriate and useful chemotherapies to treat head and neck cancers (HNSCC) requires an understanding of the biochemical processes that contribute to increased cell proliferation and overgrowth, and tumorigenesis or tumor formation. Various classes of chemotherapeutic agents are designed to interfere with cellular

processes that involve duplication of DNA, production of key metabolic building blocks needed for such DNA duplication, mitotic splitting of rapidly growing cells into daughter cells, and cellular signaling processes that help a cell understand its microenvironment and its energy needs. The decision to use one or more chemotherapeutic drugs as a general approach to treat HNSCC, however, is usually made after the oncologist initially considers the individual patient's condition and previous history, and whether surgery and/or radiation therapy are viable options. As such, the first goal in patient management after the diagnosis of cancer is to determine the extent of disease and its treatability by excision and/or targeted radiation. Surgery or radiation therapy alone, however, is often insufficient to assure all tumor cells have been removed or rendered non-proliferating, and that tumors will not reoccur. It is therefore prudent to add a chemotherapeutic regimen as a primary or as an adjunctive treatment course. This is especially true in cases of advanced and/or disseminated disease. A decision on which chemotherapeutic agent to use, how much to use and when to use it must include an assessment of the magnitude of disease and the patient prognosis, and an awareness of the mechanisms of action of different agents available.

Patients with head and neck cancer can be categorized most generally into three clinical groups: (1) those with localized disease; (2) those with locally or regionally advanced disease; and (3) those with recurrent and/or metastatic disease [153].

28.7.1 Localized Disease

Nearly a third of head and neck cancer patients have localized disease. Patients with early stage tumors of the oral cavity, oropharynx or larynx are usually treated with surgery alone in preference to non-surgical treatment such as radiation [154].

Surgery is also the preferred therapy for patients with salivary gland cancer, patients with early stage disease with no evidence of metastases, as well as patients with tumors of the oral cavity regardless of stage to avoid the long-term complications of radiation, such as xerostomia and dental decay. The type of surgery required depends on the primary site of the tumor.

28.7.2 Locally or Regionally Advanced Disease

Greater than 50% of patients with head and neck cancers present with locally or regionally advanced disease, with a large primary tumor burden and/or with lymph node metastases (i.e. Cancer stage 3 or 4). These patients can be treated with curative intent, but require multimodality therapy that goes beyond surgery or radiation therapy alone.

Multimodal therapy involves the use of two or more anticancer chemotherapeutic agents. Induction therapy refers to chemotherapy administered before surgery and/or radiotherapy in order to weaken proliferating cancer cells and improve expected outcomes of the chosen co-therapy. Concomitant therapy refers to chemo-

therapy administered simultaneously during the multi-week period of radiation therapy. Adjunctive therapy refers to chemotherapy administered post-surgery or post-radiation to protect against the statistically possible chance that not all cancer cells were effectively removed by surgery or destroyed by radiation.

The standard treatment for patients undergoing induction therapy includes a three-drug regimen of DTX (Taxotere)/cisplatin (Platinol)/5-fluorouracil (5-FU) (abbreviated "TPF" therapy). Studies show induction therapy significantly improves survival and organ preservation in locally advanced head and neck cancer with less consequent toxicity. Each drug targets a different biochemical mechanism needed for cancer cell growth and, when used in combination, contributes additive anticancer effects.

Standard concomitant therapy uses cisplatin. Such treatment usually follows surgical removal of the tumor and is given simultaneously with post-operative radiation therapy (i.e. PORT). For aggressive tumors or tumors with signs of extracapsular spread of tumor in lymph nodes or perineural invasion, cisplatin is generally used at 100 mg/m^2 on days 1, 22, and 43 of a multi-week radiation therapy regimen. After rest periods, concomitant therapy cycles are often repeated. Alternative agents tested with PORT include carboplatin and cetuximab.

Post-operative adjunctive chemotherapy may be used to lower the chance of tumor recurrence when occult cancer cells remain after surgery and/or radiation. In 2004, two large randomized studies were undertaken in Europe, by EORTC 22931, and in North America by the Radiation Therapy Oncology Group, RTOG 9501. Their results demonstrated that adjuvant chemoradiation was more efficacious in terms of local-regional control and disease-free survival compared with postoperative irradiation alone. Cisplatin-based chemotherapy is the current standard and has been administered adjunctively in the hope of improving the prognosis after radical surgery in patients with locally advanced operable HNSCC [155].

28.7.3 Recurrent and/or Metastatic Disease

Patients with recurrent and/or metastatic disease (i.e. Cancer stage 4) are generally treated with palliative intent. A traditional treatment paradigm includes systemic therapy with single-agent chemotherapeutics such as MTX, 5-FU, cisplatin, PTX or DTX. More recently, topoisomerase I inhibitors such as gemcitabine and VBN have been also used as single agent palliative treatments. Small molecule inhibitors of EGFR such as erlotinib and gefitinib are also used. Dual agent combinations involve cisplatin with 5-FU, carboplatin with 5-FU, and cisplatin or carboplatin with PTX or DTX [156]. The choice of which agents to use in combination therapy should involve an understanding of drug targets and mechanism of chemotherapeutic activities, and of non-tumor targets that are affected that can contribute to unwanted side effects. The overall survival for patients with recurrent and metastatic HNSCC remains less than a year [2]. This underscores need for novel therapeutic approaches in the management of HNSCC and the intensive efforts in the investigation of novel chemotherapeutic agents.

28.8 Summary

HNSCC is most often treated by a combination of surgical, radiation and chemotherapeutic strategies. There are a variety of chemotherapy options, which differ in how each agent alters or inhibits the growth and metabolism of tumor cells. There are four general categories of chemotherapeutic agents for HNSCC, each of which contains various drugs and/or analogs, and each with differing levels of efficacy and toxicity.

One class of drugs is designed to directly damage DNA by forming covalent bonds or cleaving DNA backbones in such a way that DNA can no longer be replicated. This class includes organoplatinum complexes like cisplatin or carboplatin. A second class of drugs is designed to interfere with DNA synthesis, thus stopping the rapid cell division that is fundamental to tumor growth. This class is known as antimetabolites; these agents are designed mostly to inhibit one of three intracellular enzymes: dihydrofolate reductase, thymidylate synthase, and ribonucleotide reductase. Key drugs in this class include 5-FU and MTX.

The third class of chemotherapeutic agents is those that interfere with cell division by disrupting microtubule assembly. By inhibiting microtubule assembly and function, these drugs prevent daughter cells from separating and tumors from proliferating. These drugs are known as antimitotic agents and include taxanes (such as PTX and DTX) and vinca alkaloids (such as VBN).

The fourth class of chemotherapeutic drugs includes agents that are designed to specifically target proteins, receptors or enzymes that are found selectively in transformed tumor cells. This class includes inhibitors of protein kinase enzymes (such as imatinib and cyclin-dependent kinases that disrupt various phases of the cell cycle), and growth receptors antagonists (such as inhibitors of VEGFR or EGFR). Some of these disrupting agents are small molecules while others are monoclonal antibodies. Some of these agents inhibit the propagation of cell growth signals; others disrupt the growth of new blood vessels (angiogenesis).

Agents from the first three groups are fundamentally non-selective. Their effect on any cell type relies on their ability to interfere with cell division. Hence, many have significant adverse effects that result directly from the damage they inflict on non-cancer cells that normally divide or remodel rapidly. In contrast, drugs that target kinases and growth receptors are representative of a new era in chemotherapy, one in which anticancer drugs can, in theory at least, selectively kill or inhibit transformed cells while sparing normal tissues.

Newer chemotherapeutics continue to be investigated as anticancer agents. Dichloroacetate is a long-known, simple molecule that is being investigated as an agent that can change the metabolism of a cancer cell and enhance its natural pathways for stimulating programmed cell death (apoptosis). Other agents known to affect both pro- and anti-apoptotic pathways are also being studied both alone and in combination with other therapies. Understanding drug agents from both a structural and functional perspective, with a keen focus on the targets of drug action and the mechanism of drug effect, will provide important information in deciding which drugs to use both alone and in combination therapy to pursue a favorable anti-tumor response.

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Chapter 29
Biological Treatments (Antibodies)

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Contents

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Abstract This chapter presents an overview of the human immune system and the potential role it plays in the immunologic treatment of SCCHN cancers. More specifically, it examines the significance of both innate antibody formation and introduction of bioengineered monoclonal antibodies, and how they interact. Further, this chapter discusses how these immunologic tools may be improved upon to more successfully address, and potentially clear various forms of SCCHN cancers. Initially, we study immune system mechanisms, immunotherapy, immunogenicity, and the formation of antibodies within the human immune system in reaction to antigens and targeted toxins. Secondly, we describe monoclonal antibody development, production, and biochemical and biomechanical behavior pathways. Third, we present current most commonly used monoclonal antibody therapy, such as; cetuximab and trastuzumab, and possible drug pathways being considered for future development and use in SCCHN. Fourth, we review various antibody and monoclonal antibody molecular combination therapies, developing and in use, such as; antibody drug conjugates and bispecific antibodies. The final portion of our discussion explores the most probable future directions for SCCHN immunotherapeutic development and applications including; nanomaterials, biophysics and mass transport/oncophysics across biological barriers, and cancer stem cell research.

Keywords Immune system response • Immunotherapeutics • Monoclonal antibodies • Nanomaterials • Recurrent and metastatic tumors • Cancer stem cells

Abbreviations

ABC	ATP-binding cassette
ADC	Antibody drug conjugates
ADCC	Antibody dependent cellular cytotoxicity
ATP	Adenosine-5′-triphosphate has a variety of functions including intracellular energy transfer
B Cells	Lymphocytes
biAbs	Bispecific antibodies
CDC	Complement dependent cytotoxicity
CDR	Complementary determining region
CSC	Cancer stem cells
DC	Dendritic cells
EGFR	Epidermal growth factor receptor
FcR	Region on IgG responsible for regulating and promoting immune and inflammatory response to immune complexes
FcγRIIB	One of four low-affinity receptors binding only to immune-complexed IgG. The only inhibitory FcR.

HAADs	Highly active agonistic antibodies
HAMA	Human anti-mouse antibody response
IAI	Induction of adaptive immunity
IC	Immune complexes antigens bound to antibodies
IgG	Immunoglobulin G IgG makes up more than 75% of serum immunoglobulins in humans
IgG (FcγRs)	Key human FcR receptors of IgG which vary in function and affinity
kDa	Kilodalton or Dalton; a unified atomic mass unit
LNM	Lymph node metastasis
mAb	Monoclonal antibody
mAbs	Monoclonal antibodies
MDSC	Myeloid-derived suppressor cells
MHC	Histocompatibility complex
NK	Natural killer cells
p53	Protein 53 involved in cancer suppression
R/M-SCCHN	Recurrent or metastatic SCCHN
TAAs	Tumor associated antigens
TECs	Tumor endothelial cells
Tregs	T regulatory cells
V_H and V_L	Two variable domains

29.1 Introduction

The expression mechanism, morphology and disease progression of squamous cell carcinoma of the head and neck (SCCHN) makes it particularly difficult to diagnosis and treat. It is only now beginning to receive recognition as a prescient precursor to the possible arrival of other forms of cancer. And with this acknowledgement, comes a significant shift in the focus of research.

Paul Ehrlich's profound realizations and dream in 1908 of a 'silver bullet' for the treatment of tumors through utilizing the human immune system, has driven enormous research efforts. Subsequent collective study has attempted to clarify and understand the functionality of the immune system, mechanics of immunology and immunogenicity, and the molecular mechanisms underlying the behavior of cancer. This concept was later formalized through the "cancer immunosurveillance" hypothesis which posits the immune system should be capable of differentiating between the antigens of normal and tumor cells, thereby providing a mechanism towards "clearance" [1].

The bio-molecular and immunotherapeutic relationship between antigen-antibody is now far better understood. This awareness has resulted in the pursuit of a variety of immunotherapeutic strategies. Key among them, targeted tumor antigen-specific monoclonal antibodies (mAbs) and polyclonal antibodies, and the resulting large scale global production of these compounds by the bio-pharmaceutical market [2].

In this chapter we describe the pathway toward the use of mAbs, how mAbs were developed, are made, used as diagnostic and therapeutic drugs, and have an evolving role in the treatment of head and neck cancers. Current and prospective research and therapy options involving various antibody configurations are also explored. Finally, we review emerging technologies and theories, and why significant promise for utilizing the human immune system for the treatment of head and neck cancer exists in the future.

29.2 Immune System and Immunotherapy

The human immune system is typically described as having two inter-functional and complementary components, innate, and adaptive, providing immunity against pathogens and disease [1]. The innate is: (1) non-malleable, (2) antigen non-specific, and (3) utilizes enzymatic pattern recognition to identify potentially harmful molecules which may be present. This system does not provide long lasting defense against pathogens. These "effectors" or cells consist of: natural killer (NK) cells, phagocytes (which include neutrophils, macrophages, dendritic cells, monocytes), mast cells, eosinophils, basophils, and natural killer cells [1]. The innate system is an important mediator in the activation of the adaptive immune system [1, 3]. The antigen-specific response capability of the adaptive immune system is facilitated by dendritic cells DC [1]. The adaptive immune system is made up of specialized leukocytes; lymphocytes, of which there are two key types: B cells and T cells. These cells originate from hematopoietic stem cells within the bone marrow [4]. T cell types have highly specialized receptor molecules which recognize specific antigen fragments from exogenous pathogens, but only after being processed into a major histocompatibility complex (MHC) molecule. These MHC molecules bind to antigen/peptide fragments which can be "antigen presented", and exist in two Classes; MHC I molecules which are on the cell surface of nucleated cells, and MHC II which are found exclusively on fully functional adaptive system cells, including macrophages or DC [1]. There are two types of T cells; killer cells which exclusively complex with Class MHC I, and helper cells which incorporate with Class MHC II. A third, less significant subtype exists, γδ T cells which serve to identify other antigens not already integrated by either class MHC I or II [5]. All facilitate the processing of antigen specific fragments by the adaptive immune system [5]. In comparison, B cells have a far less complex immune process pathway. The antigen-specific receptor site is the entire antibody molecule appearing on the B cell surface. This accommodates immediate recognition of an intact pathogen or destructive molecule, with different B cells expressing all antibodies required within the human body [4]. Upon activation B and T cells grow, with a portion of those cells providing long-term active memory retention of specific pathogens, thereby conveying a degree of immune protection from those same or related pathogens into the future. In theory, these immunological processes should have the ability to identify, and 'clear' tumors and malignant cells

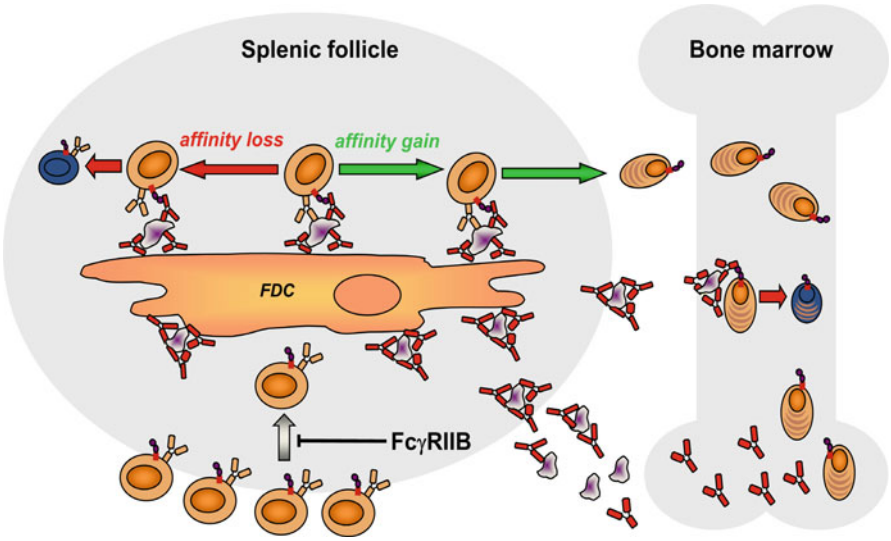

Fig. 29.1 A schematic representation of a highly probable biological model for activation of B-cell activity through IgG mediated modulation in the immune system. B-cell populations can be impacted by an immune complex binding to FcγRIIB within both the bone marrow and spleen. In the spleen, it is believed that FcγRIIB may restrict the migration of (autoreactive) B-cells into the follicle. Furthermore, FcγRIIB may also create a threshold for the activation of B cells, thereby ensuring any B cells which lose antigen specificity are cleared (indicated as *black* cells), and B cells with high affinity B-cell receptors evolve into plasma cells. It is believed that in the bone marrow immune complexes may initiate apoptosis by cross linking of FcγRIIB with plasma cells found on bone marrow. This creates areas of survival for plasma cells [8] (Adapted and reproduced from a diagram generously provided by the authors [8] and with copyright permission © 2010 John Wiley & Sons A/S Immunological Reviews 236/2010)

from the body, including cancers of the head and neck, and which might be addressed through immunotherapy [1, 6, 7]. T cells play a critical role in immunogenicity, or the eliciting of an immune response after exposure from a particular or specific antigen. DC are acknowledged to play a significant role as activators of T cells, and therefore stimulating adaptive immune response, and have become an enormously important topic for research as a potential therapeutic source for cancer immunotherapy [1]. Models believed to accurately represent a portion of the immune systems biomolecular mechanics provide further description (Figs. 29.1 and 29.2).

29.2.1 Antibodies

Antibodies are glycoproteins which originate in B lymphocytes and are generated as part of the overall immune system response to pathogens and specific antigenic molecules, for example viruses or bacteria [9]. Five classes of Igs exist: G, A, M, E and

D with greater than 75% found in the IgG class [9]. Monoclonal antibodies almost exclusively reside in the IgG class [10]. The IgG molecule is configured as the letter Y and is an aggregation of four polypeptides, two light chain (23 Kilo Dalton [kDa]

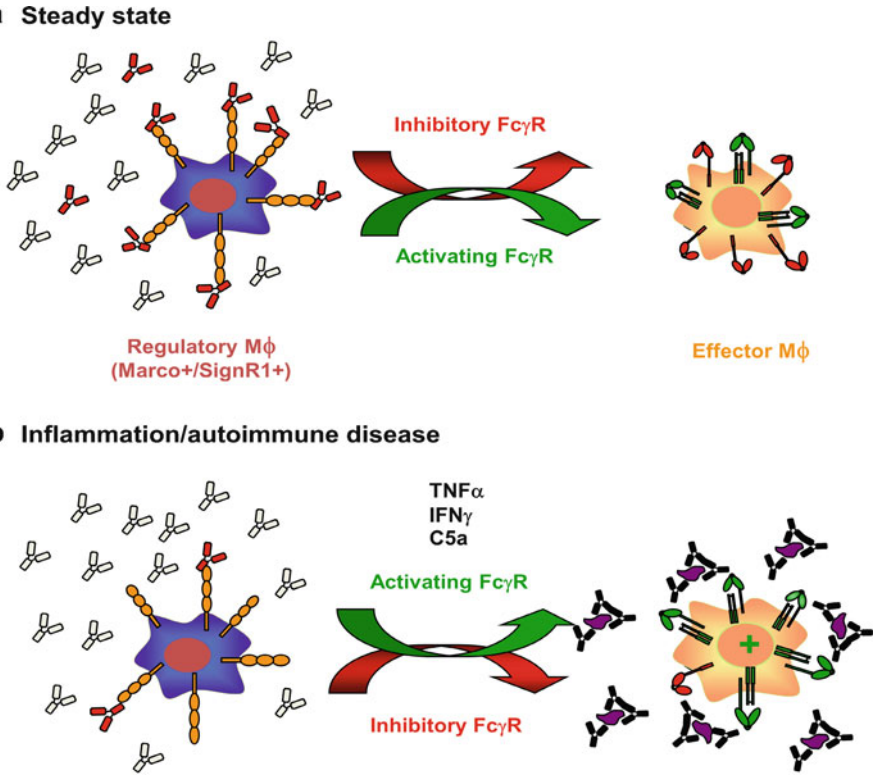

Fig. 29.2 An anti-inflammatory activity schematic for IgG. (**a**) A steady state phase where sialic acid enriched IgG in the serum initiates inhibitory signals by SignR1 expressed on MARCO + marginal zone macrophages within the spleen. This activity may cause equilibrium between expression of activating (in *green*) and non-activating (in *red*) FcγRs on innate immune effector cells; e.g. macrophages and monocytes. This relationship may play a critical role in inhibiting unspecified activation of effector cells by the limited presence of circulating immune complexes (IC). (**b**) When inflammatory processes, such as active autoimmune disease, are initiated the level of sialic acid enriched IgG decreases causing a reduction in negative regulation of effector macrophages through a lowered threshold for activation by IC. Furthermore, cytokines which promote inflammation, up-regulate activating FcγRs and down-regulate inhibitory FcγRs on innate immune effector cells, thereby providing a stimulating of cell activation through IC. (**c**) Upon introduction of high dose IgG (IVIg therapy), or alternately the sialic acid-enriched IgG fraction, immunomodulation by SignR1/DC-SIGN is reinstated resulting in improved expression of FcγRIIB. In addition, there is a reduction in expression of activating FcγRs on effector macrophages, leading to an increased threshold for activation by IC, mediating the pathway back toward a steady state [8] (Reproduced in its entirety from a diagram generously provided by the authors [8] and with copyright permission © 2010 John Wiley & Sons A/S Immunological Reviews 236/2010)

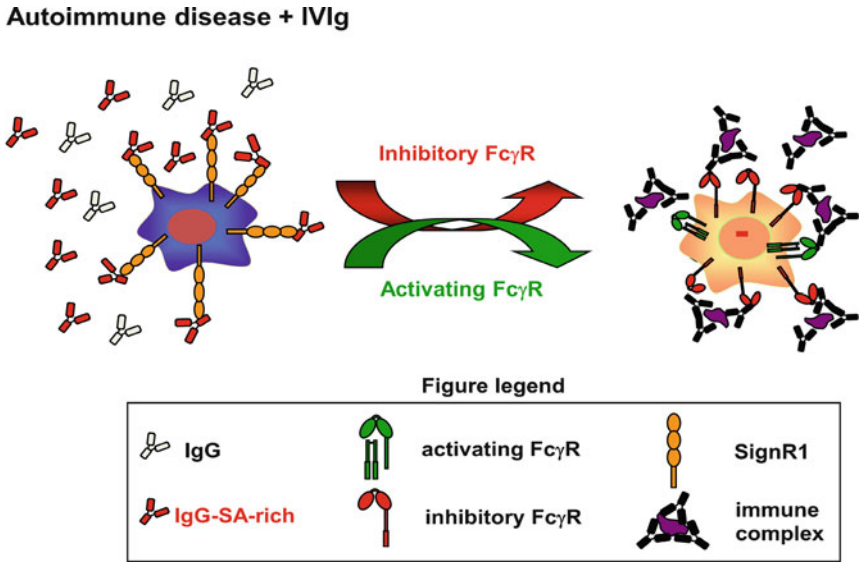

Fig. 29.2 (continued)

each) and two heavy chain (50–70 kDa), linked through non-covalent interactions and covalent disulfide bridges [11]. Variable regions (Fv) are found in the upper areas of the V and contain antigen binding sites. Each Fv is comprised of two variable domains (VH and VL), both displaying a hypervariable or complementary determining region (CDRs) [9, 11]. CDRs are the unique and specific antigen-binding location for each antibody. Two identical antigen-binding sites must take place for each molecule, or between two molecules, which elicits a conformational transformation to the bound antibody mediating additional sites on the antibody to facilitate immune system responses [9, 11]. The IgG subtype or isotype (IgG_1-IgG_4) is dictated by constant regions on the H chain, and the L chain is either κ or λ [10]. There are three domains for the heavy chain constant region, CH1, CH2, and CH3 with a proline enriched hinge spanning CH1 and CH2, thereby providing plasticity to this region of protein [9, 11]. A conformational transformation takes place upon the binding of the antibody to an antigen at the hinge region, thereby presenting additional sites on the protein to interact with the immune system response mechanisms [10]. The CH2 and CH3 domains comprise the Fc region. After the Fv region binds to an antigen, the Fc creates an effector function through binding to Fc receptors (FcRs) and/or the complement [12]. FcRs are prolific and are present throughout cell tissues within the immune system response mechanisms [10]. Critically, FcR and Fc binding is an underlying causation within immune system responses [9, 11]. Bioengineering and the manipulation of variable and constant domains within antibodies is a crucial technique in the creation of unique diagnostic and therapeutic mAbs (Fig. 29.3).

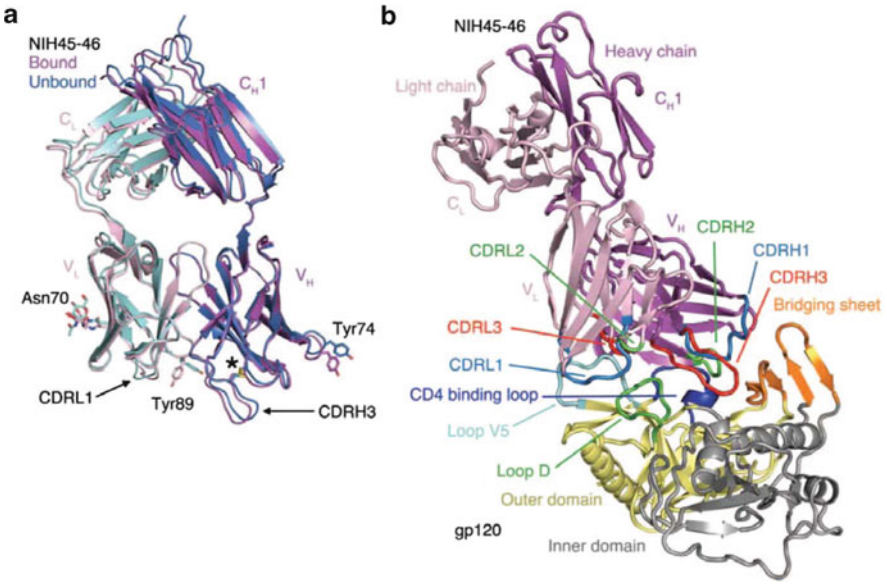

Fig. 29.3 Three-dimensional simulations of typical human antibody structures: (**a**) the NIH45-46 Fab, a highly active agonistic antibody (HAADs) which targets the CD4bs binding site on the envelope glycoprotein gp120 a key HIV-1 protein, and (**b**) a NIH45-46–gp120 complex. In this instance (**a**) depicts the free (heavy chain in *blue*, and light chain in *cyan*) and bound (heavy chain in *magenta*, and light in *pink*) Fab components [13]. The root-mean-square-distances (RMSDs) for both free and bound V_H–V_H and V_L–V_L are 0.5 Å each. An extra disulfide bond in V_H is highlighted with an asterisk, while an N-linked carbohydrate in V_L is depicted as sticks. *Arrows* highlight complementarily-determining regions (CDRs) CDRL1 and CDRH3 in bound and free NIH45-46. Structure (**b**) the NIH45-46–gp120 complex, is illustrated through a ribbon diagram of the NIH45-46 Fab (*magenta* for heavy and *pink* for light chains) complexed with the 93TH053 gp120 core, indicating inner in yellow and outer domains in *gray*. Three variable loops V1–V2 and V3 are not present, but N- and C-terminal truncations are shown [13]. The dimensionality provided in this model conveys the asymmetric structure of the antibody and its importance in permitting complete biomechanical and biophysical interactivity of the antibody

29.2.2 Immunogenicity

The immunogenicity level of different antibodies determines the relative level of effectiveness, efficacy, and safety for therapy within the body [14–21]. Typically, more fully humanized antibodies have lower immunogenicity, and therefore better performance [14]. The level of immunogenicity achieved by a particular antibody can be impacted by numerous criteria including: (1) antibody structure, (2) composition, (3) posttranslational modifications, (4) impurities, (5) heterogenecity, (6) aggregate formation, (7) degradation, (8) formulation, (9) storage conditions, (10) antigen properties, (11) individual patient immune system, (12) concomitant medications, (13) dose, route of delivery, and (14) time

and frequency of delivery [14, 21]. The historical development and production of therapeutic and diagnostic antibodies, mAbs or polyclonal antibodies will be covered in detail later in our overview.

The innate and adaptive immune systems each also have cell-mediated and humoral components which act complementary to the immune response. A cell-mediated response to an antigen involves T cells binding to the surface of any cells which presents the antigen and in so doing, elicits an immune response. Humoral activity involves antibodies dissolved or available throughout the body, typically within blood or the lymphatic system, and which bind directly to the antigen thereby creating an immune response [9].

29.2.3 Immunosurveillance

The concept of "cancer immunosurveillance" was codified by Burnet and Thomas in the 1950s who posited that antigens from tumor cells differ from those found in normal cells, and that differential may result in the capability for recognition and "immune clearance" of tumors from the body [1]. More specifically, the immune system has the potential to react with cancer in one of two ways: (1) against antigens which are specific to the tumor, and (2) impact those antigens present which may vary in paths of expression, when comparing tumor cells against normal cells [7]. Unfortunately, as has become well documented, tumors can suppress immune response both systemically and within microenvironments by producing immunosuppressive bio-molecules and enzymes [7, 22]. This finding supports the concept of cancer immunoediting. Conceptually, immunoediting suggests that constant cancer immunosurveillance creates an environment conducive to driving toward the 'natural selection' of tumor cells capable of eluding the immune system. Furthermore, tumors will continue to grow only when the cancer has developed a mechanism(s) for growth which circumvents the normal immune response regime [1]. This process has been confirmed in studies where head and neck tumors use one of two pathways to elude the immune system: (1) reduction of innate immunogenicity levels, and (2) suppression of the immune response [1]. This has been documented in nearly 50% of head and neck squamous cell carcinomas [23].

There are thousands of different forms of cancer, most with a variety of subtypes. All have similarity in the underlying origins of causation including; (1) genetics, (2) environmental, (3) epigenetics, (4) choices made in lifestyle (e.g. stress, tobacco and/or alcohol use), and (5) viral. SSCHN has a well recognized viral causation, oncogenic human papillomavirus infection with subsequent oncogenic transformation [24]. SSCHN and other forms of head and neck cancers have molecular expression pathways and immune response mechanisms which differentiates these cancers from other forms. It is these immunological pathway activities which will be the focus of our remaining discussion on the immunology of SCCHN and head and neck tumors. In 2009 there were 48,100 new cases of head and neck cancer presenting in the US [25]. Of those, 90% were SCCHN of the oral cavity, oropharynx,

hypopharynx, larynx, and with less frequent occurrence, in the paranasal sinuses and nose [26]. The two primary causal agents are alcohol consumption and/or tobacco use [27]. Generally, the survival rate from traditional therapies, usually a blend of surgery and radiation, or radiation and chemotherapy is approximately 50% for SCCHN [28]. Additionally disturbing statistics include: (1) over the past 30+ years the 5 year survival rate has seen no improvement, (2) is actually lower for patients exhibiting single homolateral lymph node metastasis (LNM), and (3) is under 25% for those with bilateral LNM [29, 30].

29.2.4 Immunotherapeutic Response Mechanisms

Cancers of the head and neck appear to elude the immune system response through a number of different dysregulation or derangement mechanisms: (1) changing immunogenicity, (2) mediating immunomodulating cell types, (3) stimulating the secretion of immunosuppressive molecules, and (4) manipulating the immune system to facilitate angiogenesis, and metastatic cellular growth behavior [1]. More specifically, once the cancer is present this is accomplished through: (1) transcription factors being highly upregulated by the tumor and therefore identified as ideal candidates for therapeutic treatment, (2) tumors secreting cytokines which appear to suppress cell-mediated immune response against the tumor, (3) taking over molecular signaling intended for lymphocyte and dendritic cell migration receptor sites, resulting in over-expression of communication normally directed to immune cells, but ending up in tumors stimulating growth, and (4) a hypothesis which proposes that cancer stem cells (CSC) have the ability to elude traditional disease treatment pathways and the immune process, thereby regenerating the tumor phenotype [1]. Cytokines are proteins, glycoproteins or peptides, which act as critical intercellular cell-signaling mechanisms involved in a variety of regulatory and communication functions. These signaling molecules are generated for use within a number of different physiological areas, key among, within the immune system [31]. Changes in the levels of bio-makers in serum, such as cytokines, have become useful indicators of immune response patterns to cancer within patients [1]. Within the cytokine category which directs immune cell migration are chemokines, made up of small heparin-binding cytokines, and are responsible for leukocyte positioning and transport [1]. Substantial overexpression of many chemokines has been shown in SCCHN and is believed responsible for: (1) nodal metastasis, (2) tumor growth, and (3) leukocyte infiltration [1]. The generation of chemokines and receptors demonstrates further manipulation of the immune system and tumor microenvironment by SCCHN in assuring the survival of tumors and aiding metastatic growth [1].

Myeloid-Derived Suppressor Cells (MDSC) are part of the myeloid cell category which originate from myeloid tissue in the bone marrow. MDSC has been found to: (1) block expression of IL-2 generation, necessary for the activation of T-cell propagation and concurrent cell-mediated immunity response, (2) are responsible for the removal of arginine and cysteine both crucial to T cell up-regulation, and (3) produce nitric oxide

and reactive oxygen species which interfere with normal T cell functionality [1]. These have been found upregulated in all forms of cancer most especially in SCCHN [32].

There are currently four known sub-categories of T regulatory cells (Tregs) all of which are believed to be immunosuppressive: (1) $CD4^{+}CD25^{high}FoxP3^{+}$Tregs which occur naturally within the thymus, (2) IL-4-dependent Tregs (Th3), (3) antigen-specific Tregs (4) IL-10-dependent Tregs (Trl), and (5) $CD8^{+}CD25^{+}$ whose complete role is still being clarified, but is suspected to be suppressive [33, 34]. Tregs are responsible for: (1) cell cycle arrest, (2) apoptosis, (3) anergy, and (4) also suppress DC cell, NK cell, and B cell activity [35, 36]. It is also now recognized that Tregs appear in higher concentrations in HNSCC patients within blood adjacent to lymph nodes, and within T cells which penetrate tumors and act as strong immunosuppressive mediators [37–39]. Numerous SCCHN studies have been conducted the results of which appear contradictory, and therefore are not yet appropriate for use in designing treatment strategies [1]. However, these research efforts have provided enough data to demonstrate the enormous immunosuppressive role SCCHN plays through significant impact on immune response mechanisms and cancer immunotherapy, including: (1) SCCHN generates immunosuppressive cytokines and other bio-molecules, and (2) severe disruption of normal cytokine levels through dysregulation and deregulation [40]. Furthermore, there is an increased presence of immunosuppressive regulatory immune cells and a significant dis-functionality to the systemic immune response within the SCCHN patient community [1].

There are a variety of genetic actions which take place in the presence of SCCHN cancers, the most important are the: (1) upregulation/overexpression of oncogenes, such as epidermal growth factor receptor (*EGFR* or *ebB1*), and (2) mutations and deletions resulting in the inactivation of tumor suppressor gene *p53* [26, 41]. These significantly impacted genetic areas have become primary targets for evolving immunotherapy strategies for treatment of SCCHN [26]. *EGFR* is a key tyrosine kinase membrane receptor based molecule, responsible for intracellular signaling pathways for cellular: (1) migration, (2) differentiation, and (3) proliferation [26]. *EGFR* is: (1) overexpressed in 80–90% of SCCHN, and (2) a strong link with gene amplification but not mutation [28, 41]. Further, *EGFR* when overexpressed within normal mucosa of SCCHN patients provides an early indication of carcinogenic behavior [41]. And finally, *EGFR* overexpression is a significant indicator of an antagonistic form of the cancer usually associated with reduced survivability [41, 42]. The *p53* tumor suppressor gene displays significant genetic alteration leading to inactivation of functionality and progression of cancer growth within SCCHN patients [43]. In addition: (1) 40–70% of SCCHN displays *p53* mutation, (2) there is a far higher level of mutation within invasive carcinomas versus non-invasive cancers, (3) *p53* overexpression found in tumors is indicative of more destructive growth, a higher level of tumor development and involvement of lymph node metastasis, (4) results of studies indicate the existence of clone-specific *p53* mutations in the microenvironment of tumors, a prescient marker for re-establishment of disease, and (5) determining that *p53* mutations are present in more 50% all cancers within the human body [44–48].

Improved understanding of the mechanisms responsible for the manipulation and suppression of gene/genetic agents by cancer-antigens and other angiogenic

bio-molecules secreted by SCCHN tissues provides a therapeutic strategy for development of better diagnostic and therapeutic drugs for the treatment of SCCHN. Key among the pathways developed and which continue to serve as a promising direction for future exploration and improved therapies, are mAbs.

29.3 Diagnostic and Therapeutic Monoclonal Antibodies

As we have discussed the immune system response mechanisms are an extraordinary array of concurrent and complementary protective methods and processes to clear the body of pathogenic agents, specific-antigens and bio-molecules. Of particular challenge is introducing biologically based therapies, such as mAbs, into the serum for an adequate time period to be effective against tumors, while not being identified and cleared by the immune system. This requires designing and engineering diagnostic and therapeutic antibodies with sufficiently low immunogenicity levels to remain undetected by the immune system [49].

29.3.1 History

Historical efforts in treating cancer involved creating polyclonal anti-sera in animals outside of the human body by introducing patient tumor fragments into those animals, and then treating the patient with the resulting anti-sera [50]. In the late nineteenth century treatment with such anti-sera initially showed improvement in patients which rapidly evolved into severe side effects making the procedure entirely ineffectual [49]. Significant progress wasn't accomplished until 1975 when Kohler and Milstein created the hybridoma through the hybridization of human myeloma cells with antibody producing B cells from mice [49]. This remarkable achievement allowed the manufacture of monospecific, or monoclonal antibodies mAbs which could then be targeted against antigen-specific for cancer and permit use in patient settings [49]. As new murine derived therapies were developed and moved into clinical trials nearly all were "recognized" by the body's humoral immune system resulting in the secretion of human anti-mouse antibody (HAMA) response [49]. As a consequence of the HAMA response there is: (1) suppressed clinical benefit, (2) neutralization and clearance of therapeutic murine antibodies from the body, and (3) infusion instigated hypersensitivity reactions with significant safety, dose frequency, and administration issues [49, 51–53]. As further progress in the design and engineering of therapeutic antibodies has been achieved, far more elaborate techniques and molecules have been created using "human germline sequences", genes, and/or genetic fragments in an attempt to minimize immunogenicity and HAMA response [49].

29.3.2 Development, Bioengineering and Production

These novel bio-engineering achievements include diagnostic and therapeutic antibodies developed and produced via a number of varying pathways: (1) Murine: the development process has been previously discussed, (2) Chimeric: takes advantage of the ability to genetically combine portions of human genes with antigen-specific murine sections, resulting in a chimeric antibody about 70% human, thereby significantly limiting HAMA response [54–56], (3) Humanized: there are a variety of approaches for this process due to intellectual property issues, but all provide similar results. At the genetic level, mAbs of mice are grafted onto a human antibody framework, resulting in a humanized antibody consisting of approximately 90–95% human genetic sequencing [57], and (4) Fully Human: sequestering of antibodies from a purely human genetic framework which is usually accomplished through one of a number of pathways: (a) *in vivo* production through transgenic mice which have been engineered to include human immunoglobulins, (b) *in vitro* creation through the use of phage-display lines with recombinant human antibody libraries, and (c) an additional technique offering enormous potential, is via human hybridoma technology [49]. Phage-display, or filamentous phages are a specialized form of bacteriophage (a virus which infects bacteria) which has been genetically engineered to infect or transfect, expression or amplification cell lines (for example *E. coli,* or mammalian), which have been developed and later selected for large-scale, bio-pharmaceutical production of a particular monoclonal antibody [58, 59]. The most typical pathway for production of diagnostic and therapeutic mAbs is initiated by the insertion of the required gene into a plasmid (DNA molecule independent from chromosomal DNA) [60], which is transfected into a chosen cell expression line system [61]. The success of the production process pathway implemented is influenced by a number of factors including, but not limited to: (1) cell type selected, (2) cell cycle and size [62], (3) the vector/promoter for transfection, (4) the final product's needs [63–65], (5) methods utilized for clone selection and transfection, and (6) the type of growth medium chosen [66]. The most commonly chosen cell lines for production of mAbs are mammalian cells due to the ability for large scale-up production capacities, and being most human-like in biological activity and immunogenetic compatibility [65, 67–70]. Monoclonal antibodies are large and complex, bio-active molecules which require production expression cell lines which can accommodate those qualities, whether selected from microorganisms, insects, mammalian cells, seeds, plants or a transgenetic variant of one of these species [10]. A number of process parameters also need to be met: (1) scalability is required, (2) post-translational processing, (3) must be compatible with human application and regulatory needs, (4) capable of high expression levels in production, (5) high cell viability, and (6) should be genetically stable over lengthy periods of time [71]. Finally, the choice of which cell line species to use is determined by: (1) product application, (2) product performance, (3) economics, (4) biopharmaceutical market need, and (5) product function [10]. Based on these and

other needs the cell line expression system, production methods and bio-processing techniques are decided upon for producing the mAbs. A comprehensive summary of comparative cell line expression data, economic yield data, and selection criteria can be found for more detail [10].

29.3.3 Pharmacokinetics

Modulating the pharmacokinetics of therapeutic mAbs has evolved into a significant antibody engineering tool in regulating efficacy, improving molecular stability, and controlling the duration of therapy [49, 72]. As we have discussed, there are two immunotherapeutic pathways mAbs can take: (1) inhibiting intracellular signaling mechanisms, and (2) redirecting the immune system response to identify and clear SCCHN tumor cells [49]. Key design and performance characteristics for optimizing the pharmacokinetics of an mAb molecule includes: (1) minimizing immunogenicity, (2) displaying high affinity, (3) discriminating specificity, (4) has low reactivity [73], (5) dosing facilitates best bioavailability, (6) distribution, (7) uptake, and (8) rate of clearance [74]. Structural changes made to mAb molecules can also alter pharmacokinetics by impacting: (1) aggregation status, (2) electric charge (pI), (3) hydrodynamic volume, and (4) functional changes which effect receptor binding capabilities [72]. In general, mAbs which are smaller than 50–65 kDa are susceptible to rapid "first-pass" clearance by the kidneys [75]. Unfortunately, those smaller molecules also demonstrate an improved capacity to penetrate tumors, but are prevented from doing so completely by an inadequate serum half-life, and the consequent "first-pass" recognition and clearance taking place by the immune system [49]. Research has shown the larger the molecule, the greater the longevity of the mAb. However, larger molecules also can have significantly reduced penetration of tissue, as well as poor tissue to blood ratios [72]. An optimal pharmacokinetic range for the size of mAbs is approximately 50–80 kDa [49, 72]. This dichotomy has resulted in the development of two primary pathways to engineer bioactivity, stability, longer lasting mAbs molecules, while still remaining effective in size: (1) by attachment of a chemical entity, such as albumin (67 kDa in size) or a hydrophobic polymer, through "chemical conjugation" thereby changing the mAbs physiochemical behavior (minimizing immunogenicity or improving solubility), and (2) through recombinant/genetic techniques which utilize genetic engineering to modify the mAbs functionality or molecular structure [72].

29.3.4 Molecular Structure and Biodistribution

It has been demonstrated that the molecular configuration, structure and biochemical profile of mAbs has a direct correlation on biodistribution levels, and therefore significantly impacts availability of therapeutic antibodies for adequate

transport throughout the body and consequent penetration into tumors [76]. The morphology of tumors presents a number of significant challenges to the effective delivery of mAbs. The physiology and anatomical characteristics of tumors is entirely dissimilar as compared to those of normal tissues [2]. Key differences include: (1) rapid tumor growth, (2) tumor necrosis, (3) elevated interstitial fluid pressure, (4) heterogeneous and leaking vasculature, and finally, (5) tissue porosity [2]. Furthermore, the level of antigen expression and density affects the pharmacodynamics, pharmacokinetics, and biodistribution of mAbs [77–83]. This is particularly evident for the IgG class, more specifically for isotypes IgG_1, IgG_2, IgG_4, and murine IgG_{2a} of which all approved mAbs are a part [2]. There are two recognized forms for moving molecules across tissue membranes, active and passive transport [2]. Active requires some form of energy, typically a biological carrier to mediate the transfer of mAbs [2]. Passive is the straightforward dispersal of the mAbs and is affected by: (1) surface area, (2) concentration, (3) cross membrane pressure differentials, (4) construction and thickness, and (5) the permeability of tissue [2]. Systemic control for the transfer of molecules from blood to tissues is impacted by: (1) drug size and its degree of lipophilicity, charge and polarity, (2) structure and porosity of the membrane, dynamics of blood flow, concentration and pressure gradients [2]. The phenomenon of convection is also believed to be responsible for the transvascular movement of mAbs, by taking advantage of the pressure gradient differential between vascular and interstitial cellular structures [2]. The blood transport and distribution vasculature system consists of four different capillary types: (1) continuous; which have complete membranes and combine with endothelial cells to provide almost uninterrupted linings, (2) fenestrated; present in gastrointestinal, renal glomeruli and some glands, (3) sinusoids; present in the liver, spleen and bone marrow, and (4) capillary endothelium; found within the brain [84–87].

29.4 Therapeutic mAbs

29.4.1 Immune Response Pathways

A number of concepts have evolved to explain the anti-tumor behavior of antigen-specific therapeutic monoclonal antibodies. mAbs are believed to initiate the tumor specific immune system response through one of three pathways: (1) Antibody Dependent Cellular Cytotoxicity (ADCC), (2) Complement Dependent Cytotoxicity (CDC), and (3) Induction of Adaptive Immunity (IAI) [1, 88]. ADCC is facilitated by NK cells, possibly monocytes and neutrophils as well, and is significantly impacted by the degree of genetic polymorphisms present [1]. A variety of studies demonstrate that polymorphisms in specifically targeted gene coding/antibody domain regions results in increased binding of antibodies, and overall enhanced ADCC response for different forms of cancer [wsw-51 to 55] [89–93]. The CDC mechanism is another

effector of the humoral immune response and mediated by NK cells and T-cells, and is specific to tumor-associated antigens [1]. ADCC and CDC both mediate through forms of passive immunotherapy [88]. However, there is increasing evidence which suggests that IAI provides a "cross-presentation" capability by inducing adaptive immune responses through DC and cytotoxic T lymphocytes, both effective in cancer treatment, including in SCCHN tumors [94–96].

One the most common forms of cancer immunotherapy is the use of mAbs [1]. An enormous amount of research, development and investment by the biopharmaceutical industry has been conducted on two mAb immunotherapeutic drugs, which now appear to be extremely promising for treatment of SCCHN cancers: cetuximab (Eribitux) and trastuzumab (Herceptin) [1, 7, 26, 88, 97]. Cetuximab is a murine-human chimeric mAb and an IgG_1 anti-EGFR molecule which targets EGFR that is found to be upregulated in 80–90% of SCCHN tumors, and mediates: (1) tumor cell proliferation, (2) angiogenesis, (3) invasion, (4) tumor survival, and is therefore associated with lowered survival rates and poor prognosis [98, 99]. Cetuximab appears to suppress the expression of EGFR which then precluded continued activation of ligands. This results in the restriction of growth for cell lines with upregulated EGFR, and thereby improves the effectiveness of radiation and chemotherapy [100–102]. Trastuzumab is a humanized anti-HER2 mAb. EGFR and HER2 are part of a number of tyrosine kinase membrane receptors which are encoded proto-oncogenes [26]. Trastuzumab appears to: (1) downregulate HER2, (2) interfere with important signaling activities, (3) impede the progress of cell-cycle, (4) cause apoptosis, and (5) improve cytolytic T lymphocyte behavior targeted toward HER2 upregulated tumor tissues [103, 104]. Furthermore, this mAb also improves chemotherapy treatment and antitumor activity efforts within SCCHN [26].

29.4.2 Cetuximab and Trastuzumab

Cetuximab and trastuzumab have a number of immmunotherapeutic pathways evolving which are strategies for use and development. *Concurrent*: The utilization of more traditional anti-tumor treatment paths for SCCHN such as radiotherapy, cytotoxic chemotherapy based treatments including: platinum, cisplatin, taxane, or carboplatin and 5-fluorouracil, in combination with a separate dose infusion of cetuximab or trastuzumab, particularly in cases of recurrent or metastatic (R/M)-SCCHN [105–108]. These applications are being aggressively pursued through modified first-line and second-line therapy approaches for treatment therapy models using cetuximab. This also includes numerous phase I, II, and III clinical trials for combinatorial drugs using cetuximab or trastuzumab, in conjunction with one or more cytotoxic chemotherapy drugs, which are in various stages of development, submission or approval for use with SCCHN [97]. The concept of utilizing mAbs in conjunction with cytotoxic chemotherapy, antigen-specific toxic molecules, or nanocompounds to create antibody-drug conjugates has produced an enormously important area for future development of immunotherapies. The role of generating

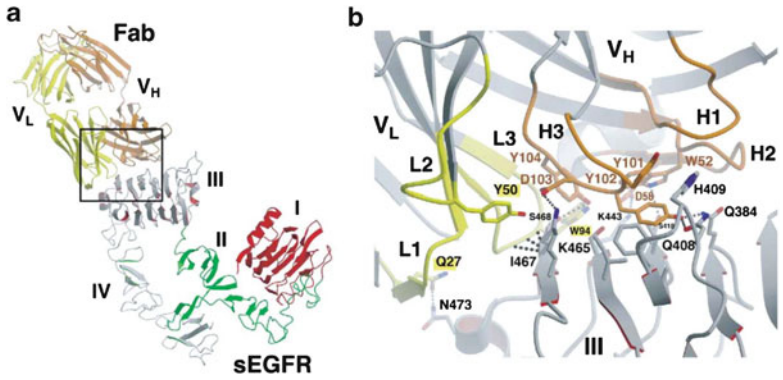

Fig. 29.4 Superimposed molecular structures of cetuximab binding to Domain III of an attached sEGFR molecule. Image (**a**) is a ribbon depicting the FabC225:sEGFR complex with the V_L chain of FabC225 is shown in *yellow*, the V_H chain in *orange*, Domain I of sEGFR appears in *red*, and Domain II in *green*. Domains III and IV both appear in *gray*. The secondary structure components edges are red and green, correspondingly. The black box highlights the amplified area found in (**b**). Image (**b**) is a magnified perspective of the FabC225:sEGFR interface with the CDRs appearing in *yellow* for the V_L chain, *orange* for the V_H chain with the remaining portion of FabC225 in *gray*. Side chains responsible for important interactivity are also shown. Amino acid labels appear in orange for the V_H of FabC225, *black* with a *yellow* background for the FabC225 V_L, and *black* with a *white* background for sEGFR. A *dashed gray* line highlights hydrogen bonds [109]

antibody drug conjugates (ADCs) through the use of highly antigen-specific mAbs, and the resulting applications in cancer immunotherapy, will be discussed in more detail below. A second approach to monoclonal antibody therapy is *Monotherapy or Stand-Alone Biological Immunotherapy*: This involves therapy through the exclusive use of an mAb, such as cetuximab or trastuzumab as the only treatment agent on selected patient populations [26]. There are numerous worldwide phase I, II and II studies and submissions underway for both immunotherapeutic drugs focused on SCCHN and R/M-SCCHN which are providing encouraging results [26]. A 3-D example of cetuximab co-joined with the soluble extracellular region of (sEGFR) can be found below (Fig. 29.4).

29.4.3 Potential and Future mAbs

There are a number of additional mAbs believed to have strong potential for future treatment applications in SCCHN and R/M-SCCHN immunotherapy which are under clinical investigation [26, 97]. These include: (1) Panitumumab, (2) Matuzumab, (3) Zalutumab, and (4) Bevacizumab [26, 97]. Panitumumab is an IgG_2 fully human mAb with exceptional binding capability with the ligand-binding domain of EGFR, thereby interfering with ligand binding to EGFR which prevents normal receptor functionality, and creates signal pathway shutdown resulting in cessation of cell-cycle, arrest of growth and apoptosis [110]. Matuzumab is an IgG_1humanized mAb which

also binds to EGFR, and provides extended serum half-life, requiring less frequent dosing administration [26]. Zalutumab is another fully human IgG1 mAb and an EGFR targeting agent providing encouraging data towards future use [26]. Bevacizumab is a humanized VEGF-A targeting mAb with promising potential for use in SCCHN treatment [97]. These mAbs have numerous clinical studies underway and are in various stages of development or phase I, II, or III study for regulatory submission, review, and approval [26, 97]. More recently, the mAb Nimotuzumab received FDA approval for use against SCCHN. Nimotuzumab is a humanized IgG_1 murine-human chimeric which appears to have fewer side effects than other EGFR targeting agents [97].

29.5 Antibody Drug Conjugates (ADCs)

The therapeutic value of cytotoxic chemotherapeutic drugs is well recognized to be limited due to: (1) a restricted therapeutic window of opportunity for impact, (2) possessing indiscriminate cytotoxicity, (3) having poor pharmacokinetics, and (4) organ distribution [111]. Most of these cytotoxic drugs have been found to be unsuccessful in clinical trials due to disproportionately high toxicity levels, resulting in insufficient therapeutic benefit at maximal tolerated dose (MTD) levels [112]. This precludes the possibility of achieving the cellular cytotoxicity levels which might otherwise be therapeutically beneficial in destroying tumor cells [112]. As we have discussed mAbs have a variety of immunotherapeutic advantages, key among them: (1) selectivity/specificity, (2) biodistribution, (3) good pharmacokinetics, (4) moderate to limited systemic toxicity, (5) extended retention time in circulation, and (6) functionality associated with antibodies [112]. The raison d'être for developing ADCs was to combine the immunotherapeutic strengths of mAbs with the desirable cytotoxicity levels found in chemotherapeutic drugs [113–120]. The functional profile for high performance ADCs includes the following criteria: (1) possess the pharmacokinetics and functionality of mAbs, (2) remain intact and non-toxic whatever the systemic form of delivery, (3) be active within tumor, (4) deliver sufficient levels of drugs to destroy tumor cells, (5) maintain an optimal combinatorial balance between cytotoxic drug and immunotherapeutic mAb, (6) stimulate and take advantage of humoral immune responses through ADCC, CDC and IAI, and (7) capture other mAb causation activities such as antibody-dependent cell phagocytosis, inhibition of receptor signal transduction, and inducing apoptosis [112].

29.5.1 Designing ADCs

A first significant consideration in ADCs design is differentiating between 'tumor-specific antigens' and 'tumor-associated antigens'. The latter phrase more accurately describes the fact that antigens expressed on cancer cells, are also expressed to a degree in normal tissues, and only those antigens directly and specifically linked to the tumor surface morphology should be targeted for therapy [112]. Key antigen-based

parameters determining how effective an ADC is include: (1) the amount of antigen expression by the cell surface, (2) rate of internalization for antigen-ADC complexes, (3) rate and direction of intracellular flow, (4) rate and/or amount of antigen-ADC complex processing taking place thereby facilitating drug release [112]. A second criterion is the structure of the ADCs must maintain the immunotherapeutic functionality of the mAb selected for use after conjugating with the other components of the bio-molecule [112]. Finally, the ADCs molecular configuration has to permit administration to patients at doses high enough to be effective [112].

29.5.2 Key Molecular Components

There are three major bio-molecular components to ADCs: (1) the mAb, (2) a cytotoxic drug of choice, and (3) a biochemical linker which covalently binds the antibody and drug to one another [112]. The mAb chosen can be murine, murine-humanized (chimeric), humanized or fully human depending upon need. More specifically, important performance criteria for mAb use should be considered, including: (1) high binding affinity, (2) specificity, (3) lengthy serum half-life in circulatory system, (4) strong immune effector functionality ADCC, CDC or IAI, (5) cellular phagocytosis, (6) if possible, tumor suppression from antigen biological activity levels, and (7) minimal loss mAb functionality when conjugated with chosen drug [112]. The cytotoxic drugs used usually falls into one of two types: (1) DNA damaging, for example N-acetyl-γ-calicheamicin dimethyl hydrazide used in gemtuzumab [112, 121, 122], or (2) drugs which are directed at mircrotubules, such as maytansine or maytansinoids [112]. The last element is a linker which has a number of significant criteria to be met including: (1) attachment site on the mAb, (2) the average number of sites which are attached on the mAb, (3) polarity, and (4) the cleaving capacity of the linker, how easily is the chemical bound broken, thereby facilitating release of the drug [112]. This linkage usually takes place at amino groups within lysine residues, or in thiol groups in cysteine residues [114, 123–125]. While ADCs conceptually are a powerful biological technology in the immunotherapeutic treatment of SCCHN, their use to is not without concern or issue. The chemotherapeutic drugs conjugated typically have high inherent toxicity levels which have the potential to exceed MTDs before being systemically metabolized and cleared from the body [112]. An additional issue is the possibility of erroneously targeting tumor antigens which are also found in normal tissues [112].

29.6 Bispecific Antibodies, BiTE Bispecific and Bispecific Immunotherapeutics

Monoclonal antibodies have evolved to become a significant category of protein-framework drugs which are being used as therapy against many forms of cancer, including SCCHN [126–132]. As part of that evolutionary process a variety of

immunotherapeutic mAb approaches have been developed to improve efficacy, efficiency, and design mAbs to exhibit increasingly more responsive behavior toward tumor specific antigens [133]. ADCs which incorporate numerous types of different effector molecules in combination with an mAb is one such pathway in this process. However, the addition of toxins, cytotoxic drugs, or radionucleotides in many instances may make mAbs less effective, by impacting antibody binding capability, or interfering with the functionality of effector agents [133].

In response to these challenges a path next pursued was the development of bispecific antibodies (biAbs), antibody proteins made through the combining of either entire mAbs, mAbs fragments, or dual-targeting antibodies [133]. BiAbs have a number of functional characteristics which are highly attractive for increased effectiveness in targeting tumor antigens: (1) by providing two separate binding specificities, and (2) can be infused alone or used in conjunction with effector cells to mediate cytolytic impact [133]. The molecules can also be engineered to offer different biAb configurations including: (1) quadroma, (2) $F(ab')_2$, (3) diabodies, and (4) tandem diabodies and single-chain antibody (scFv)-based structures [134–137]. A later improvement on biAbs technology was the development of a modified form of biAbs known as a bispecific T cell engager (BiTE) [133]. BiTE bio-molecular structure consists of linked variable heavy (V_H)/variable light (V_L) pairs from the same mAb are linked to scFvs, then two scFv are interconnected by a linker to a form a polypeptide [136]. These improvements have resulted in extended serum half-life and the binding affinity of BiTE biAbs [133]. A subsequent advance created trifunctional (tri) biAbs to further enhance serum half-life and efficacy. This was accomplished through combination of fragment antigen-binding (Fab) with engineered heterologous fragment crystallizable (Fc) variants [137, 138]. More recently, additional work has led to the creation of multivalent and multifunctional dock-and-lock (DNL) tibiAbs [139].

Since T cells do not have Fc receptors, biAbs have the ability to recruit T cells via the CD3 complex interconnected to T cell receptors within all T cells, thereby directing cytolytic T-lymphocytes to eradicate tumor cells [133]. Furthermore, because of biAbs dual specificity capability these molecules can also stimulate immune effector cells in a variety of ways: (1) via the CD3 complex, (2) by co-stimulating the CD28 molecule on T cells or Fcγ receptors (FcγRs) on accessory cells, or (3) by binding concurrently to tumor-associated antigens (TAAs) on tumor cell surfaces [140–144]. These engineered bispecific immunotherapeutic technologies engage the anti-tumor potential of both cellular and humoral/antibody mediated immunotherapy in tandem, in a highly directed manner, and with minimal toxicity [133]. BiAbs and triAbs are in phase I and II clinical trials with two promising compounds for possible future cancer treatment: (1) an biAb, blinatumomab that seems effective against tumor cells in blood, lymph node lesions, spleen, and bone marrow [145], and (2) the triAb catumaxomab which has been approved in the EU for use on malignant ascites [146].

SCCHN cancers are highly heterogenic due to the variety of different tissue types involved. These tumors are well recognized to originate in the oral cavity, oropharynx, nasopharynx, hypopharynx, and larynx regions [147]. The genetic progression of SCCHN includes oncogenes/biomarkers and tumor suppression genes/biomarkers known to be involved in the SCCHN disease process [147, 148]. These biomark-

Table 29.1 List of therapeutic mAbs, biAbs, triAbs, and conjugates under investigation, clinical development, or in clinical use for treatment of SCCHN or solid tumors

Antibody	Expression target	Antibody format (FDA approval date)	Ref.
mAbs			
Bevacizumab	VEGF-A	Humanized IgG2 (2004)	[1, 88, 97]
Cetuzimab	EGFR	Chimeric Human-murine IgG1 (2004)	[1, 26, 88, 97]
Matuzumab	EGFR	Humanized-murine IgG1	[1, 26, 97]
Nimotuzumab	EGFR	Humanized-murine IgG1	[97]
Panitumumab	EGFR	Fully Human IgG2 (2006)	[1, 26, 88, 97]
Trastuzumab	HER2	Humanized IgG1 (1998)	[26, 149]
Zalutumumab	EGFR	Humanized IgG1	[1, 97]
BiAbs			
Anti-CD64 x anti-EGFR	CD64/EGFR	$F(ab')_2$/Solid Tumors	[133]
TriAbs			
None for SCCHN			[133]
ADCs		*Linker Type/Target*	
Lorvotuzumab mertansine	CD56	Hindered disulfide, SPP-DM1, maytansinoid/Solid Tumors and SCCHN	[112, 150]
Pre-clinical			
Dacetuzumab	CD40	Targeting Tumors and SCCHN	[88]
Tremelinumab	CTLA4	Targeting Tumors and SCCHN	[88]
Daclizumab	CD25	Targeting Tumors and SCCHN	[88]

Abbreviations: *FDA* US Food and Drug Administration (http://www.fda.gov), *CTLA4* Cytotoxic T Lymphocyte antigen 4, *HER2* Human epidermal growth factor receptor 2, *EGFR* Epidermal growth factor receptor, *SPDB* N-succinimidyl-3-(2-pyridyldithio) butyrate, *SPP* N-succinimidyl-4-(2-pyridyldithio) pentanoate, *VEGF* Vascular endothelial growth factor

ers are then targeted and used for immediate investigation and development of potential new immunotherapeutic mAbs applications, for example in additional ADCs or Bispecific complexes. These biomarkers also serve as direction for identifying and developing other promising immunotherapeutic drugs for the future. Table 29.1 provides a summary of immunotherapeutic drugs in use and development for SCCHN (Please refer to Chap. 30 for more information regarding tumor biomarkers and receptors).

29.7 Future Directions in Nanomaterials

29.7.1 Mass Transport and Transport Oncophysics

It has long been recognized that the indigenous vasculature, blood vessel morphology, and neo-vascular activity within tumors is uniquely essential for tumor cellular survival, angiogenesis, and metastatic mobility. This realization has driven research over

the past 10 years to clarify, and provide a more complete understanding of the underlying tumor-associated biological mechanisms involved. These accomplishments provide further knowledge toward the possibility of developing future generations of tumor-directed therapeutic drugs with greater effectiveness and better outcome for patients [76, 151]. As a result of these efforts there is a much enhanced appreciation of tumor behavior in a number of relevant disciplines of biomolecular investigation, including: (1) pathophysiology, (2) biophysical relationships, (3) biomechanical/mechanobiological, (4) cellular biophysics, and (5) most importantly; the underlying mass transport dynamics or 'transport oncophysics' activities involved at the cellular level, in tumor microenvironments, and within the extracellular matrix/environment [76, 151, 152].

A prime causality for the aberrant behaviors exhibited by tumor cells is mass transport or 'transport onconphysics' dynamics within cells [76]. This is particularly relevant when examining how tumor cells manage to successfully infiltrate biological barriers which usually are impervious under normal circumstances [76]. This phenomenon is of particular importance when describing the penetration of surrounding tissues by tumor cells, and metastasis which involves a number of interdependent stages to facilitate cellular migration, including: (1) improved motility in cells, and (2) negotiation through vascular endothelia, both locally and within remote lesion producing locations [76]. These alterations in transport dynamic characteristics are critical to both tumor cell migration and metastasis and include: (1) motility, (2) biomechanical properties at the cell level, (3) stromal support, and (4) infiltration past vascular endothelium via a variety of biological mechanisms which change the endothelial barrier, thereby permitting increased penetration [151, 153–157]. These modifications in transport dynamics are also found in angiogenesis, effecting neovascular permeability through formation of large numbers of fenestrations in the endothelium, varying in size from a few microns to hundreds of nanometers [158, 159]. Significant variation in to the transport dynamics present in angiogenesis provides a morphological environment conducive to tumor growth through: (1) anastomoses, (2) vessel structure changes which dramatically impact the properties of blood flow, (3) adversely impacting transport within the vascular compartment, and (4) facilitating movement into adjacent tissues [158]. These and other angiogenic events, including: (1) molecular fractionation, (2) cell margination, and (3) endothelial adhesion during restricted flow through lacunae-based angiogenic vessels, all vary from transport dynamics taking place within normal tissue [76]. All of these angiogenic phenomena facilitate a significant increase in mass transport within cancer tissues [76]. Additionally, when combined with: (1) upregulated proliferation growth, (2) inadequate co-development of lymphatic drainage, and (3) differentials in the permeability of neovascular endothelia, the accumulated impact of which is a lack of balance between hydrostatic osmotic and interstitial fluid pressures [160]. As a consequence, these changes in mass transport dynamics result in the formation of a biophysical barrier resistant to normal flow dynamics between vascular and tissues, thereby creating a convection flow away from the tumor, and inhibiting or preventing cells from receiving large therapeutic molecules, such as mAbs [76].

29.7.2 Biological Barriers

The endothelium is made up of endothelial cells, and found lining the innermost surface of both blood and lymphatic vessels, forming a continuous distribution and communication mechanism between the lymph and circulatory systems [152]. The endothelial cell type (phenotype) is determined by two means: (1) the physical characteristics of the extracellular environment, for example biochemical and biomechanical factors which initiate unique signaling pathways, thereby producing site-specific differentials in cell phenotype, and (2) vascular-bed-specific changes in DNA and histone proteins, which may result in epigenetic changes, and are believed caused by signals from the extracellular matrix [152]. It is well recognized that endothelial cells play a crucial role in most human pathologies, either as a major cause or being impacted by the results [152]. It is also well known that tumors critically depend upon blood vessel morphology for access to adequate supplies of oxygen and nutrients for growth [161], and that tumor endothelial cells (TECs) are phenotypically abnormal and intimately involved in overall tumor physiology, thereby making TECs a potential for therapeutic targeting [152]. Interfering with tumor vessel formation has been proposed as a therapeutic pathway and can be accomplished through one of two methods: (1) blocking tumor-derived angiogenic signals or surface receptors on the endothelium of new blood vessels, and (2) vascular targeting of existing vasculature, via delivery of a suitably toxic agent which would interact with the tumor endothelium. This agent could be a cytotoxic drug or β-emitter conjugated and transported by a carrier such as an mAb [162–164].

The endothelium layer is but one example of many biological barriers or membranes which must be navigated via mass transport with consistency if targeted tumor therapeutics, and associated-agents including: cytotoxins, drugs, nanomaterials, or other biologically targeted molecules, are to be effective in therapeutic applications [76]. Both biologically targeted molecules and nanoparticles encounter similar complexity in arriving at intended treatment destinations. It is well recognized that only one in 1,000–100,000 molecules injected actually arrive at the desired site resulting in a variety unintended systemic consequences [165, 166]. For example, it has been demonstrated that the mAb, trastuzumab causes cardiactoxicity [167]. Similarly, nanoparticles which use mAbs as a carrier also encounter heightened difficulties with mass transport through biological barriers [76]. In an attempt to circumvent this issue, nanoparticle or nanodrug technology was improved upon and now permits a far higher therapeutic index being achieved in treatment [168–172]. One approach taken utilizes liposomal encapsulations of doxorubin, and in a second application, an albumin conjugate was formed with Cremaphor®-free taxanes, also known as a ‘chaperoning’ technology to improve mass transport dynamics into tumors, and which received FDA approval [173–176]. Such successes have led to the development of a $5.4 billion annual market using nanoparticles in many cancer therapeutic applications, including SCCHN and provide a pathway for continued research and development into the future [177].

29.7.3 Nanomaterials

As a result of these advancements a variety of nanomaterials are now under investigation and assessment for safety, biocompatibility, and efficacy for feasible use with mAbs or antibody complexes, these include: (1) gold nanoparticles, (2) copolymer membranes, (3) carbon nanotubes, and (4) detonation nanodiamonds (NDs) [171, 178–181]. The functionality and performance criteria for NDs is also typical for most other nanomaterials: (1) must be biocompatible, (2) cells maintain morphology and integrity when exposed to nanomaterials, (3) NDs in particular have high surface area ratios permitting high loading capacities, (4) highly functional surface areas enhancing conjugation and absorption of desired molecules, (5) evidence suggesting high retention of therapeutic functionality for ND-therapy conjugates both *in vitro* and *in vivo*, and (6) tests results infer drug function remains after ND absorption and release [182–193].

29.8 Future Directions in Cancer Stem Cells (CSC)

29.8.1 Directed Therapeutics for SCCHN Cancers

Angiogenic or neoplastic SCCHN tumors are remarkably heterogeneous, and how they become so has been a topic of intense research, debate, discussion, and at times, controversy [194–196]. There have been two primary theories embraced in an attempt to explain the high level of heterogeneity found in SCCHN tumors. The first describes a step by step evolution of numerous cellular and molecular pathways, but does not adequately address the long known existence of cellular ‘sub populations’ or ‘side populations’ found in solid tumors and the associated biological behavioral characteristics those ‘side populations’ exhibit, including metastatic growth [197–199]. The second embraces an increasing body of work which suggests the ‘sub population’ hypothesis as more accurate, and therefore supports the presence of cancer stem cells (CSCs) [200–205]. Despite the fact that CSCs have not yet been definitively identified within SCCHN tumors, this ‘side population’/’sub population’ hypothesis is providing vision for future investigation and development toward future potential therapies [29]. Numerous studies are being conducted in effort to provide further clarification of underlying CSCs processes and mechanisms. Representative of this research is a critically important work regarding solid tumor CSCs conducted in 2003 involving the identification of breast cancer CSCs and associated biomarkers [206]. This effort was rapidly followed by other work which identified CSCs in a variety of cancer types including brain, prostate, lung, colon, pancreas, liver, melanoma, and skin [207–209].

CSCs have been defined as; “a small subset of cancer cells that constitute a pool of self-sustaining cells with the exclusive ability to maintain the tumor” [29], and are believed to be derived through one of two genetic mechanisms: (1) when normal stem cell genetic material mutates producing angioplastic cells, or (2) from already

differentiated tumor cells which undergo genetic change or mutation, thereby producing dedifferentiated cells and assuming CSCs-based qualities [29]. CSCs display three key behavioral criteria: (1) differentiation, providing heterogeneity to subsequent cell progeny, (2) maintaining an intact stem cell subset for growth and self-renewal, and (3) homeostatic control between differentiation and self-renewal based upon environment and the genetic profile of every organ tissue, thereby ensuring tissue specificity within CSCs [29]. Collectively, these significant insights are suggesting pathways for CSCs involvement in supporting tumor initiation, and aggressive tumor behavior such as chemoresistance and metastasis. These findings are also identifying potentially predictive and diagnostic applications for further investigation, and development for of new tumor therapeutic drugs. Examples of those areas under exploration include: (1) targeting of upregulated ATP-binding cassette (ABC) drug transporters, molecules which prevent damage to cancer cells by cytotoxic drugs, (2) identification of overexpressed CSC-specific biomarker signaling pathways; Nanog/Oct-4/CD133, ABCG2, CD44s, CD44v6, and ALDH1 which may lead to development of drugs to inhibit these pathways, (3) identification of chemoresistant genes; *ABCB1, ABCG2, CYP2C8*, and *TERT* all linked to the upregulation of the biomarker CD44' which appears to be implicated in oral cancers, and (4) the overexpression of integrin β1which may interfere with cellular differentiation and apoptosis, thereby allowing the CSC compartment to grow, resulting in support of tumor growth and metastasis [210–212]. Further work has also been reported on the Wnt/β-catenin signaling pathway which has been identified as a potentially significant target for the eradication of CSCs in lymph node metastatic SCCHN [213]. The Wnt/β-catenin signaling pathway is recognized to mediate stem cell renewal [213]. This effort verified that Wnt/β-catenin is highly upregulated in side populations, and therefore there may well be a relationship between Wnt/β-catenin and side population cell type [213]. These findings strongly suggest this signal pathway justifies further investigation for development of a drug to block the signaling pathway.

There is increasing evidence and therefore acceptance of the CSCs theory as originating from 'side or subpopulations' of solid tumor cells and their vital role in aggressive tumor behavior exemplified by: self-propagation, angiogenesis, differentiation into solid tumors, thereby creating tumor growth and metastasis. Given the importance of these characteristics CSCs have become a highly attractive area for research and development of potential therapies which specifically target, and eliminate CSCs. This hopefully would create new less toxic immunotherapeutic drugs, with more effective control over the elimination of recurrent and metastatic forms of cancers, including SCCHN and provide significantly improved survival rates [24].

29.9 Conclusion

The human immune system is a remarkable, adaptive, and at times, powerful biological system which has allowed us to survive and thrive for many tens of thousands of years. However, the many diseases of cancer, with all of its complexities

and underlying myriad causations are particularly difficult for the human immune response systems to address therapeutically, and SCCHN cancers are no exception. SCCHN tumors are in fact, cancers which still have among the poorest survival rates. That said, the past 100 years have brought remarkable scientific advancements toward the understanding of underlying causes. Further, there has been substantial improvement of immunotherapeutic treatments and the development of an entire mAb biopharmaceutical industry segment with 10 new drugs directed at the treatment of cancers. These drugs continue to evolve and become more sophisticated, safer, less toxic, and provide better efficacy. Most importantly, therapies are becoming uniquely targeted and tumor antigen-specific as the underlying science, immune system response behavior, and interdependent immunotherapeutic and biomolecular mechanisms become further understood. These accomplishments present an optimistic future for improved immunotherapeutic treatments and better survival rates for SCCHN cancer patients.

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Chapter 30
Role of Mitochondria in Head and Neck Cancer

Humberto De Vitto and Antonio Galina

Contents

Abstract It is known that cancer cells have a different metabolic profile when compared to normal cells. Generally, increased aerobic glycolysis, glutaminolysis (mitochondrial activity from glutamine catabolism), lactate production, production of reactive oxygen species (ROS), and frequent mitochondrial DNA (mtDNA) mutations, are all hallmarks of cancer. In addition, cancer cells need a proper microenvironment for them to grow and metastasize. In this regard, a series of recent

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studies have elegantly shown that the ROS and reactive nitrogen species (RNS) may provide the necessary stimulus by driving DNA damage, inflammation, and cancer metabolism in the tumor microenvironment. The essential roles of mitochondria in energy metabolism, generation of ROS, initiation of apoptosis, and other aspects of tumor biology have implicated the importance of mitochondrial function in the neoplastic process. In this chapter, we will focus on the metabolism of head and neck squamous cell carcinoma (HNSCC), trying to debate the role of mitochondria in the process of malignant cell transformation. The text will be divided in three parts. First, will be an introduction to mitochondrial biogenesis and bioenergetics. Then we will address the reaction involved in the production and removal of reactive oxygen and reactive of nitrogen species. Finally, we will cover how mitochondria can be considered a new candidate to target and treat cancer, including HNSCC therapeutically.

Keywords Head and neck squamous cell carcinoma (HNSCC) • Mitochondria • Reactive oxygen species (ROS) • Reactive nitrogen species (RNS)

Abbreviations

ADP	Adenosine diphosphate
APE	Apurinic/apyrimidinic endonuclease
ATP	Adenosine-5′-triphosphate
a-TOS	α-tocopheryl succinate
Chks	Checkpoint kinases
CO_2	Carbon Dioxide
DCA	Dichloroacetate
DETA-NONOate	Nitric oxide donor
DNA	Deoxynucleic acid
D-loop	Displacement loop
mtDNA	mitochondrial Deoxynucleic acid
EFQO	Flavoprotein-ubiquinone Oxidoreductase
EGFR	Epidermal Growth Factor Receptor
ERL	Erlotinib
ETS	Electrons Transfer System
ETSbs	Electrons Transfer System blockers
$FADH_2$	Flavin adenine dinucleotide
FDG-PET	Fluorescent deoxy-Glucose Positron Emission Tomography
GSTpi	Glutathione S-transferase
H^+	ions Hydrogen
H_2O_2	Hydrogen Peroxide
HIF-1α	Hypoxia Inducible Factor- α
HNSCC	Head and neck squamous cell carcinoma

HPV	Human papilloma virus
LDH	Lactate dehydrogenase
LOH	Loss of Heterozygosity
NADH	Reduced Nicotinamide adenine dinucleotide
NCI	National Cancer Institute
NFkB	Necrosis Factor kβ
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
NOX	NADPH Oxidase
O_2	Oxygen
$O2^{\bullet-}$	Superoxide anion
$ONOO^-$	Peroxynitrite
OXPHOS	Oxidative phosphorylation
PARP	Poly ADP Ribose Polymerase
PDH	Pyruvate Dehydrogenase
PDK	Pyruvate Dehydrogenase Kinase
Pi	Inorganic phosphate
pmf	protonmotive force in millivolts
Q	Ubiquinone
QH_2	Ubiquinol
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
UV	Ultra violet
VDAC	Voltage-Dependent Anion Channels
VEGF	Vascular Endothelial Growth Factor
STAT3	Signal Transducer and Activator of Transcription 3
ΔpH	Chemical proton gradient
ΔΨm	Mitochondrial membrane potential

30.1 Introduction

Head and neck cancer can be defined as a cancer which arises in the head or neck region such as, in the nasal cavity, sinuses, lips, mouth, salivary glands, throat, or larynx, according to The National Institute of Cancer. Approximately, 90% of the head and neck cancers are classified as head and neck squamous cell carcinoma (HNSCC). The HNSCC originates in the cells that form the lining of the mouth, nose, throat, ear, or the surface layer covering the tongue. Head and neck cancer often spreads to the lymph nodes of the neck, and this is often the first sign of the disease at the time of diagnosis. Head and neck cancer is strongly associated with certain environmental and lifestyle risk factors, including tobacco smoking, alcohol consumption, UV light, and certain strains of viruses, such as human papillomavirus (HPV) [1]. At least 75% of head and neck cancers are caused by tobacco and alcohol use [2]. Since these risk factors generate reactive oxygen species (ROS) and reactive

nitrogen species (RNS) chronically, understanding whether mitochondria, act as a ROS production center and how they may play a pivotal role in the head and neck cancer progression would be important. This could serve as a unique basis to develop new therapeutic approaches to treat head and neck cancer.

The HNSCC is the fifth leading cause of cancer related death with an annual incidence of 500,000 cases worldwide. In the United States, 40,000 new cases of HNSCC are diagnosed annually [3]. The 5 year survival rate is among the lowest of all cancers due to their poor survival outcome. Over the past 20 years, despite multidisciplinary treatment approaches, including preoperative or postoperative chemotherapy and/or radiotherapy with reconstructive surgery, there has been modest improvement in clinical outcomes; therefore, it represents a significant public health problem. The development of suitable methods for early detection and disease evaluation which employ molecular biology methods might play an important role to define molecular biomarkers which provide new information regarding prognosis, treatment selection, surveillance for recurrence, and second primary tumor development. Some potential candidates for biomarkers have been extensively studied in HNSCC, including human papilloma virus integration in oropharyngeal squamous cell cancer, the epidermal growth factor receptor (EGFR), and inactivation of tumor suppressor genes by loss of heterozygosity (LOH) [4].

However, to understanding the entire carcinogenic process, first, it is mandatory to introduce some concepts about how cellular energy and redox metabolism are regulated, and how they contribute to malignant cell transformation. Life depends on a set of biological processes that require energy. In fact, every biochemical reaction within living cells involves the transduction of some degree of free energy that is ultimately derived from the oxidation of dietary nutrients. In order to conserve this free energy, it is made biologically available as phosphoanhydride high energy bonds (very sensitive to water; the solvent of ATP; see [5]). ATP is continuously being synthesized by two major pathways either glycolysis or oxidative phosphorylation, and hydrolyzed by many pathways and enzymes that utilized ATP as substrate (ATP-turnover). In this way, our cells drive energy dependent reactions, such as building up ion gradients through membranes, muscle contraction, protein synthesis, and DNA replication, etc. [6].

It is known that the generation of ATP can occur by several association energies of ADP + Pi to energy transducing enzymes in biological systems involving hydrophobic-hydrophilic transition processes, but the extent of this energy conversion and the kind of energy transductions in cellular systems, are not yet completely elucidated [5]. The best known processes of ATP formation are the phosphocreatine-ATP shuttle, glycolysis and oxidative phosphorylation (OXPHOS) [7, 8]. OXPHOS is the process which couples the electron transport system (ETS) from NADH and $FADH_2$ reducing equivalents to oxygen (driven by the redox potential levels) to the ATP synthesis from ADP and Pi through proton gradients formed by ETS through the inner mitochondrial membrane. The ETS contains an array of redox systems that are completely dependent on the availability of oxygen, and this takes place in mitochondria. However, the utilization of oxygen by cells

can partially be reduced to oxygen intermediates, called reactive oxygen species (ROS), which play key roles in cellular redox homeostasis [9]. The current hypothesis that oncogenic transformation might be induced by ROS, suggests that mitochondria play an important role in the tumorigenesis and cell transformation [10].

Mitochondria are organelles which combine hydrogen and oxygen to generate water and the major cellular source of energy currency, ATP [11]. As toxic by-products of OXPHOS activity, mitochondria generate ROS. These have been extensively characterized in the literature to signal tumor growth [12–14]. Also, mitochondria are unique organelles which have their own DNA (mtDNA), inherited maternally, and replicated and transcribed semiautonomously; therefore mtDNA lineages are clonal [15, 16]. As Otto Warburg suggested more than 70 years ago, cancer cells have an impaired mitochondrial respiratory function, and the role of aberrant mitochondrial function in tumor development has been supported [17]. More recently, studies demonstrating multiple cancer-related mitochondrial DNA mutations [18, 19], as well the participation of the mitochondria role in apoptosis supports this hypothesis [20]. Interestingly, tobacco smoking (a potent source of ROS and RNS) is strongly associated with head neck cancer, strengthening the idea that mitochondria play a role in head neck cancer progression. Particularly, the aerodigestive mucosa is exposed to multiple carcinogenic agents arising from tobacco smoke, as well as from environmental, and dietary factors. Once these carcinogens are not fully metabolized to nonhazardous forms, these carcinogens lead to DNA damage, (both genomic and mitochondrial) and contribute to induce squamous cell carcinoma. Cigarette smoking can cause an increase in ROS such as hydrogen peroxide (H_2O_2) and superoxide (O_2^-). In addition, many tobacco smoke metabolic products contain DNA alkylating agents that can accumulate preferentially in the mitochondria and lead to DNA damage [21]. The mtDNA encodes 13 polypeptides, seven (ND1, 2, 3, 4L, 4, 5, and 6) of the 45 polypeptides of Complex I, one (cytochrome b, cytb) of the 11 polypeptides of Complex III, three (COI, II, III) of the 13 polypeptides of Complex IV, and two (ATP6, ATP8) of the approximately 17 polypeptides of Complex V. mtDNA also encodes 12S and 16S rRNA, as well as 22 transfer RNAs. All the 13 mtDNA genes that encode proteins are central to the mitochondrial energy transduction process of OXPHOS. These 13 proteins function as the central electron and proton nanowires for energy of the H^+ pump. Electron flow through Complexes I, III, and IV is accompanied by proton flow from the matrix to the intermembrane space, producing both a chemical gradient and an electrical gradient. The inner mitochondrial membrane is impermeable to protons; protons can reenter the matrix only through proton-specific channels (Fo). The proton-motive force that drives protons back into the matrix provides the energy for ATP synthesis, catalyzed by the F_1 complex associated with Fo, so called complex V.

This vectorial passage of protons through the inner mitochondrial membrane at the Fo portion, reverses the catalytic cycle of the enzyme in the direction of ATP synthesis. Furthermore, the mtDNA has a small region, 1.1 Kb in size, called Displacement loop (D-loop) that controls both mitochondrial replication and

transcription [22]. Studying the role of mtDNA in cellular functions could lead to a better understanding of the cellular oxidative/reductive (redox) signaling. These processes have been linked to numerous mitochondria metabolism defects, including (1) age-related disorders [23], (2) degenerative diseases [16], and (3) various forms of cancer [18, 24, 25]. In fact, several studies have reported multiple mtDNA somatic mutation in primary HNSCC patient samples [26, 27].

A body of evidence implicates mitochondria as a participant in the oncogenic process, although the use of mitochondria as a target to treat cancer is still in the early phase of clinical testing. Recently, some groups have shown a general property of oncogene transformed cells with dysfunctional mitochondria and the associated increased ROS production that is a consequence of this state. These dysfunctional mitochondria exhibit a lower threshold of sensitivity to ROS-induced apoptosis as a means for eliminating them. Increasingly, and in line with the evidence already presented, it is highly likely for cancer cells (relative to normal cells) to have altered mitochondrial ETS that are more efficient in ROS (O_2^- and H_2O_2) production inducing a state of chronic metabolic oxidative stress. Therefore, it follows that therapies that are able to specifically target the respiratory chain to further elevate ROS production in cancer cells should selectively push these cells into apoptosis. Excellent examples of such agents are the mitochondrially targeted anti-cancer drugs (mitocans) which have been recently reviewed [28–30].

In line with this proposal is the first intracellular enzyme of glucose metabolism, the mitochondrially bound hexokinase (mt-HK). mt-HK is bound to VDAC impairing the binding of pro-apoptotic proteins Bax, Bid, Bcl 2, and BclxL, causing the cancer cells to stay in an anti-apoptotic condition [31] which is typical for many tumors. Besides these observations, it was demonstrated by Galina's group that the mt-HK activities promote an ADP recycling mechanism at the mitochondrial outer-membrane surface. This leads to an activation of respiration by decreasing $\Delta\Psi_m$ in mitochondria that were isolated from both mammals and plants [32–35]. The slight decrease in the $\Delta\Psi_m$ reduces dramatically the escape of electrons from ETS to form ROS [36]. Thus, despite the fact that mt-HK catalyses phosphate transfer reactions it apparently is not involved in electron transfer directly at the level of ETS. mt-HK activity impacts greatly the generation rate of mitochondrial ROS. It is attractive to hypothesize that in tumors cells, besides the ROS generation by tumor mitochondria as a result of the depression of respiration by ETS dysfunctions, that mt-HK activity may additionally modulate negatively the tumor mitochondria ROS generation. It has been recently demonstrated [37, 38] that the alkylating agent 3-bromopyruvate, which has been claimed to be an mt-HK specific inhibitor, is in fact a strong inhibitor of the glycolytic enzymes glyceraldehydes dehydrogenase (GAPDH) and 3-phosphoglycerate kinase (3-PGK); and mitochondrial dehydrogenase, pyruvate, glutamate and succinate dehydrogenases. Interestingly, the mt-HK activity is not inhibited by the 3-bromopyruvate, maintaining mitochondrial respiration and cellular redox balance. The specific targets of the alkyl-inactivation are the mitochondrial dehydrogenases enzymes, as above mentioned.

30.2 The Eukaryotic Cell: Two Organisms, One for Replication and One for Energy Transduction

It is believed that genetic alterations and multiple environmental factors are the causes of metabolic diseases, such as degenerative diseases, cancer, and aging [23]. Extensive effort has been applied using genomic methods to indentify genes responsible for these common diseases. All of these efforts however, have found only a slight contribution to diseases risk, and all of the nuclear DNA variants explain less than 20% of the all variances put together [39]. Cleary, the low statistical correlation between genome variations and common diseases reflects that the environmental factors have contributed in a wide-scale process to the predisposition of common diseases; however the nature of these environmental factors remains unexplained [40]. For example, HNSCC and aerodigestive cancers in general are epidermal growth factor receptor (EGFR) positive. Although EGFR-driven molecular pathway aberrations are altered in 90% of HNSCC, they are not considered the dominant genetic alteration in the molecular pathogenesis of HNSCC [4].

To better understanding the association between common diseases and environmental factors, it is a priority to define what we mean by *environmental*. All organisms are restricted to maintain, growth and reproduction by the quantity of the free energy available. When energy (calories), is limited, organisms reduce growth and reproduction to conserve energy until energy resources become available again. On the other hand, when abundant energy is available, organisms grow and reproduce robustly, permitting the organism`s genetic information to pass to the next generation, thus sustaining the species information heritage. In fact, the demand for energy availability drives the accumulation of genetic information and creates biological complexity that can culminate in cancer [41]. Urgently, it is necessary understand how cellular energy and redox metabolism are regulated and how they contribute to malignant cell transformation.

Biochemically, the flux of energy might be represented by the flux of the carbon which an organism acquires by ingesting carbohydrates, fats and amino acids. These resources of energy might be able to transfer H^+ and electrons (e^-) by universal electron carriers (NADH and $FADH_2$) in different metabolic pathways (i.e. glycolysis, Krebs cycle, β-oxidation), and push the energy onto the OXPHOS. The OXPHOS process via multiple steps reduces oxygen to water and synthesizes ATP molecules. The equation for ATP synthesis is sometimes written [42].

$$\mathrm{ADP} + \mathrm{Pi} + n\mathrm{H_p}^+ \rightarrow \mathrm{ATP} + \mathrm{H_2O} + n\mathrm{H_p}^+$$

The ATP molecule is the main cellular source of energy and therefore, mitochondrial dysfunctions can be implicated in a cellular imbalance of ATP production. As a consequence, this aberrant energy demand observed in cancer could drive the modification of cellular gene expression profiles, genetic composition, and others metabolic alterations. Interestingly, the symbiotic contribution between mitochondria and nuclear DNA is responsible by the maintenance of the information encom-

passed in two broad categories: information for structure and information for energy production. Therefore, any common diseases, such as cancer, need to be understood between the interface in the mitochondrial function and epigenetic origin.

In the next sessions, a detailed description of the mitochondrial biogenesis and bioenergetics will be addressed. We will also mentioned the main mechanisms of production and removal of ROS and RNS. In addition, a new therapeutic candidate which targets mitochondria will be discussed and now it is being applied to the treatment of head and neck cancer.

30.3 Mitochondrial Biogenesis and Bioenergetics

30.3.1 The Mitochondrial Energetic: Oxidative Phosphorylation

The idea that the mitochondria are the site of OXPHOS in eukaryotes cells was published in 1948. This discovery marked the beginning of the study of mitochondria as the biological component that unities many diseases. As shown in the Fig. 30.1, structurally, the mitochondria are organelles with two very distinct membranes: an outer membrane which is readily permeable to small molecules(*M*r 5,000) and ions, and an inner membrane which is protein-rich and highly selective to most small molecules, ions, and protons (H^+). As a consequence of these two membranes, mitochondria are divided in two different compartments: (1) the intermembrane space and, (2) the mitochondrial matrix. These compartments are not only structurally, but also functionally distinct. The Krebs cycle enzymes are located within the matrix, whereas the proteins that comprise the electron transport system (ETS) are found at the inner mitochondrial membrane. In fact, the redox reactions mediated by different compounds from ubiquinone to iron/copper-sulphur clusters, cytochromes, and finally oxygen reduction to water (respiration), take place at the inner mitochondrial membrane. The inter membrane space contain enzymes involved in the control of adenine nucleotide pools involved in the mitochondrial energy charge buffer system which balances the adenine nucleotide pools of [AMP], [ADP] and, [ATP] in mitochondria. These reactions are catalyzed by adenylate kinase, nucleoside diphospho kinase, and creatine kinase. The bioenergetic function of these enzymes are not completely understood, but it has been demonstrated to play a role in the [NTP]/[NMP + NDP + NTP], [PCr]/[Cr][Pi] ratios. This has been demonstrated to control the permeability of transition pore formation (PTP- a process that involves oxidation of -SH groups by ROS and RNS, aggregation of integral proteins located at the inner membrane, and fusion of inner and outer mitochondrial membranes). The PTP opening represents a crucial process in both apoptotic and non-apoptotic cell death because the PTP leads to loss of $\Delta\Psi_m$ and pmf; and releases cytochrome c, confined exclusively to inter mitochondrial membrane space to the cytoplasm which in turn actives caspases of the cell death pathway. This biochemical anatomy of a mitochondria provided

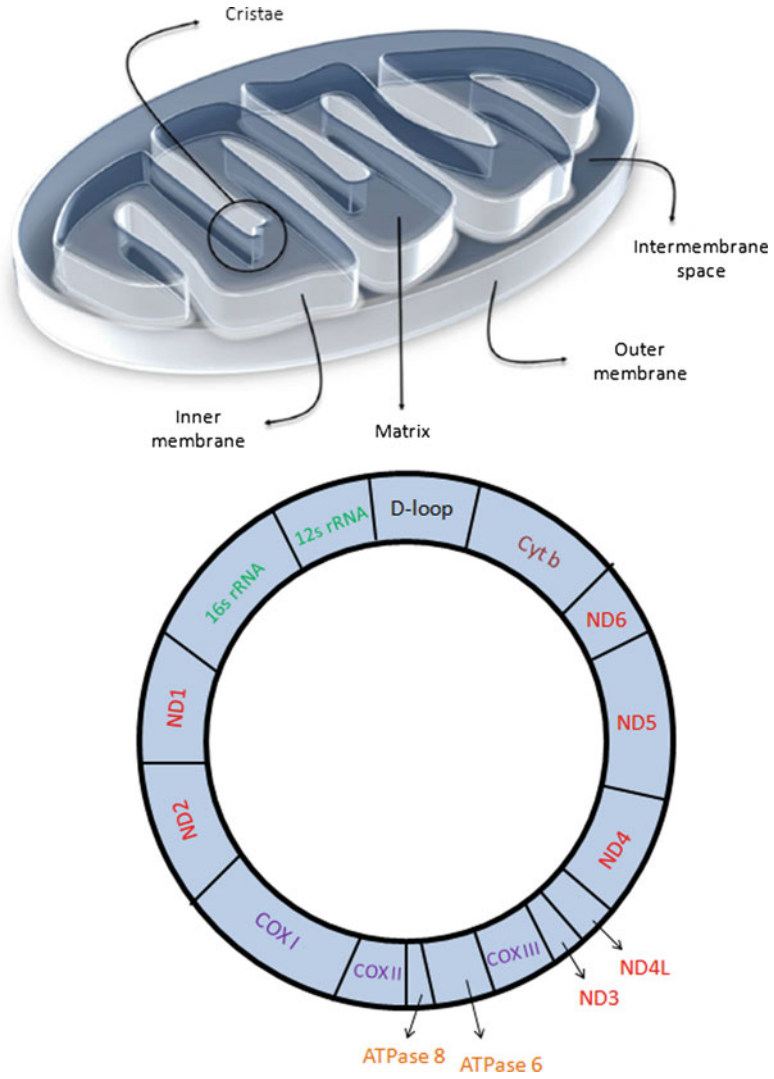

Fig. 30.1 Schematic representations of the mitochondrial, their different compartments and the mitochondrial genome

insight for the chemiosmotic theory introduced by Peter Mitchell in 1961. The theory was that transmembrane differences in proton concentration are the reservoir for the energy extracted from biological oxidation reactions which then generate energy by the ATP production [43]. Mitochondria are also the site of numerous metabolic pathways such as lipid metabolism, the urea cycle, and heme biosynthesis. Furthermore, the mitochondria have their own DNA, inherited maternally, that encodes some genes of the OXPHOS process (Fig. 30.1) [44].

The OXPHOS process is defined by the energy conversion by the cellular aerobic metabolism. The ETS is essentially composed of proteins that contain an array of redox centers that are organized in complexes commonly listed from I to IV. The OXPHOS process begins with the entry of electrons from the catabolic pathways into the ETS, and involves the reduction of O_2 to H_2O, generating ATP as a final product. There are two main universal acceptors that donate protons (H^+ and electrons) called NADH and $FADH_2$ (Nicotinamide nucleotide–linked dehydrogenases and Flavoproteins). Complex I (NADH:ubiquinone oxidoreductase) for example, is a large enzyme composed of 45 different polypeptide chains, including an FMN-containing flavoprotein, and at least six ironsulfur centers. Complex I oxidizes the substrate NADH originating from the Krebs cycle, through flavoprotein-ubiquinone oxidoreductase (ETF-QO) to the ubiquinone. Complex II (succinate dehydrogenase) is composed of five prosthetic groups of two types and four different protein subunits, which oxidize succinate, also originating from Krebs cycle, to the ubiquinone (Q). The electrons that reach the complex III (cytochrome *bc*1 complex or ubiquinone: cytochrome *c* oxidoreductase) are then channeled, via ubiquinol (QH_2) to cytochrome c. In the last step of the respiratory chain, Complex IV (cytochrome oxidase) carries electrons from cytochrome *c* to molecular oxygen, reducing it to H_2O. Interestingly, the free energy released during the electron transport by the ETS complexes is linked to the transport of protons across the inner mitochondrial membrane. Due to its impermeable nature to protons, an electrochemical proton gradient is established [43]. This electrochemical proton gradient has two components; one chemical (ΔpH) and the other electrical ($\Delta\Psi_m$) in nature, which together represent the protonmotive force (*pmf*). Finally, the free energy accumulated in the form of *pmf* can be converted to chemical energy by means of the complex molecular motor activity of the F_1F_o ATP synthase, which allows the return of protons back to the mitochondrial matrix coupled to ATP production (Fig. 30.2) [45].

30.3.2 Cancer Metabolic Alterations: From Warburg Effect to Reverse Warburg Effect

In an environment with a limited supply of oxygen, glycolytic pyruvate is reduced to lactate in the cytoplasm by lactate dehydrogenase (LDH) with the purpose of regenerating the oxidized form of NAD + for glycolysis to proceed (Pasteur Effect). Cells in a normoxic condition oxidize pyruvate to CO_2, in the mitochondria. First, by the activity of pyruvate dehydrogenase (PDH), followed by the activity of the Krebs cycle enzymes, and finally, by the mitochondrial activity which drives the electron flux into the enzymatic mitochondrial complexes. Thus, there is an electrochemical gradient formation that is able to generate energy, during ATP production.

Glucose generates enough energy for macromolecules biosynthesis which is required for cell proliferation. Glucose also participates in the pentose phosphate pathway, which generates ribose 5-Phosphate for nucleic acid synthesis and

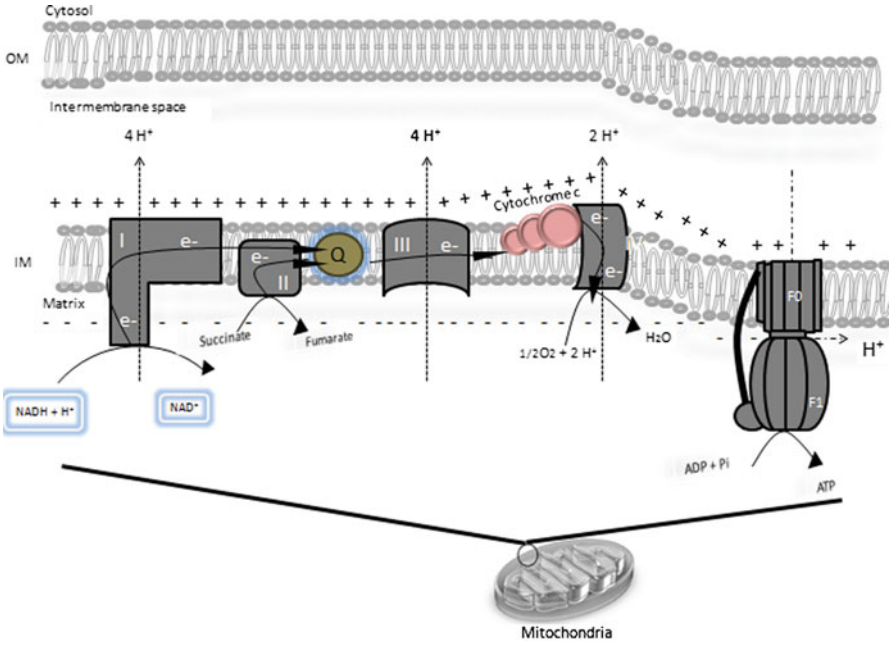

Fig. 30.2 Schematic representation of the electron flow into the electron transport system, and ATP synthesis. In the figure: *OM* outer membrane, *IM* inner membrane, *I* NADH dehydrogenase, *II* succinate dehydrogenase, *Q* ubiquinone, *III* ubiquinone:cytochrome *c* oxidoreductase, *IV* cytochrome c oxidase and e- electron

NADPH, an essential component in the scavenger process of ROS [46], (see Sect. 30.4.1). The Krebs cycle plays an important role in cellular metabolic regulation, generally in pathways for the catabolism and anabolism. The Krebs cycle intermediates, such as oxaloacetate and α-ketoglutarate, which produce aspartate and glutamate, respectively, are important building block molecules to make other components, such as purines and pyrimidines. Others studies have shown that citrate plays a role in fat and steroids production. Glutamine also plays a crucial role to generate oxaloacetate, which plays a key role in the carbon skeleton maintenance and cell proliferation (Fig. 30.3) [47].

As a universal signature of cancer, tumor cells that should be prone to use glucose as the main substrate to drive ATP production, even in normoxia, shift their metabolism from oxidative to fermentative. This is called the Warburg Effect. Otto Warburg described how cancer cells displayed a decreased respiration and increased in lactate production, suggesting that cancer cells were dependent on fermentative metabolism for ATP production [48]. One plausible explanation for the Warburg effect in cancer cells is that the OXPHOS machinery is impaired. Over the past 70 years, because of this Warburg Effect, cancer cell metabolism has and still remains, a puzzle. Other concepts about glucose metabolism in cancer cells have arisen, such as the reversible repressive effect of glucose over respiration, which is

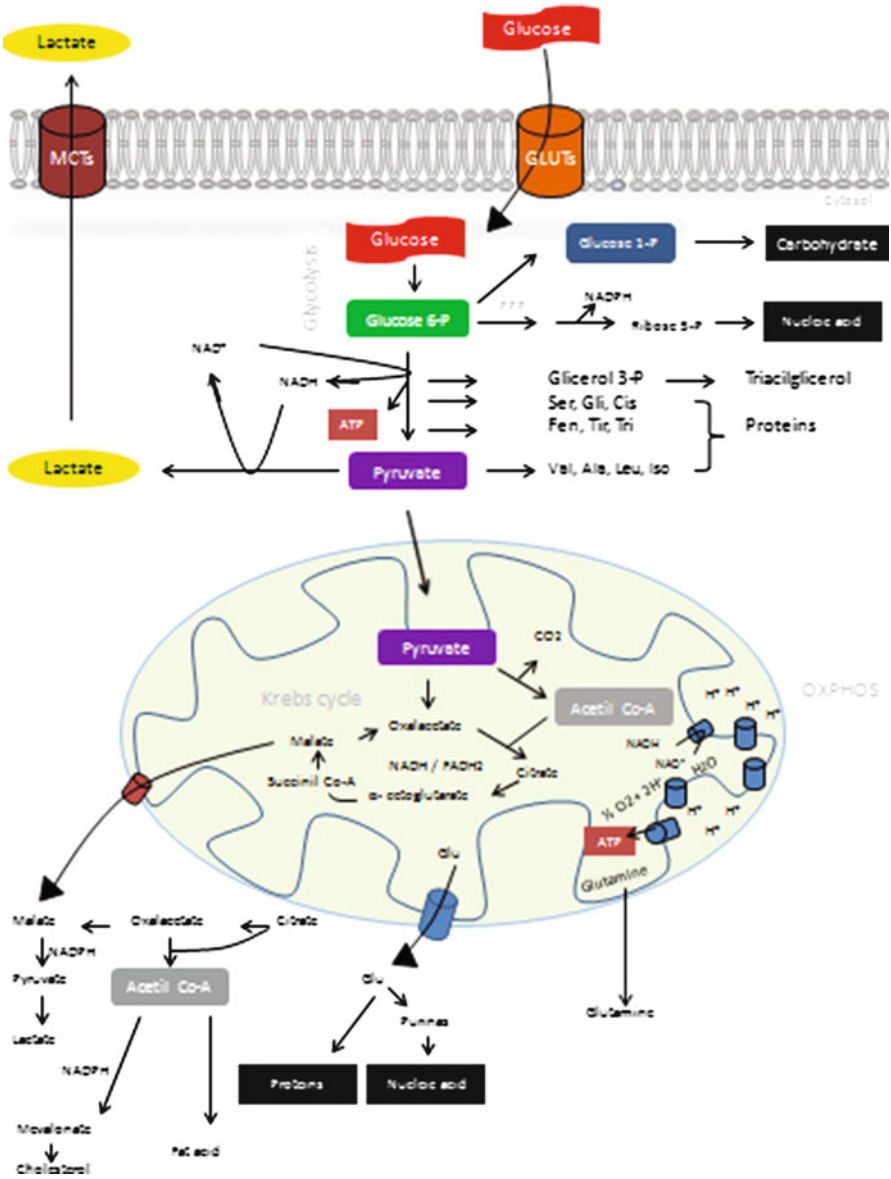

Fig. 30.3 The mainly biologic pathway of glucose metabolism. Glycolysis, Pentose Phosphate Pathway (PPP), Krebs cycle, OXPHOS, amino acid metabolism and glutamine metabolism

known as the "*Crabtree effect*" [49]. The *Crabtree effect* has the same metabolic signature as observed in the Warburg effect, although the shift from oxidative to fermentative metabolism is observed in a reversible fashion, even in normoxia, with functional oxidative phosphorylation machinery. Herein, the OXPHOS is rapidly and reversibly down-regulated by the repressive effect of glucose, whereas in the

Warburg effect, there is a long irreversible effect favoring fermentation due to the increased expression of proteins involved in glucose transport and metabolism.

An interesting point that should be addressed is the seemingly paradoxical role of mitochondria in cancer cells. The Warburg hypothesis says that all cancer cells derive most of their energy from fermentative metabolism [17]. However, recent studies have shown that there is additional dependence on oncogene-stimulated mitochondrial biogenesis for energy generation [50]. In fact, other studies have shown the importance of functional mitochondria in cancer cells. Accord to this hypothesis, the lactate could be an energetic substrate for tumor cells. This proposed lactate shuttle between tumor cells and stromal cells, could feed the tumor cells as the tumor cells utilize mitochondria to generate energy. As a consequence, tumor cells might signal for tumor clonal expansion process by inducing oxidative stress in adjacent tumor cells. It has been demonstrated that increases in nitric oxide from stromal fibroblasts could generate mitochondrial dysfunction by ROS production. This would induce the cells to undergo autophagy and mitophagy, due to increased aerobic glycolysis, and support lactate as a substrate to the cancer cells. This process has been described by Martinez-Outschoorn and co-workers as a reverse Warburg effect [51] when oxidative stress in cancer associated fibroblasts functions as a "metabolic" and "mutagenic" motor, driving epithelial cancer cell evolution (Fig. 30.4).

30.3.3 Somatic and Germline Mutations in Head & Neck Cancer

It is known that environmental and dietary factors such as tobacco smoking and alcohol are factors risk associated with the carcinogenesis progress in head and neck cancer. In fact, cancers have been associated with increased levels of ROS production such as H_2O_2 and O_2^-, which can be accumulated in the mitochondria and lead to DNA damage. Over the last 20 years, somatic mtDNA mutations have been reported in many primary human tumors [24, 52], including head and neck cancer. Fliss and colleagues in 2000, detected somatic mtDNA mutations in saliva of patients in head and neck cancer, suggesting a possible role as a biomarker in early diagnosis [53]. Ha and coworkers, have found an increase in somatic mtDNA mutations in the D-loop C-tract region in precancerous lesions in head and neck cancer [54]. Furthermore, an increased in the mtDNA copy number as a result of somatic mtDNA mutations was observed in pre-malignant and malignant head and neck lesions [55, 56].

Functionally, the first relevant work in human squamous cell cancer of the head and neck was performed by Zhou and colleagues. They sequenced the whole mitochondrial genome in 83 HNCSS samples in which, forty-one (49%) of the tumors contained mtDNA mutations. Also they analyzed the p53 status and showed that mtDNA mutations correlated positively with p53 mutations. Finally, they cloned one somatic mtDNA mutation (NADH, subunit 2) based on a primary tumor mutation and associated mitochondrial mutagenic event with increased anchorage-dependent and -independent growth. This was accompanied by increased ROS production and

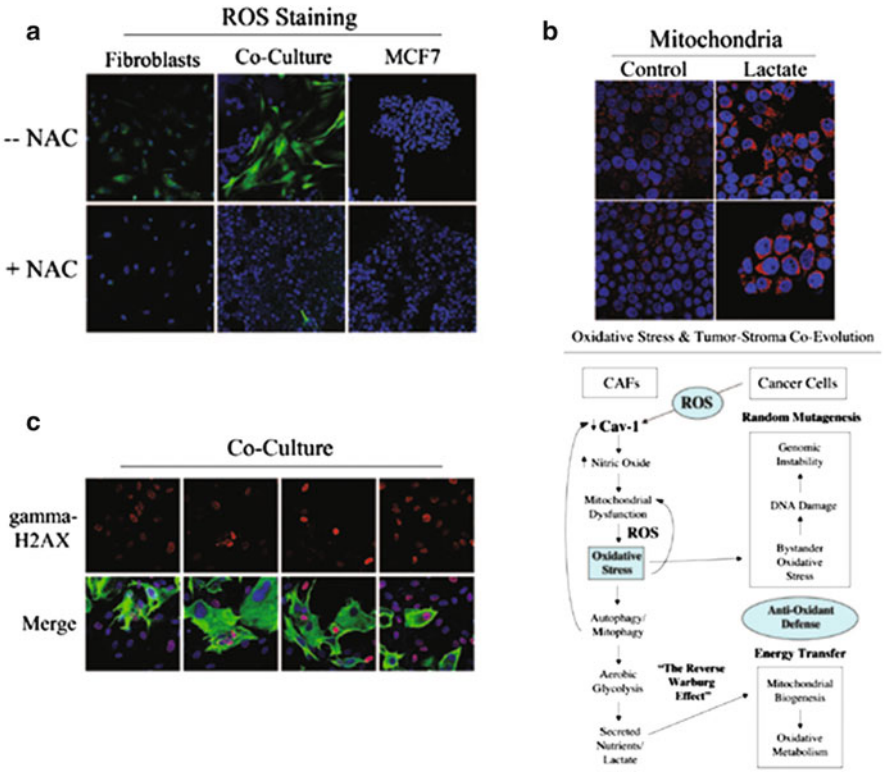

Fig. 30.4 Oxidative stress in cancer associated fibroblasts functions as a "metabolic" and "mutagenic" motor, driving epithelial cancer cell evolution. ROS are elevated in fibroblasts co-cultured with MCF7 cells. (**a**) CM-H2DCFDA staining (*green*) was performed on hTERT-fibroblasts co-cultured with MCF7 cells. Cells were counterstained with Hoechst nuclear stain (*blue*). Samples were then immediately imaged using a 488 nm excitation wavelength. Magnification, 20×. (**b**) Fibroblast-MCF7 co-cultures show increased DNA damage. To detect DNA double strand breaks, co-cultures of hTERT-fibroblasts and MCF7 cells and corresponding homotypic cultures were immunostained with anti-gamma- H2AX (*red*) and anti-K8/18 (*green,* detecting tumor epithelial cells) antibodies. DAPI was used to stain nuclei (*blue*). Magnification, 40×. (**c**) Lactate treatment promotes mitochondrial biogenesis in MCF7 cells. Homotypic cultures of MCF7 cells were treated with 10 mM L-lactate or vehicle alone (H_2O) for 48 h. Cells were fixed and immunostained with an anti-intact mitochondrial membrane antibody (*red*). DAPI was used to stain nuclei (*blue*). Magnification, 63× (Figure modified of [51] *Cell Cycle*)

an aerobic glycolytic metabolic phenotype with hypoxia-inducible factor HIF-1 expression [26]. Interestingly, a body of evidence suggests that more than 20% of HNSCC have D-loop mutations. In this context, the D-loop region may be an interesting molecular marker in the evaluation of the tumorigenic potential of head and neck lesions in individuals at high risk of this cancer. Ha and coworkers have shown this to be an early event in head and neck carcinogenesis. Their reported frequency was 22% in the earliest head and neck premalignant lesions, and increased with the degree

of dysplasia to reach 50% in lesions of severe dysplasia, and 61% in carcinomas in situ. [54]. These data were observed by Lievre and coworkers and suggested that D-loop mutations should be considered as a cancer biomarker that may be useful for the early detection of HNSCC in individuals at risk of this cancer [57].

More recently, one study was performed to understand the nature and timing of mtDNA mutation in histological negative margins, of tumors in HNSCC patients who developed local recurrence during the follow-up. The mitochondrial genome was sequenced in matched normal lymphocytes, histological normal margins, and tumors of recurrent HNSCC patients. Interestingly, mutations were detected in the tumors and were also detectable in the corresponding histological normal margin of the patients [58]. This finding can be one explanation for what was reported as the so-called reverse Warburg effect [51], when oxidative stress in cancer associated fibroblasts functions as a "metabolic" and "mutagenic" motor, driving epithelial cancer cell evolution.

30.3.4 Mitochondrial Medicine: An Integrated Mitochondrial Model for the Etiology of Cancer and Chronic Disease

Is carcinogenesis a mitochondriopathy? What is the relationship between mitochondrial dysfunction and carcinogenesis? The impairment of mitochondrial function has been a subject of extensive debate until quite recently. For decades, mitochondria have been described as organelles that function to produce cellular energy. First, mitochondria function was described to production ATP through OXPHOS. Otto Warburg, 70 years ago, suggested alterations in respiratory activity in cancer cells, and ascribed the abnormal aerobic metabolism of cancer cells to an impaired bioenergetic function of mitochondria. Warburg`s proposal followed the principle of metabolic regulation established by Louis Pasteur. In this way, Warburg's hypothesis was passionately debated for many years and mostly abandoned or considered as irrelevant epiphenomenon of cell transformation [59, 60], until its recent rediscovery was mostly propitiated by the use of FDG-PET imaging in oncology [61, 62]. Recently a body of evidence, confirmed by molecular techniques, showed that these dynamic structures play a pivotal role in cell transformation. As example, genetic and metabolic aberrations in mitochondria have been shown to be the cause or contributing factors of pathogenesis in a broad range of human diseases, including cancer. In this regard, impaired pyruvate dehydrogenase activity has been shown in embryonic tissues [63]. The Krebs cycle has been shown to be partially truncated in tumor mitochondria and as a consequence, glutamine serves as an alternative carbon skeleton to fuel cancer cell [47]. Deficiencies in enzyme complexes of the respiratory chain and oxidative phosphorylation in cancer cells have also been described, including some other alterations such as mitochondria have less crista in cancer than in normal cells, and cancer cells have a diminished mitochondrial complement when compared to non-cancerous tissues. In addition, a vast array of mutations has been described in mitochondrial DNA in many different types of

human carcinomas [46]. All these findings suggests that mitochondria, whether functional or not, play a central role in malignant transformation. However, the bottleneck of the cancer can be attributed for the role that mitochondrial ROS plays to sustain tumor survival, apoptosis evasion, migration, invasion, and metastasis. Human tumor cells produce large amount of ROS that contribute to tumorigenesis [64]. ROS production in cancer cells could result from oncogene activation of NADPH oxidases and/or the consequence of hypoxic insults in the mitochondrial respiratory chain that allows a direct electron transfer to molecular oxygen to generate the superoxide anion. Likewise, the physiological and/or pathological alterations of mitochondrial oxidative phosphorylation are also associated with high levels of ROS production. ROS in turn damages mitochondrial components and contribute to the deterioration of cellular functions. ROS also, sustain the pivotal oxidative stress mechanism that increased lactate production, increased acidosis, generated cumulative genetic mutations, up-regulates survival genes, and provides the glycolytic signature for cancer cells.

Therefore, ROS generation and removal mechanisms might be candidate targets to treat cancer. Scientists are exploring new mitochondrial drug approaches that are reflective of the redox profile of the tumors under treatment. ROS based treatment, would thus select combinations of pro-oxidant and antioxidants agents that would best counteract the anomalous oxidative stress generated. Raj and collaborators have been shown that cancer cells from different types of tumors, but not normal cells, were effectively killed by piperlongumine. In addition, the authors were able to demonstrate that the cytotoxic effect of piperlongumine was achieved through interference with the anti-oxidant systems of the tumor cells. Such an approach has the added advantage that inhibitors targeting anti-oxidant systems could also be prescribed in the preventive setting [65]. Attempts to make a metabolic model of reprogramming, in cancer, is still premature, because there are no data which fit a coherent mechanism. However, the understanding of the mitochondrial metabolic contribution could be the key to the etiology of cancer, and also to treat other chronic diseases.

30.4 ROS/RNS and Cancer

30.4.1 ROS/RNS Biology of Cancer: The Role of Hydrogen Peroxide and Nitric Oxide

ROS and RNS might be considered as toxic to the cells by direct or indirect effects on biomolecular targets. This cytotoxic effect is regarded as concentration dependent, and by duration of the stimulus. There are specific forms of ROS and RNS include hydrogen peroxide (H_2O_2), superoxide (O_2^-), nitric oxide (NO), and peroxynitrite ($ONOO^-$). In fact, the imbalance of ROS and RNS levels depends on the regulation between mechanisms that generate, as well as, remove them. When

ROS and RNS are present in a low concentration, they are signaling molecules that could coordinate metabolic and genetic process. As example, H_2O_2 could modulate multiples transcriptor factors, including p53, HIF-1, STAT3 and NF-kB. The general mechanism that H_2O_2 regulates transcription factors involves oxidation of cysteine residues and phosphatases, as a consequence, these signaling effectors drive cell proliferation. However, when ROS and RNS are at high levels, they damage organelles, particularly the mitochondria. Oxidative damage and the associated mitochondrial dysfunction may result in energy depletion, accumulation of cytotoxic mediators, cell death, and cellular clonal expansion. As reported by Jenkins and colleagues, NO has been shown to cause mutational events which may lead to cancer [66]. Also, NO has been described to induced tumor cell transformation to a more aggressive phenotype in HNSCC. The same results were shown in clinical samples [67].

Mitochondria are the main sources of ROS in a mammalian cell. ROS is generated by a small portion of oxygen that is partially reduced to H_2O by cytochrome *c* oxidase. Also, complexes I, II and III of ETS are sources of ROS. Furthermore, there are important alternatives sites of ROS generation, such as perioxisomes, the endoplasmic reticulum, and NADPH oxidize enzymes. The family of enzymes NADPH, called NOX is expressed in several types of cancer, including colon, prostate, ovarian, and thyroid. One recent study has shown an EGFR tyrosine kinase inhibitor, erlotinib (ERL) was mediated by induction of oxidative stress in HNSCC cells. ERL elicited cytotoxicity in vitro and in vivo while increasing a panel of oxidative stress parameters which were all reversible by the antioxidant N-acetyl cysteine. This work suggested that ERL-induced cytotoxicity is based on a specific mechanism of oxidative stress mediated by H_2O_2 production through NOX_4 signaling [68].

Therefore, understanding the role of ROS, which drives normal cellular processes to disease progression, including angiogenesis, mitochondrial dysfunction, and aerobic glycolysis could be the key to define the cellular redox signaling involved in the tumor progression [69]. High concentrations of H_2O_2 could be able to disrupt the anti-oxidant process, resulting in a compromised of redox homeostasis. In fact, ROS levels must be raised above a certain threshold steady-state level whereby the anti-oxidant cellular enzymes that otherwise counteract this build up become inhibited [70]. The imbalance between ROS generation and removal might lead to oxidative stress. There are three different antioxidant systems to protect against the oxidative stress that may be divided into: of enzymes preventive, scavengers, and repair. First, UCPs and hexokinase that bind to mitochondria VDAC complex can be classified as a preventive antioxidant mechanism. Functionally, both enzymes reduce mitochondrial membrane potential, and as a consequence induce mitochondrial depolarization. Interestingly, the interaction between hexokinase and mitochondria VDAC protein is reported as a hallmark in cancer cells to maintain the high glycolytic flux typical of cancer cells [71]. However, this association between hexokinase and VDAC was observed to protect tumor cells by maintenance of the redox balance of the ADP recycling mechanism [32]. The scavenger antioxidant systems may be divided into two categories: enzymatic (superoxide dismutase, catalase and gluta-

thione peroxidase) and non-enzymatic (α-tocopherol, thioredoxin). Finally, repair antioxidant defenses include the poly (ADP ribose) polymerase (PARP) and aldehyde dehydrogenase.

ROS and RNS both potently trigger activation of hypoxia inducible factor 1α (HIF-1α), leading to hypoxic signaling, such as increased VEGF production and enhanced glycolysis. ROS-mediated HIF-1α induction is dependent on oxygen levels, whereas NO induces HIF-1α independently of oxygen levels [72, 73]. Recently, Sun and co-workers described that mitochondrial mutations contribute to HIF1α accumulation via increased reactive oxygen species and up-regulation PDK2 in HNSCC [74]. As shown in the Fig. 30.5, this may provide insight into a potential mechanism by which mitochondrial mutations contribute to HNSCC development.

The free radical, nitric oxide (NO), has been known to play a dual role in human physiology and pathophysiology [75]. A set of studies have shown that low dose of NO acts as an anti-tumoral inflammatory response, however at higher levels and/or prolonged and unregulated expression of NO, this free radical has been shown to cause multiples mutational events in DNA, proteins, and lipids, which are associated with cancer [76]. As shown in Fig. 30.6, NO plays an important dose-dependent role that may provide multiple tumor biology cell modifications.

In a eukaryotic cell, the free radical NO is produced in a two-step pathway divided into: L-arginine converted to NG-hydroxy-L-arginine and then to generate L-citrulline and NO. This reaction is catalyzed by the enzymatic family of nitric oxide synthases (NOSs). There are three different NOS isoforms: (1) nNOS/NOS_1, a calcium-dependent enzyme discovered in neurons that is involved in neural transmission; (2) iNOS/NOS_2, a calcium-independent enzyme that releases large amounts of NO in response to macrophage activation with endotoxin and cytokines, and is involved in cytotoxicity; and (3) eNOS/NOS_3, also a calcium-dependent enzyme that is constitutively expressed, isolated from endothelial cells, and is found in normal vascular endothelium [77, 78]. In fact, some studies have shown that NO participated in multiple biologic functions, such as antitumor and microbial immunity, a signaling pathway as a second messenger, and angiogenesis [79, 80]. NOSs up-regulation leads to increase NO production, which is how this enzyme can initiate NO-dependent signal transduction, influence the redox state of cells, and induce modifications of proteins, lipids, and DNA [81]. Therefore, the free radical NO is able to generate oxidative stress during tumor cell transformation, resulting in DNA and protein damage, impaired anti-oxidant mechanism, and gene expression profile alterations [82]. More recently, Radosevich et al. published a long-term adaptation process with increasing concentrations of DETA-NONOate, a nitrogen-based NO donor, in three different HNSCC cell lines. In the same study, the adapted HNO cells grew better than their corresponding normal cells in the presence of H_2O_2, an oxygen-based free radical donor. In fact, these studies suggested that the presence of RNS in the tumor cell environment up-regulated defense mechanisms that may contribute to their aggressive expression profile. These properties included a greater S-phase percentage, radioresistance, and elevated expression of GST-pi, APE1, Chk1, Chk2 [83]. In this context, cancer cells that are able to survive in a supposedly hostile microenvironment of high ROS and RNS could be regarded as a

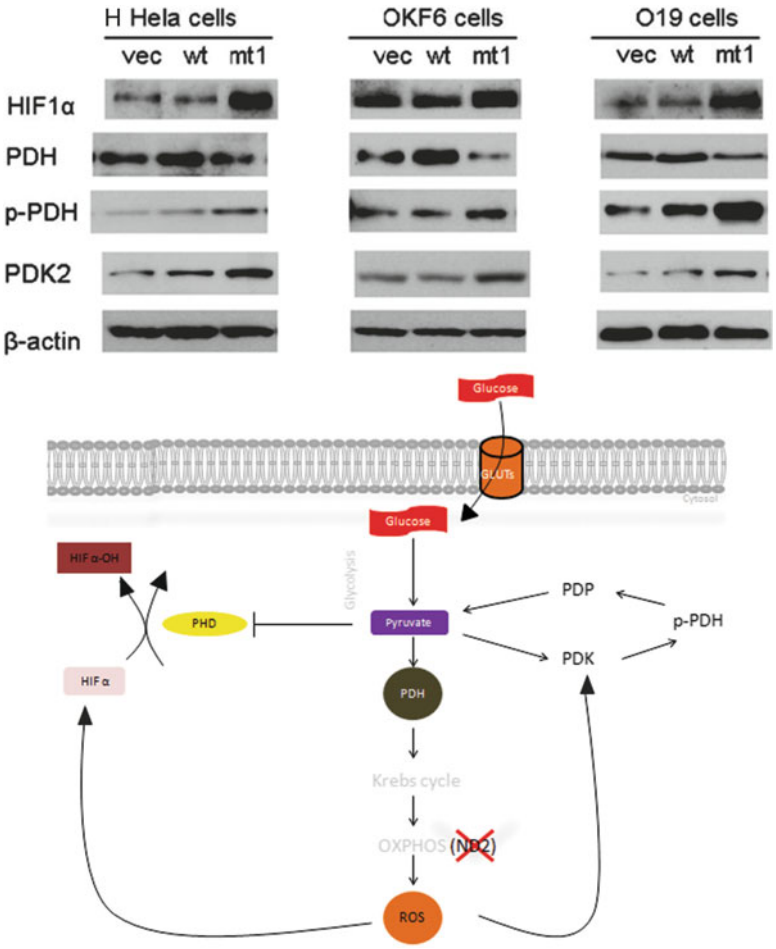

Fig. 30.5 Mitochondrial ND2 mutant promoted head and neck cancer cell growth through HIF1α accumulation, decreased PDH, increased phospho-PDH, and thereby increased pyruvate production, and elevated PDK2. The protein levels of HIF1α and PDK2 were determined 4 h following switching from culture medium to Krebs-Henseleit buffer in Hela, OKF6, and O19 cells. Mutant 1 (mt1) transfection of HeLa, OKF6 and O19 cells induced decrease of PDH and increase of phosphor-PDH, compared with wild type (wt). After 48 h of transfection, cells were incubated with glucose-free Krebs buffer for 4 h. Immunoblots were quantified via densitometry and ImageJ software. In the figure, GLUTs, glucose transporters; HIF-α-OH, HIF-α, Hypoxia Inducible Factor- α+hydroxyl; Hypoxia Inducible Factor- α; PHD, prolyl hydroxylase domain; PDH, Pyruvate Dehydrogenase, ND2, NADH dehydrogenase subunit 2; PDK, Pyruvate dehydrogenase kinase; PDP, Pyruvate dehydrogenase phosphatases (Figure modified of [74]. *Clin Cancer Research*)

subpopulation that were selected in terms of their particular metabolic adaptations. A molecular mechanism induced by RNS that supports this metabolic adaptation is the relationship between NOS_2 and p53. This provides insight into the divergent

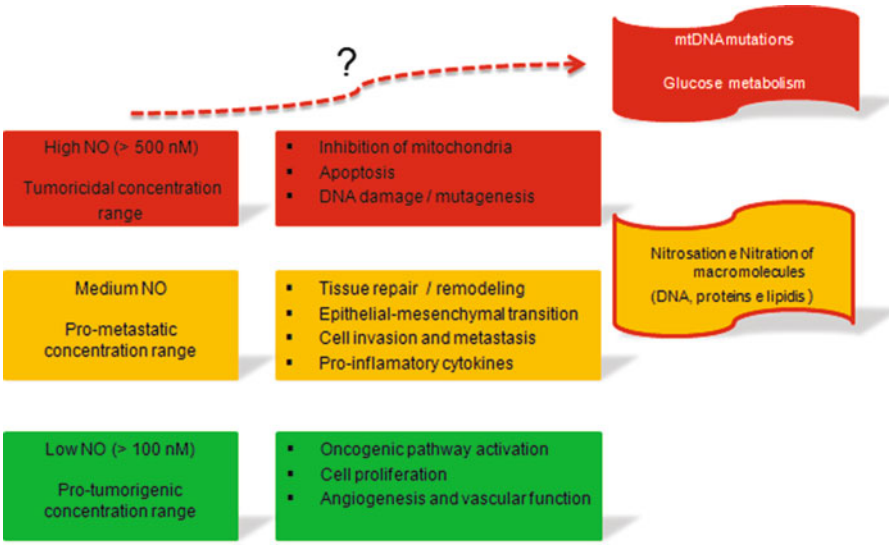

Fig. 30.6 Concentration-dependent effects of NO in tumor biology. (?) No experimental evidence has been provided mtDNA damage and anaerobic metabolism at this concentration range

properties of NO in that cancer wild-type p53 antagonizes NOS_2 via two mechanisms. p53 binds to the TATA-binding element in the promoter region of the NOS_2 gene to inhibit expression [84]. Furthermore, p53 binds directly to the NOS_2 protein, which attenuates NOS activity [85]. By contrast, NO stabilizes p53, leading to apoptosis [86]. NO-mediated apoptosis of leukemia cells requires wild-type p53, because NO does not induce apoptosis in p53 null cells [87]. In addition, p53 mutant carcinoma cells expressing NOS_2 have accelerated tumor growth and increased vascular endothelial growth factor (VEGF) production compared to wild-type p53 tumors [88], suggesting that p53 status plays a significant role in determining the pro- or anti-tumorigenic role of NO. These results have been shown in breast and head neck cancer.

30.5 Implications for Cancer Therapy and Why Mitochondria Provide Excellent Targets

30.5.1 The Mitocans, Dichloroacetate, and Cisplatin

A difference between tumor and normal cell metabolism is observed but is different in various types of cancer. A number of metabolic pathways that seem to be important for tumor growth are being touted as novel targets for anticancer drug development. In a tumor microenvironment, tumor cells have been shown to use anaerobic

metabolism, as a universal metabolic signature. Sixty to eighty percent of human tumors, use anaerobic metabolism as their primary mechanism to generate energy. In this context, the flux of carbon skeletons is driven to generated pyruvate, then lactate. The formation of lactate seems to be the fuel that feeds tumor cells, driving cancer cell evolution. The signaling that maintains this malignant process is supported by the mitochondrial oxidative stress generated by ROS. In this context, drugs that disrupted ROS signaling and/or reverse the Warburg effect with a consequent shuttle from fermentative to oxidative metabolism have been highlighted as possible new ways to treat cancer.

One of the candidates in this class of drugs that is being investigated is dichloroacetate (DCA), a molecule used for over 25 years in the treatment of children with inborn errors in mitochondrial function. This pyruvate mimetic compound stimulates mitochondrial function by inhibiting the family of regulatory pyruvate dehydrogenase kinases (PDK1-4). The stimulation of mitochondrial function, at the expense of glycolysis, reverses the Warburg effect and it is thought to block the growth advantage of highly glycolytic tumors. As recently shown by Seth and collaborators, the inhibition of LDH-A in a glycolytic NSCL tumor cell line, results in ROS-mediated apoptosis and increased sensitivity to the chemotherapeutic drug paclitaxel. Also, the inhibition of fermentative glycolysis either through inhibition of LDH-A or by activation of PDH by DCA can be monitored in a noninvasive real-time manner through hyperpolarized pyruvate. The same result was observed (markedly enhanced toxicity of paclitaxel and 2-deoxy-D-glucose in combination in NSCLC xenografts) because LDH-A inhibition acts by directing the trafficking of pyruvate to acetyl CoA to also decrease glycolytic flux, as does 2-deoxy-D-glucose.

A general property of oncogene transformed cells with dysfunctional mitochondria and associated increased ROS production is that they exhibited a lower threshold of sensitivity to ROS-induced apoptosis. Interestingly, this is highly likely for cancer cells relative to normal cells. One explanation is that for cancer cells to have altered mitochondrial electron transport systems (ETS), that are more efficient in ROS (O_2^- and H_2O_2) production, result in inducing a state of chronic metabolic oxidative stress. Therefore, it follows these therapies that are able to elevate ROS production in cancer cells, should selectively push these cells into apoptosis. Such agents are the mitochondrial targeted anti-cancer drugs, or so called mitocan (an acronym for mitochondria and cancer). Pelicano and collaborators have shown that drug combinations with mitochondrial ETS blockers (ETSbs) (to enhance oxidative stress) and cytotoxicity produced greater gains in anti-cancer efficacy [89]. Also, the combination of ETSbs including rotenone or antimycin A with 2-deoxy-D-glucose induced oxidative stress and cytotoxicity in colon cancer cells, results in cell death [90]. Likewise, normal cells did not have enhanced cytotoxicity, providing further evidence that cancer cells are more susceptible to inhibition of glucose metabolism in the presence of ETSBs and increased ROS. Other mitocan such as ubiquinona, α-tocopheryl succinate (a-TOS) and vitamin k3 induce the generation of ROS leading to apoptosis in cancer cells, but not in related normal cell types [91, 92]. The importance of ROS in mediating apoptosis induced by a-TOS has been confirmed

in several reports where the efficacy with which a-TOS induces apoptosis closely paralleled the level of ROS accumulation and cells with low level anti-oxidant defenses were more vulnerable to a-TOS. Another example, has been shown in that HCT116 colon cancer cells, when treated with Vitamin k3 inhibited DNA polymerase c by more than 80%, also caused impairment of mtDNA replication/repair, and induced significant increases in ROS leading to apoptosis. New drug combinations which increased ROS production, and reverse the metabolic status of the cancer cells will be useful in treating a vast number of different types of cancer.

In head and neck cancer, cisplatin is a the most important chemotherapeutic agent developed to date. Cisplatin may have important direct interactions with mitochondria which result in induce apoptosis. Cisplatin has been extensively characterized as a DNA damaging agent and the cytotoxicity of cisplatin has generally been attributed to the ability to form inter- and intra-strand nuclear DNA crosslinks. It was soon appreciated that chemotherapy combinations based on cisplatin were highly active in head and neck cancers. The overall responses of 70–90% with complete responses of 20–30% have been reported when cisplatin is combined with 5-fluorouracil [93]. But these results together could suggest that a combination of cisplatin with other drugs that improve a chronic oxidative stress condition, or that reverses the metabolic profile may be more effective to treat head and neck cancer. Interestingly, these findings will provide a new approach to treat patients, since roughly 20,000 patients per year will present with recurrent or metastatic head and neck disease.

30.6 Conclusion

Cancer cells have a different metabolic profile when compared to normal cells. The Warburg effect (increased aerobic glycolysis) and glutaminolysis (increased mitochondrial activity from glutamine catabolism) are well known hallmarks of cancer and are accompanied by increased lactate production, increased production of reactive oxygen species, and frequent mtDNA alterations have been documented in different stages of cancer progression. Nobel laureate Dr. Otto Warburg stated that cancer cells rely on glycolysis or substrate phosphorylation to generate ATP, and suppress their mitochondrial activities. With more advanced technologies, recent studies have confirmed the ATP production aspect of the Warburg hypothesis, but revealed that mitochondrial activity is not suppressed in cancer cells. Instead, mitochondria play a pivotal role in providing substrates to maintain cell division. These and other areas of investigation may provide a more comprehensive understanding of the role of mitochondria in tumorigenesis.

A body of evidences suggests that for cancer evolution an imbalance between production and removal of ROS is needed in the mitochondrial microenvironment. In this way, antioxidant therapy showed promise as anticancer therapy. Mitocans act via mitochondrial destabilization, with activation of mitochondrial mediators of apoptosis. These inducers of apoptosis elude the frequent mutations in mtDNA that occur in cancers which may be responsible in making tumors resistant to many

established chemotherapeutic drugs. Mitocans may be favorable in the fight against cancer because of low levels of side effects due to their greater target selectivity. Mitocans are still in the early phase of clinical testing, although preliminary data suggest a promising clinical outcome. Mitocans, when used in combination with other drugs such as DCA, cisplatin,or 2-deoxy-D-glucose could offer new opportunities for additive or synergistic therapeutic effects, including the opportunity to treat recurrent or metastatic head and neck cancer.

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Chapter 31
Genetic Susceptibility to Head and Neck Cancer

Athanasios I. Zavras and Angela J. Yoon

Contents

Abstract This chapter summarizes current knowledge of association between inherited genetic variation and likelihood of acquiring cancer. Slight difference in certain gene segments make some individuals more prone to developing cancer, which is known as 'genetic susceptibility'. Various gene segments that are different for different individuals, accounting for individual susceptibility to cancer are covered in this chapter. Moreover, not all individuals exposed to environmental toxins will acquire cancer. The chance of developing cancer depends on the amount of exposure to toxin and the inherited genetic function to degrade and reduce harmful effects of the toxin that has entered into the body. There are also dietary factors that may boost the genetic function to guard against the cancer. Such relationship

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between the environment (both toxins and dietary factors) and inherited gene is collectively known as gene-environment interaction, which is also discussed in this chapter.

Keywords Polymorphism • Head and neck cancer • Cancer susceptibility • Genome-wide association studies • Gene-environmental interactions

Abbreviations

ADH	alcohol dehydrogenase
ALDH1	aldehyde dehydrogenase 1
BER	base excision repair
CCL5	CC chemokine ligand 5
CCR5	CC chemokine receptor 5
CNVs	copy number variations
CYP2E1	cytochrome P450 2E1
EGFR	epidermal growth factor receptor
ERCC5	excision repair cross-complementing rodent repair deficiency complementation group 5
ESCC	esophageal squamous cell carcinoma
FGFR4	Fibroblast growth factor receptor 4
GCA	gastric carcinoma
GSTs	glutathione S-transferases
GWAS	genome-wide association studies
HNSCC	head and neck squamous cell carcinoma
HPV	human papilloma viruses
IGF1R	insulin-like Growth Factor 1 Receptor
IGF2R	insulin-like Growth Factor 2 Receptor
LD	linkage disequilibrium
MMP	matrix metalloproteinases
MMR	mismatch repair
MT-1	metallothionein-1
NAT	N-acetyltransferase
NER	nucleotide excision repair
NQO1	NAD(P)H:quinone oxidoreductase
NSCLC	non-small-cell lung cancer
OC	oral cancer
OPL	oral premalignant lesions
OR	odds ratio
PAHs	polycyclic aromatic hydrocarbons
RA	retinoic acid
RFLP	restriction fragment-length polymorphism
SAM	S-adenosyl methionine

SNPs	single nucleotide polymorphisms
TCE	T. catappa leaves
TGF-β	transforming Growth Factor-beta1
UADT	upper aerodigestive tract cancers

31.1 Introduction. The Concept of Genetic Susceptibility to Cancer

Are we susceptible to cancer from early on? Does our DNA contain valuable information to help us prevent cancer or diagnose it early? The quick answer is "yes". Emerging scientific evidence suggests that inherited genetic variation affects cancer susceptibility. This notion certainly applies to certain rare forms of familial cancer such as in retinoblastoma or in the solid tumors developed in patients with Fanconi Anemia, where the genetic component is predominant. However, genetic susceptibility plays a significant role, and has a much larger public health impact even in spontaneous cancers that are not considered to be genetic. Previous findings are further supported by the advent of high-throughput technologies that allow a complete screening of the genome to accurately identify single nucleotide polymorphisms (SNPs). In fact, in addition to validating well-known candidate genes such as p53, genome wide association studies have identified significant genes that had not been on the radar screens of cancer geneticists [1].

A single nucleotide polymorphism is a single variation in the sequence of nucleotides A,C,T,G, that occurs between people, usually as a result of natural selection. In addition to sequence changes in a single base, copy number variations (CNVs) are DNA sequence changes that involve multiple bases in a whole section of the DNA. The focus of this chapter is the single nucleotide polymorphism because of the larger volume of science that exists around SNPs as opposed to the emerging field of CNV epidemiology. The genetic polymorphisms indeed are closely linked to cancer susceptibility, especially in those "spontaneous" cancers, where there is a little evidence for familial inheritance. SNPs have been described in many classes of genes associated with carcinogenesis, such as tumor suppressor genes, oncogenes, and DNA repair genes [2].

Tumor suppressor genes are negative regulators of carcinogenesis and can be viewed as biologic switch boards that are always "on" when functioning, exerting a required cellular protection via regulation of the cell cycle and apoptosis (committing a cell to suicide, a normal process that eliminates a potentially malignant cell from replicating). If a person has inherited one or more of the genetic alterations that impedes the function of the tumor suppressor, fewer steps are needed for the chemicals to cause cancer, putting this person at a greater risk [3].

Oncogenes are positive regulators of carcinogenesis and can be viewed as switch boards that are turned "off" – however, once activated or over-expressed they promote tumor development via various pathways such as bypass of apoptosis, signal transduction, promotion of vascularization and invasion, etc.

DNA repair genes control the process of repair of the DNA that is constantly under assault. There are various forms of such repair, ranging from base excision repair (BER, for a single base) to nucleotide excision repair (NER, for bulkier lesions) to mismatch repair (MMR, for replication and recombination errors). According to Wikipedia, "DNA repair refers to a collection of processes by which a cell identifies and corrects damage to the DNA molecules that encode its genome. In human cells, both normal metabolic activities and environmental factors such as UV light and radiation can cause DNA damage, resulting in as many as one million individual molecular lesions per cell per day." Specific polymorphism linked with suboptimal function of DNA repair genes may result in accumulation of DNA damage, manifested as increased levels of DNA adducts, alterations in chromosome number, structural chromosome modification, activated oncogenes and their protein products and higher incidence of cancer.

Another important category of genes are those genes regulating metabolizing enzymes. Since the metabolizing enzymes activate and/or inactivate procarcinogens, the polymorphism in these enzymes may act in concert with environmental toxins to exert their effect that may ultimately lead to carcinogenesis. This is evidenced by the dose-association studies with smoking and lung cancer, and the dietary factors of colon cancer [2].

Genetic polymorphisms are currently being utilized as markers of susceptibility. These markers aid in determining inherited predisposition to risk of adverse health effects because they either have a direct effect (independent of environmental carcinogens) or they interact with environmental chemicals (gene – environment interactions). These genetic markers also help explain why inter-individual differences confer sensitivity or resistance to environmentally induced disease (i.e. why one smoker develops lung cancer while another smoker does not).

Discovering genetic polymorphisms that increase the risk of cancer is of importance in the public health arena. Such discoveries may have a clinical utility via a molecular diagnostic that assesses a person's risk or through a chemotherapeutic that targets a certain domain of carcinogenesis or a certain cancer pathway. Yet another clinical utility exists in the area of prevention, primary prevention to avoid a certain high risk behavior or secondary prevention to discontinue the high risk behavior. Information from genotyping may be conveyed to the individuals at higher risk of cancer so that the person is fully aware of his/her predisposition to cancer as compared to the general population when engaged in a particular activity that might be hazardous, like smoking or even a low level workplace exposure to chemicals like aromatic amines. Research shows that genetic susceptibility tests act as motivational triggers in helping people avoid exposure to carcinogens through high risk behaviors. In smoking cessation literature, a notoriously difficult task, Young et al. demonstrated that utilizing tests of genetic susceptibility personalizes the risk; such tests were reported to achieve quit rates of 25%, rates that are comparable with those achieved when using pharmacotherapy to control nicotine addiction [4]. The high risk individuals may also opt for chemopreventive intervention to lower their risk of developing cancer [2].

31.2 Polymorphisms in Metabolic Enzymes for Environment Carcinogens

Cancer is responsible for 500,000 deaths each year in the United States. 80% of these cancer-related deaths could be prevented since most malignancies are a result of environmental factors rather than inherent biological conditions. When combining knowledge about external factors related to lifestyle and environmental or occupational exposure to chemicals with how genetic polymorphisms cause variations in human response to environmental toxins, it will be possible to answer questions like why certain groups of people are prone to acquiring cancer after exposure to a carcinogen and others are not. Molecular epidemiology is an emerging new field that combines highly sensitive molecular techniques for identifying gene alleles that alter the functional capacity of genes, which may increase susceptibility to or have a protective effect against cancer [3].

31.2.1 Alcohol Dehydrogenase

Even though alcohol is a major risk factor for head and neck cancer, the mechanism by which it causes the disease is unclear, especially as pure ethanol does not act as a carcinogen in experimental models. One possibility is that the carcinogenic effect of alcoholic drinks is due to acetaldehyde, the initial metabolite of ethanol. Acetaldehyde is a recognized mutagen and animal carcinogen; it has been found to cause mutations, to form DNA adducts, and to inhibit DNA repair [5, 6]. In humans, the exact role of acetaldehyde as a cause of oral cancer has not been firmly established. However, given that fast alcohol metabolizers will have the greatest peak exposure to acetaldehyde, it has been hypothesized that possession of alcohol dehydrogenase 2 and 3 (ADH2, ADH3) genotypes encoding for fast alcohol metabolization will confer an increased risk. In a case–control study, no overall (marginal) association was found between oral cancer risk and ADH3 genotypes. However, our data suggested that an interaction exists between ADH3 genotypes and levels of alcohol consumption. In nondrinkers, the ADH3*1/1genotype had higher risk than the ADH3*1/2 or 2/2 genotypes, but for subjects consuming high levels of alcohol the relationship is reversed [7].

31.2.2 Glutathione S-Transferases

The glutathione S-transferases (GSTs) are a multigene family of phase II detoxification enzymes that catalyze the conjugation of both endogenous and exogenous electrophiles with the nonprotein thiol glutathione, resulting in a conjugate that is more water soluble and less toxic. Of the six classes of GSTs (five cytosolic and one membrane-associated) identified, the GST p and q class genes have been well characterized with their polymorphism closely associated with cancer [1].

31.2.2.1 GSTT1

The GST q class gene T1 conjugates halmethanes such as soil fumigants and pesticides. The frequency of the GSTT1 null genotype ranges from 10 to 60%, depending upon ethnicity. Zavras' group [8] studied GSTT polymorphisms and oral squamous cell carcinoma in a case–control study. Among current smokers, those with GSTT1 null genotype had ten times the risk of developing oral cancer than current smokers with at least 1 GSTT1 allele present. For individuals with the GSTT1 genotypes, current smokers exhibited an odds ratio (OR) of 3.4, whereas former smokers had an OR of 1.49. The OR for current smokers with GSTT0 was 34.7, compared with an OR of 2 for former smokers with the same genotype.

31.2.2.2 GSTP1

Among the polymorphisms identified in the p class GSTP1 gene, an A-to-G transition at nucleotide 313 has been most extensively evaluated. The resulting Ile-Val substitution decreases the specific activity and affinity of the GST enzyme for certain substrates [9, 10]. Moreover, an association between this polymorphism and oral and pharynx squamous cell carcinomas but not for laryngeal carcinomas [11] has been reported. Katoh et al. [12] conclude that the GSTP1 A-to-G genotype is a moderate risk factor for oral squamous cell carcinoma in the Japanese population.

31.2.3 Cytochrome P450s

Thirty isoforms of cytochrome P450s are expressed in human tissue, and about nine of these are known to be polymorphic. Of these, polymorphisms in isoforms CYP1A1, CYP2D6, and CYP2E1 are the most extensively studied as potential contributors to cancer susceptibility [13].

The CYP1A1 gene is located on human chromosome 15 and is expressed only in extrahepatic tissues, including the lung. CYP1A1 converts polycyclic aromatic hydrocarbons (PAHs), carcinogens found in cigarettes. CYP1A converts PAH to reactive arene oxides, which has the ability to cause DNA mutation and initiate carcinogenesis [13]. A number of allelic variants of CYP1A1 have been identified. A point mutation in the 3′ noncoding region results in the generation of an MspI restriction fragment-length polymorphism (RFLP). This variant is linked to an isoleucine-to-valine (Ile-Val) substitution at codon 462 in exon 7, which is the heme-binding domain of CYP1A. Mspl and exon 7 variants leads to increased enzyme inducibility and has been associated with increased risk of lung cancer especially among Asians. Moreover, nicotine, a known carcinogen from cigarette smoking, is an inducer of pulmonary CYP1A1 activity [14].

CYP2D6 (debrisoquine hydroxylase) is involved in the metabolism of 25% of all prescribed drugs [15]. At least 29 allelic variants of CYP2D6 has been identified which

accounts for extensive inter-individual variability in drug metabolism [16]. Nucleotide substitutions, deletions, aberrant splicing, and gene duplication lead to the absence of functional CYP2D6 protein in approximately 6% of whites. However, CYP2D6 is not inducible. CYP2D6 can activate 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone (NNK), a carcinogenic component of cigarette smoke and a putative inducer of human lung adenomas. Although phenotypic studies continue to suggest that extensive metabolizers are at increased risk of lung cancer, genotypic studies fail to confirm this association. The role of CYP2D6 variants in other malignancies remains unclear [1].

CYP2E1 can activate several environmental toxins including nitrosamines. Ethanol can induce CYP2E1 activity. It is expressed both in liver as well as extrahepatic tissues. Three polymorphisms have been identified within the CYP2E1 gene. RsaI RFLP is located in the 5′ flanking region of the gene, while DraI and TaqI RFLPs are present in introns 6 and 7, respectively. No association between the variant alleles and altered CYP2E1 activity has been established in vivo. However variant genotypes may have protective effect again the lung cancer as the individuals with homozygous variant genotypes (RsaI variant) were estimated to be ten times less likely to develop any type of lung cancer or, specifically, adenocarcinoma (DraI variant) [1, 17].

31.2.4 NAD(P)H:Quinone Oxidoreductase (NQO1)

NQO1 catalyzes the two-electron reduction of quinones and their derivatives, thus preventing their participation in redox cycling. In contrast, NQO1 can also metabolically activate procarcinogens that are present in tobacco smoke (i.e., heterocyclic amines) [18]. A C-to-T transition at codon 609 of the NQO1 gene has been identified. This polymorphism, which occurs predominantly in the white population at a frequency of 13–25%, leads to a reduction or absence of enzymatic activity [18]. Although the contribution of this polymorphism to lung cancer susceptibility remains controversial, other study involving 767 white, Japanese, and Hawaiian subjects revealed an inverse correlation between the presence of the variant NQO1 allele and lung cancer risk. Steiner et al. reported that whites with this variant allele are not at increased risk for either prostate cancer or benign prostatic hyperplasia [19].

31.2.5 N-Acetyltransferases

Two isoforms of N-acetyltransferase (NAT1 and NAT2) exists and both are involved in activation and detoxification (O- and N-acetylation, respectively) of aromatic amines. Aromatic amines are constituents of cigarette smoke, occupational carcinogens, and the heterocyclic amines in cooked red meat. Seven allelic variants have been identified for NAT1 gene, and more than 20 variants in NAT2 have been

described. Of these, the NAT1*10 variant allele and the NAT2 can slow acetylator function, thereby increasing the smoker's risk of bladder cancer [20]. Moreover, the Physicians' Health Study indicates that rapid acetylators for both NAT1 and NAT2 (specifically males aged 60 years or over) who eat more than one serving of red meat per day are at a significantly increased risk for colorectal cancer (relative risk = 5.8), compared with men who eat less than half a serving per day [21]. Consistently, an examination of NAT1 and NAT2 polymorphisms in Japanese patients with oral squamous cell carcinoma revealed that the NAT1*10 variant allele significantly increases an individual's risk [12]. Moreover, individuals with both a mutation in the mismatch repair gene MLH1 and the NAT1*10 allele have a lower median age of colon cancer diagnosis and more frequently have distal colon neoplasms [22]. A significantly increased frequency of slow acetylators has also been reported in individuals carrying mutations in MLH1 and MSH2 [22].

31.3 Polymorphism in DNA Repair Genes

Molecular epidemiological studies of polymorphisms in DNA repair genes may provide insight into the relationships between DNA repair genes and cancer susceptibility. Such studies may identify empirical associations indicating that a DNA repair gene polymorphism has an impact on cancer, independent of metabolic regulatory mechanisms and other genetic and environmental variability [23].

Emerging evidence supports strong association between DNA repair polymorphisms and cancer susceptibility, in which the carriers of specific allele are at increase risk of cancer. The *C* allele at codon 326 in OGG1 (S326C) was associated with an increased risk of esophageal cancer, lung cancer, and prostate cancer [24–26]. The H allele at BRCA2's codon 372 (N372H) were consistently associated with increased breast-cancer risk, OR ranging from 1.1 to 1.8 [27]. Conversely, certain polymorphism may confer a protective effect against the cancer. The *W* allele at codon 194 in XRCC1 (R194W) was associated with lower risk of bladder cancer, breast cancer, lung cancer, head and neck squamous cell carcinoma (HNSCC), and stomach cancer [28–31].

One of more recent studies reported an association between ERCC5 polymorphism and liver cancer risk [32]. Excision repair cross-complementing rodent repair deficiency complementation group 5 (ERCC5, XPG) is a key molecule in DNA damage repair, specifically playing a prominent role in the Nucleotide Excision Repair. The study looked for the contribution of ERCC5 rs751402 polymorphism in increased susceptibility to hepatocellular carcinoma (HCC) and found that homozygocity for allele C conferred statistically significant protection (OR = 0.56) against HCC, whereas rs751402 T alleles were associated with increased risk (OR = 1.69). Individuals with inherited ERCC rs751402 CC genotype may experience significant protection against HCC, whereas individuals with the T alleles seem to be exposed to higher risk.

Functional studies of polymorphisms in DNA repair genes are being conducted to gain understanding of underlying molecular mechanism of carcinogenesis. The

236C allele in OGG1 gene reduced the repair of 8-oxoguanine or the substrate specificity in E. Coli [33], although no strong association was found in studies with human cell-line with functional activity as measured by 8-oxoguanine levels, or 8-oxoguanine glycosylase activity [34]. Similarly, human studies of XRCC1 R194W reported no associations with indicators of DNA-repair capacity such as DNA-adduct levels, frequency of mutations in glycophorin A, or sensitivity to ionizing radiation [35]. A comparison of BRCA2 N372H genotypes among spontaneous abortions and live births suggested an in utero selection against female fetuses with an HH genotype [27]. Additional studies are required to elucidate whether it is the polymorphism itself, a variant that is in linkage disequilibrium, or another unknown factor that may play a causal role in carcinogenesis or development [23].

DNA-repair polymorphisms have also been evaluated in the presence of DNA-damaging agents, such as tobacco smoke or ionizing radiation [36]. When the association between XPD and lung cancer were examined in smokers and non-smokers, risk of lung cancer in the carriers of D312N or L751Q alleles was higher among nonsmokers (or lighter-smokers) than among smokers (or heavier-smokers) [37]. These results are consistent with the hypothesis that the effect of *XPD* genotype on risk of lung cancer may be apparent only in the presence of lower levels of DNA damage than those caused by smoking [37]. Another gene-environment interaction study reported association sunburn-related squamous cell carcinoma and XRCC1 R399Q polymorphism. Individuals with QQ genotype, three or more sunburns conferred a 6.8-fold increased risk, whereas individuals with RR genotype, only a 1.5-fold increase in risk were seen [38]. Such study of particular gene-by-exposure effects may be particularly useful in the context of an *a priori* biological hypothesis [23].

DNA repair polymorphism is not only associated with cancer risk, but also with the response to various cancer therapies and prognosis [39]. Because DNA repair polymorphism is associated with DNA repair capacity, these may be targeted to alter the DNA repair capacity of cancer cells during chemo or radiation therapy [39]. In terms of cancer survival prognostication, a study found that a polymorphism in the DSB repair gene LIG4 was associated with poorer survival time after breast cancer diagnosis [40], and another study found that combined genotype at the MMR gene MLH1 and cytochrome P450 1A1 (involved in xenobiotic metabolism) predicted event-free survival time after an acute lymphocytic leukemia diagnosis [41]. Similarly, other studies of colorectal cancer have reported associations between XRCC1 R399Q and XPD L751Q and poorer response to platinum-based treatment. Because cancer-treatment regimens are often based on the induction of DNA damage, polymorphisms in repair pathways may be important for treatment response, toxicity, and survival [23].

DNA repair polymorphisms were demonstrated to be associated with risk of various cancer including adult glioma, bladder cancer, breast cancer, esophageal cancer, lung cancer, prostate cancer, HNSCC, skin cancer (melanoma and nonmelanoma), and stomach cancer. The polymorphisms in DNA repair genes play a role in carcinogenesis as well as in therapeutic response. Additional epidemiological analyses will provide essential information in relationship between the DNA-repair mechanisms and carcinogenesis [23].

31.4 Inherited Genetic Defects that Increase the Risk of Cancer

Numerous genes have been identified to serve as positive (proto-oncogenes) or negative (tumor suppressor genes) regulators of cell growth, cell cycle and apoptosis. Rare hereditary disorder involving these genes are associated with increased susceptibility to cancer. The common polymorphisms in these genes, i.e., p53, have demonstrated association with various cancers arising in breast, endometrial, ovarian, bladder, colon, lung, thyroid, gastric, nasopharyngeal, esophageal, multiple myeloma, and head and neck [42]. Polymorphisms in tumor suppressor and proto-oncogenes have low penetrance and do not in themselves confer high individual cancer risk. However, as a large proportion of the population may be carriers of alleles that increase risk of cancer, their attributable risk in any given population can be quite high. Moreover, the combination of several high risk alleles in an individual may have substantial increases in relative risk due to gene-gene interaction. When combined with a known environmental carcinogen exposure (i.e. nicotine from cigarette smoke), the probability of developing cancer in such persons becomes extremely high [42].

PTEN (MMAC1/TEP1) is a tumor suppressor gene located at 10q23.3. It encodes a dual-specificity phosphatase with lipid and protein phosphatase activities and participates in signal transduction pathways to regulate cell growth, proliferation, and apoptosis. PTEN also controls cell cycle by down-regulating cyclin D1 and up-regulating p27 [52]. Polymorphism of PTEN gene has been associated with various disease and cancers. The C to G substitution at the untranslated region of exon1 (−9G) results in a significantly higher level of protein expression compared with the wild-type allele (−9C). The substitution of C with G has been associated with susceptibility to type 2 diabetes. The IVS4 insertion polymorphism which is an ACTAA insertion occurring at the 109 bp downstream of exon4 in intron4 was reported to be related to a lower mean age at the diagnosis of breast cancer. The IVS7 deletion (15-53del39), located at the intron7-exon8 splicing boundary, was recently confirmed among African Americans and its role in disease development has not been reported [43].

Ge's group [43] reported that the variant homozygote (+/+) of the PTEN IVS4 polymorphism is associated with reduced risk of the esophageal squamous cell carcinoma (ESCC) and gastric carcinoma (GCA). However, in a study of breast cancer, the variant homozygote has been associated with younger onset of breast cancer, while this genotype has been correlated with reduced incidence of high grade/stage prostate cancer among men less than 69 years old. Such inconsistency in data may suggest that the effect of PTEN IVS4 polymorphism is tumor specific. Moreover, the two loci of the PTEN polymorphism may be partially in linkage disequilibrium, and the −9C/IVS4- haplotype was demonstrated to be associated with a increased risk of the ESCC and GCA development. These two polymorphisms may interactively influence susceptibility to certain cancers, possibly by modifying transcription or expression of the PTEN gene.

The p53 tumor suppressor gene, located on chromosome 17p, encodes a nuclear phosphoprotein, which induces apoptosis, thereby suppressing cellular transformation and proliferation [44]. Mutations in p53 gene are the most common genetic alteration in human cancers. More than one-half of all cancers show either absence of the p53 protein function or mutations in the gene. Mutant and wild-type p53 may oligomerize, thereby disrupting the function of the tetrameric complex [44].

Codon 72 of the p53 gene was found to be a site of frequent polymorphism and is associated with cancer susceptibility. The frequencies of allelic variants at this codon significantly differ among different ethnic groups [44]. The p53 codon 72 polymorphism is associated with increased risk of cervical cancer as p53-R72 is readily degradable by the E6 oncoprotein produced by high-risk human papillomaviruses (HPV). Increased degradation of p53 by E6 results in reduced levels of p53. Hence higher incidence of HPV-associated cancers is observed in individuals with p53-R72 homozygotes [45]. Conversely, p53-P72 genotype has been associated with an earlier median age of onset of HNSCC and hereditary non-polyposis colorectal cancer. In terms of the prognosis, individuals with p53-R72 genotype with breast, lung or HNSCC had higher response rates to chemotherapy and radiation therapy and longer survival after the treatment [45].

Several genetic polymorphisms associated with cell-cycle regulation and control has been the target of many studies. Two such biomarkers are the oncogene Insulin-like Growth Factor 1 Receptor gene (IGF1R) and the tumor suppressor Insulin-like Growth Factor 2 Receptor gene (IGF2R). Because IGF2R mutations have recently been implicated in several forms of cancer, a number of hypotheses exist about their role. One of the main functions of IGF2R is the binding and transporting of glycoproteins. Two important lysosomal enzymes linked to apoptosis, the proteases cathepsin B and cathepsin D, depend on the IGF2R trafficking system [46]. Defects in the trafficking system result in increased levels of pro-cathepsin B and D and decreased levels of mature enzymes. Such events have been reported in breast tumor cells [47, 48]. IGF2R mediates the internalization and degradation of IGF2, a mitogen that normally acts through the IGF1 receptor. In this manner, the receptor serves as a suppressor of IGF2 proliferative actions, and thus plays an important role in the suppression of cell growth. In addition, IGF2R helps activate the homodimeric cytokine Transforming Growth Factor-beta1 (TGF-β), a potent growth inhibitor [49]. In many cells, TGF-β inhibits cellular growth by arresting the cell cycle at the late G_1 phase and affects angiogenesis. IGF2R is also involved in the anti-neoplastic pathway of retinoic acid (RA) and its analogues, the retinoids. Retinoids exhibit diverse biological effects on cells. They control normal growth, fetal development, differentiation, morphogenesis, metabolism, and homeostasis and induce apoptosis [50, 51]. This last function of retinoids in the protection against cancer, apoptosis, seems to be mediated by IGF2R [52, 53].

Zavras' group [54] conducted a case–control study of non-small-cell lung cancer (NSCLC) and another for breast cancer. In the lung cancer study, there were 48 cases with histologically confirmed non-small-cell lung cancer and 84 male controls. Smoking in men was associated with increased risk for lung cancer (OR of 3.6). The B2/A2 allele was present in 25/48 lung cancer cases (52.0%) and in 17/84

controls (20.2%). Subjects carrying the IGF2R- B2/A2 genotype had a four-fold increase in their risk of lung cancer compared with subjects with other genotypes (OR of 4.2). These findings suggest that genetic variation of IGF2R may significantly influence the risk of lung cancer. Thus, IGF2R seems to be a very important target for future studies of genetic predisposition to cancer.

Another study examined the association between A2/B2 allele and development and/or progression of NSCLC [55]. A total of 103 NSCLC patients free of IGF2R allelic imbalance aberrations were enrolled and their IGF2R 30 UTR polymorphism was assessed. Because oncogenic mitogens can escape degradation by IGF2R, and activate p53 through a DNA damage response, the patterns between p53 status and IGF2R genetic constitution were also evaluated. The A2/B2 variant was significantly more common in lung cancer patients (25 vs 15%). Its presence was accompanied by high cellular proliferation along with increased tumor cell growth and also was significantly found in advanced stages of cancer. Also, patients carrying the A2/B2 in their genetic constitution that exhibit aberrant p53 expression have faster growing tumors and progress more rapidly to the advanced stages. From this study, it was concluded that the IGF2R-A2/B2 variant provide a selective advantage for NSCLC progression through increased tumor growth.

31.5 Head and Neck Cancer and Inherited Cancer Susceptibility

Head and neck squamous cell carcinomas (HNSCC), which includes cancers of the oral cavity, pharynx and larynx, is the 6th most frequent cancer and the seventh leading cause of cancer-related death worldwide [56]. There are approximately 540,000 new cases and 271,000 deaths each year worldwide. Once diagnosed, the mortality rate is approximately 50% [56]. In the United States, HNSCC represents ~3% of all cancers, whereas it is much more prevalent in other parts of the world, such as India, Thailand and Brazil [57, 58]. A radical surgical excision of the tumor with or without adjuvant chemo and radiation therapy is the standard treatment. Despite the advances in treatment modalities, the overall survival of have not improved substantially in past 20 years. In individuals with early-stage tumor, secondary tumors represent the most common cause of death [59]. Furthermore, patients with advanced staged HNSCC have a high risk of primary treatment failure, metastasis and death.

There are number of risk factors associated with HNSCC. Major risk factors include tobacco and alcohol consumption, and chewing betel quid [60, 61]. For tobacco smoking, a dose–response relationship to cancer is observed and the relative risks of laryngeal and oropharyngeal cancers are 1.8 and 1.3, respectively, for persons who smoke ≤30 cigarettes per day and 7.7 and 2.9, respectively, for persons who smoke >30 cigarettes per day compared with non-smokers [62]. Alcohol consumption is also linked to increased risk of HNSCC. Individuals who consume >4 drinks (=47.5 g of pure ethanol) per day, the relative risks of HNSCC are 4.5 and

7.2, respectively, compared with nondrinkers [62]. A synergistic effect was observed in tobacco and alcohol use and when the combined, the risks of HNSCC are 34.6 and 21.2, respectively, among those who smoke >30 cigarettes a day and consume >4 drinks per week.

There is evidence of gene-environment interplay in development of HNSCC and of other cancers [63–66]. Individual variations in cancer risk have been associated with specific polymorphism harboring variant alleles of different genes that are present in a significant proportion of the normal population. Recent studies support a strong association between HNSCC and genetic polymorphisms. Various genes may be associated with carcinogenesis, including genes involved in carcinogen metabolism, DNA repair and cell-cycle control and oncogenes [56].

Initially, technologies were limited to studying one or a few polymorphisms at a time. Earlier studies focused on particular genes or pathways, specifically candidate genes or pathways suspected to be important in carcinogenesis, such as those involved in DNA repair, carcinogen metabolism, cell cycle control and hormone synthesis. The early studies examined single nucleotide polymorphisms (SNP) that were thought to be functionally important. Gradually, these studies were extended to sets of tagged SNPs correlated with all known common variants across a gene. However, very few well-validated associations have discovered from these candidate gene polymorphism studies [56]. Additional susceptibility genes in which rare coding variants are associated with a moderate cancer risk have, however, emerged through candidate gene resequencing, including ATM, CHEK2, BRIP1, PALB2 in breast cancer, and MYH in colorectal cancer [56].

Later on, genome-wide association studies (GWAS) was introduced as a powerful approach to identifying susceptibility loci. GWAS utilizes genotyping platforms that can type hundreds of thousands of SNPs simultaneously, using sets of SNPs that tag most known common variants in the genome. Such approach allows to search for associations without prior knowledge of SNP function or position [67]. Over the years, data from GWAS have been published for breast, prostate, lung and colorectal, and malignant melanoma, each reporting well-validated novel associations and more than 20 new cancer susceptibility loci were identified. Additional scans are ongoing in many other cancer types, including cancers of the haemapoietic system, pancreas, bladder, kidney, testis and ovary [56].

31.5.1 Candidate Gene Approach

With the completion of the human genome map, genetic polymorphisms of candidate genes have become increasingly studied as potential risk factors in various cancers [68], including gastric cancer, hematologic malignancies, non-small cell lung cancer, colorectal cancer, breast cancer, and esophageal cancer [69–75]. In the case of HNSCC, several studies have explored a selected few candidate polymorphic variants. These include genes involved in carcinogen metabolism, DNA repairs, as well as tumor suppressor genes and genes that regulate cell cycle, cellular growth and inflammation.

31.5.1.1 Cell Cycle

Cyclin D1 is a protein encoded by the CCND1 gene and it plays a critical role in cell cycle regulation. Its overexpression has been associated with cellular proliferation [76, 77]. The CCND1 A870G polymorphism has been associated with reduced disease free survival rate in HNSCC, in which the hazard ratio ranged from 2.3 to 3.72 [78–80]. A similar finding was reported in a study with 66 laryngeal cancer patients of all stages [80]. Moreover, CCND1 G1722C polymorphism was discovered to be in strong linkage disequilibrium with CCND1 A870G and was associated with poor prognosis for HNSCC [80].

31.5.1.2 Growth Factor Pathways

Fibroblast growth factor receptor 4 (FGFR4) is a tyrosine kinase receptor and plays a central role in cellular growth [81]. The FGFR4 GA polymorphism is associated with worse prognosis of the breast, lung, and prostate cancers as well as high-grade soft tissue sarcoma [82–84]. The FGFR GA polymorphism studies in HNSCC patients reported that the A allele was associated with worse overall survival rate. Similarly, Streit et al. [85] and da Costa Andrade et al. [86] found that carriers of the FGFR4 A allele had poorer prognosis than individuals carrying GG in HNSCC patients. In addition, the epidermal growth factor receptor (EGFR) intron 1 CA dinucleotide polymorphism has also been studied and no significant association was found in 112 HNSCC patients [87].

31.5.1.3 Matrix Metalloproteinases, CC Chemokines, Inflammatory, and Other Pathways

The matrix metalloproteinases (MMP) is involved in the Fas/Fas ligand pathways and modulates patient response to cisplatin and 5-fluorouracil. The MMP3 6A/6A genotype was demonstrated to have significantly higher response to chemotherapy in a study with 148 HNSCC patients of all stages undergoing neoadjuvant cisplatin/5-fluorouracil chemotherapy followed by either surgery or radiation. In contrast, the MMP1 -1607insG, MMP7 -A181G, and MMP7 -C153T polymorphisms did not show significant association with clinical outcomes. Few other studies also suggest potential roles for polymorphisms of the immunologic pathway and of DNA methylation in HNSCC prognosis [68].

Inflammation can be induced by cytokines, chemokines, and their receptors, and it is believed to be a risk factor on tumor initiation and progression. The contribution of CC chemokine ligand 5 (CCL5) and CC chemokine receptor 5 (CCR5) on the risk and prognosis of oral cancer was studied by Zavras' group [88]. In this case–control study, a total of 253 oral cancer patients and 347 healthy controls were recruited and the genetic polymorphisms of CCL5-28, -403 and CCR5-59029 were analyzed. The individuals with CCL5-28 CG, CCL5-28 CG or GG, and CCL5-403 TT polymorphic

genotype as well as the individuals with the combinations of CCL5-28 CG/-403 CT and CCL5-28 CG/-403 TT genotypes had a significant higher risk to oral cancer than those with wild-type genotypes. Moreover, the oral cancer patients with the combination of CCL5-28 CG/-403 TT genotype presented a lower risk for developing a moderately or poorly differentiated status as compared to those with the combination of CCL5-28 CC/-403 CC genotype. These results suggest that the SNPs in CCL5-28 and −403 genes could increase the risk to have oral cancer, and the combinative effect of CCL5-28 CG and −403 TT genes might also increase the oral cancer risk but reduce the clinicopathological development of oral cancer patients.

31.5.1.4 DNA Repair

A study was conducted by Zavras' group assessing the relationship between the polymorphism in the DNA repair gene ERCC5 and the likelihood of premalignant oral lesions progressing to oral cancer [89]. This study showed that in the individuals with a premalignant condition, ERCC5 played a significant role in carcinogen processing since individuals who used tobacco and had the T variant of ERCC5 exhibited significantly higher risks compared with individuals who did not use tobacco and had the C variant of ERCC5. In another ongoing study by the same group, ERCC5 was demonstrated to have a direct role in carcinogenesis. After controlling for known confounders such as age, tobacco use, areca nut use, and alcohol, individuals who harbored the CC genotype experienced significantly lower odds to develop cancer, as compared with individuals with the T allele [90].

31.5.1.5 Tumor Suppressors

M6P/IGF2R is known to have multiple important biological functions, some of which are critical in the suppression of cell growth and hence may play a crucial role in carcinogenesis. A loss or mutation of the M6P/IGF2R gene (chromosomal location 6q25-q27) could theoretically be associated with increased cancer risk. Such increased cancer risk for certain short tandem repeat genotypes has been described in several types of malignancies, including carcinomas of the breast, liver, endometrium, stomach, colorectum, and Wilm's tumor [91].

A hospital-based case–control study was undertaken to investigate the effect of high-risk genotypes in oral cancer risk [91]. This study evaluated if inherited short tandem repeat polymorphisms of the IGF2R is associated with oral cancer risk. The 197 individuals with oral cancer were enrolled and their DNA extracted from blood and saliva for genotyping. It was shown that the individuals carrying the heterozygous 167-bp IGF2R genotype had a 2.7-fold higher risk of oral cancer compared with subjects with other genotypes. These results suggested that genetic variation of IGF2R may influence significantly the risk of oral cancer [91].

In another hospital-based case–control study, investigators [91, 92] assessed if genetic variation in the mitogen binding domain of IGF2R, Gly1619Arg, disrupts

normal function of IGF2R and contributes to further progression and distant metastasis of localized oral squamous cell carcinoma (OSCC). Gly1619Arg polymorphism of IGF2R domain 11 (rs629849) was assessed in blood samples of 113 OSCC patients, and IGF2R genotypes were correlated with the stage of tumor. A three-fold increased risk of advanced stage of OSCC were noted in those subjects who had one or two copies of the IGF2R-A allele as compared with the GG genotype. In contrast, when compared with carriers of the A allele, the GG genotype demonstrated to be protective against advanced disease (OR = 0.32). IGF2R genetic polymorphism may be associated with decreased function of IGF2 receptor, thereby contributing to advancement and distant metastasis of localized oral cancer.

31.5.1.6 Zinc and Copper Metabolic Pathway and Antioxidant

Metallothionein-1 (MT-1) is an intracellular protein involved in homeostasis of zinc and copper and plays an antioxidant role. MT-1 is inducible both by areca quid and tobacco and increased expression of MT-1 is reported in various cancers including OSCC. Evidence suggests that genetic variations in MT-1 may contribute to increased cancer risk. Specific MT-1 allelotypes may result in abnormal expression of MT-1, which may lead to uncontrolled oxidative stress, dysregulation of metal homeostasis, and ultimately to carcinogenesis [93].

Zavras and his colleagues conducted an independent analysis of MT-1 rs8052394, rs11076161, rs8052334, rs964372, rs7191779, and rs708274 in 587 individuals who were either healthy controls or individuals with OSCC [93]. The study demonstrated that MT-1 is involved in regulation of zinc and copper homeostasis. It also is a potent antioxidant and its polymorphisms correlated with the risk for OSCC. Rs11076161 A, rs964372 C, and rs7191779 C alleles were protective against OSCC, whereas rs8052394 A alleles were associated with increased risk. Areca quid chewing and tobacco use were strong risk factors for developing the disease and were associated with 20- and 8-fold increases in risk, respectively. Individuals with inherited the MT-1 rs11076161 AA, rs964372 CC, and rs7191779 GC genotypes may experience significant protection against OSCC, whereas individuals carrying the MT-1 rs8052394 A allele seem exposed to higher risk.

31.5.2 Genome-Wide Association Studies

Genome-wide association studies (GWAS) have led to a paradigm shift in the discovery of gene–disease associations. The number of published data from GWA studies now reaches several hundreds since 2007, including several dozen on cancer phenotypes [94]. From these studies a number of novel gene-disease associations have been identified pertaining to common genetic variants, with minor allele frequencies typically exceeding 5% in the general population [95]. These discoveries include many associations with susceptibility to various cancer types.

McKay's group [96] conducted a genome-wide association study to discover common genetic variation and susceptibility to upper aerodigestive tract cancers (UADT), including HNSCC, within the International Head and Neck Cancer Epidemiology (INHANCE) consortium, comprising genome wide analysis of 2,091 UADT cancer cases and 8,334 controls. Five genetic variants at three loci, 4q23, 12q24 and 4q21, were found to be significantly associated with UADT cancers.

The 12q24 variant (rs4767364) is located in an extended region of linkage disequilibrium (LD) that contains multiple genes, including the aldehyde dehydrogenase 2 (ALDH2), another key gene in alcohol metabolism. The minor allele carriers of ALDH2 variants rs737280 and rs4648328, in LD with rs4767364 are associated with increased susceptibility to UADT. The rs4767364 variant was also associated with UADT cancer risk in a smaller series of African Americans implying that this effect may be relevant to other populations [96]. Moreover, the 4q21 variant (rs1494961) was also significantly associated with UADT cancers, which is located 20 Mb proximal to the ADH gene cluster [96]. rs1494961 is a single stranded DNA-dependent ATPase and DNA helicase involved in DNA intra-strand cross-linking repair. rs1494961 is in a LD region spanning approximately 90 kb, which contains additional genes such as a second DNA repair-related gene FAM175A (or Abraxas and CCDC98), that interacts directly with the BRCT repeat region of BRCA1 [97]. Association between rs1494961 and lung cancer suggests that the causal variant may be relevant for cancers influenced by tobacco consumption in general [96]. In addition, the 4q23 variants (rs1573496 and rs698 and correlated variants) correlates with increased UADT cancer risk [96].

In the subsequent analysis, McKay's group [96] found strong heterogeneity with rs1229984 when stratifying by alcohol consumption, in which an association was observed in 'Ever drinkers-Never smokers', but not in 'Never drinkers-Ever smokers', suggesting the effect with the rs1229984 variant is mediated through alcohol drinking rather than tobacco smoking. On the other hand, there was lack of heterogeneity for rs1573496 when stratified by alcohol use. This may imply that the underlying mechanism of carcinogenesis differs among these ADH variants.

Following the study of UADC by McKays group, 19 candidate SNPs were identified and analysis of the potential gene-gene and gene-environment interactions in HNSCC risk was performed, using 575 cases and 676 controls [98]. Both ADH1B and HEL308 modified the association between smoking pack-years and HNSCC. In addition, a higher-order interaction between smoking status, ADH1B, FLJ13089, and FLJ35784 in HNSCC risk was found, in which, compared with ever smokers carrying ADH1B T/CþT/T genotypes, smokers carrying ADH1B C/C genotype and FLJ13089 A/GþA/A genotypes had the highest risk of HNSCC. These results suggest that HNSCC risk associated with these variants may be more specific in patients with risky habit such as smoking.

The GWAS studies in HNSCC is far few and limited. There are ongoing efforts in this field to discover the association between genetic polymorphism and cancer susceptibility, which will significantly contribute to prevention and treatment of HNSCC that is tailored to each individual.

31.6 Gene-Environment Interactions

Not all individuals exposed to environmental toxins will acquire cancer. The chance of developing cancer depends on the amount of exposure to toxin and the inherited genetic function to degrade and reduce harmful effects of the toxin that has entered into the body. There are also dietary factors that may boost the genetic function to guard against the cancer. Such relationship between the environment (both toxins and dietary factors) and inherited gene is collectively known as gene-environment interaction.

For example, tobacco and alcohols are environmental toxins that may increase one's risk of cancer. A recent case–control study evaluated the association between alcohol consumption and the incidence of oral premalignant lesions (OPL) [99]. Participants were 41,458 men in the Health Professionals Follow-up Study. Alcohol consumption was assessed every 4 years using validated food frequency questionnaires. This study showed that the increased risk of OPL were 1.7 for drinkers of 0.1–14.9 g/d, 2.9 for 15–29.9 g/d, and 2.5 (1.3–5.1) for 30 g/d, compared with nondrinkers. Approximately one additional drink per day (12.5 g) was associated with a 22% increase in risk. The associations did not vary by beverage type, frequency, or consumption with meals. Results were similar when restricted to cases of oral epithelial dysplasia. Alcohol increased OPL risk in never users of tobacco as well as in past or current users. An interaction between alcohol and tobacco was apparent by their more-than-additive joint effects. The study concluded that alcohol is an independent risk factor for OPL, regardless of beverage type or drinking pattern. Recommendations to reduce alcohol intake have the potential to reduce incidence of OPL in nonsmokers and smokers alike.

Although alcohol is a risk factor for cancer, the chance of acquiring cancer also depends on one's ability to metabolize alcohol. Recent reports strongly implicate the metabolite of ethanol, acetaldehyde, as the main carcinogen in oral cancer. Acetaldehyde has been found to cause mutations, form DNA adducts and inhibit DNA repair. Acetaldehyde levels are regulated primarily by 2 enzymatic systems: alcohol dehydrogenase that oxidizes ethanol to acetaldehyde and acetaldehyde dehydrogenase that converts acetaldehyde to acetate. Oxidation of ethanol occurs primarily in the liver, but also in the gastrointestinal tract and oral cavity [7].

Seven human genes coding for ADH have been identified to date and three of these (ADH1, ADH2 and ADH3) are located in a cluster on chromosome. Single nucleotide polymorphisms that exhibit different enzymatic properties have been reported for some of these ADH genes. For example, it has been shown that cells with the ADH3 for ethanol oxidation that is 2.5-fold higher than that that of the ADH3 genotype exhibit a V_{max} for ethanol oxidation that is 2.5-fold higher than that of the ADH3 genotype. Ethanol is also metabolized, to a lesser extent, by CYP2E119 and genetic polymorphisms have also been identified for this gene. Because alcohol consumption is a major risk factor for oral cancer, this SNP in ADH3 is a prime candidate for mediating differences among individuals in oral cancer susceptibility [7].

The effects of interaction between a polymorphism in the alcohol dehydrogenase 3 (ADH3) gene and alcohol consumption levels on oral cancer (OC) risk was assessed using a hospital-based study of 93 cases and 99 controls conducted in Athens, Greece [7]. Polymorphisms in CYP2E1, another gene involved in ethanol metabolism, which was reported to be associated with OC risk in a European population, was also investigated. Data on genotypes and risk factors obtained from interviews were analyzed using multivariate logistic regression, accounting for potential confounders. While no overall association was found between OC risk and ADH3 genotypes, an interaction between ADH3 genotypes and alcohol consumption levels was noted. In non-drinkers, the ADH3 1–1 genotype has higher risk than ADH3 1–2 or ADH3 2–2 genotypes, but for subjects consuming alcohol, lower risk was observed for ADH3. As for the risk associated with each alcohol drink consumed per week, OC risk increased by 31.5% per drink/week for the ADH3 2–2 genotype, 4.1% for the ADH3 1–2 genotype and 1.6% for the ADH3 1–1 genotype. Evidence of genotype-environment interaction was suggestive. This finding is opposite to that reported for a population in Puerto Rico, where the ADH3 1–1 genotype seemed more sensitive to ethanol exposure. In Greece, genetic variation at the CYP2E1 is almost entirely absent, with only 1 case and 1 control heterozygous for the variant. By contrast, in a population in France where an OC association was reported, the frequency of CYP2E1 heterozygotes was 5% in controls and 9% in OC cases. These findings illustrate the importance of replicating SNP associations both within and between different racial and ethnic groups and geographic regions [7].

Dietary factors also modify one's risk of cancer. The interaction of folate and alcohol consumption has been shown to have an antagonistic effect on the risk of oral cancer. Studies have demonstrated that increased intake of folate decreases the risk of oral cancer, while greater alcohol consumption has an opposite effect. However, what is poorly understood is the biological interaction of these two dietary factors in relation to carcinogenesis. A cohort study was conducted to quantify the effect of alcohol on the risk of oral cancer in different strata of folate intake. A cohort of 87,621 women in the Nurses' Health Study was followed up from 1980 to 2006, and 147 incident oral cancer cases were reported and confirmed. Data on alcohol intake and diet were obtained through self-reported food frequency questionnaires every 4 years. When compared with nondrinkers, the relative risk of cancer for alcohol drinkers were 0.59 for 0.1–14.9, 1.15 for 15–29.9, and 1.92 for ≥30 g/d. A significant interaction between alcohol and folate intakes was observed. The cancer risk for subjects with high alcohol (≥30 g/d) and low folate (<350 μg/d) intakes was significantly elevated as compared with nondrinkers with low folate intake. The risk associated with high alcohol intake (≥30 g/d) was reduced to 0.98 in the high-folate (≥350 μg/d) group as compared with nondrinkers with high folate intake. This study concluded that high alcohol intake is associated with significantly increased oral cancer risk, especially in women with low folate intake. A significant interaction between alcohol and folate intakes seems to affect oral cancer risk in women [100].

As the underlying mechanism of folate-alcohol interaction, it was hypothesized that cytochrome P450 2E1 (CYP2E1) and the family of aldehyde dehydrogenase 1 (ALDH1) enzymes may play a causal role in the occurrence of oral cancer. Chronic

and high alcohol use has been implicated in the induction of CYP2E1, which oxidizes ethanol to acetaldehyde. Acetaldehyde is a known carcinogen. As the first metabolite of ethanol, it has been shown to interfere with DNA methylation, synthesis and repair, as well as bind to protein and DNA to form stable adducts, which lead to the eventual formation of damaged DNA and cell proliferation. Studies using liver cells have demonstrated that S-adenosyl methionine (SAM), which is a product of folate metabolism, regulates the expression and catalytic activity of CYP2E1. As increased levels of folate lead to higher concentrations of SAM, SAM antagonizes the expression of CYP2E1, which results in decreased conversion of ethanol into acetaldehyde. Thus, the lower levels of acetaldehyde may lower risk of oral cancer. There are also two enzymes within the ALDH1 family that play an important role both in ethanol metabolism and the folate one-carbon pathway. The first, ALDH1A1, converts acetaldehyde into its non-carcinogenic byproduct, acetate, as part of the second step in the ethanol metabolism pathway. The second, ALDH1L1, also known as FDH, is required for DNA nucleotide biosynthesis, and is upregulated at high concentrations of folate. ALDH1L1 appears to be a chief regulator of cellular metabolism as it is strongly downregulated at certain physiological and pathological conditions, while its upregulation can produce drastic antiproliferative effects. ALDH1 has three known response elements that regulate gene expression (NF-Y, C/EBPβ, and RARα). On the other hand, it is also possible that folate interacts with one of these response elements to upregulate ALDH1A1 and ALDH1L1 expression in order to decrease acetaldehyde concentrations and promote DNA stability, thereby decreasing cancer susceptibility. Conducting future metabolic and biochemical human studies in order to understand this biological mechanism will serve to support evidence from epidemiologic studies, and ultimately promote the intake of folate to at-risk populations [101].

Zavras and his colleagues also found an interesting association between fruit consumption and risk of cancer [102]. In a prospective study, fruit and vegetable consumption and the incidence of OPL among 42,311 US men was conducted in the Health Professionals Follow-up Study. Diet was assessed every 4 years by food frequency questionnaires. The authors confirmed 207 cases of clinically or histopathologically diagnosed oral premalignant lesions occurring between 1986 and 2002. Significant inverse associations were observed with citrus fruits, citrus fruit juice, and vitamin-C-rich fruits and vegetables, indicating 30–40% lower risks with greater intakes (i.e., citrus fruit juice quintile 5 vs. quintile 1 relative risk ¼ 0.65). Inverse associations with fruits did not vary by smoking status and were stronger in analyses of baseline consumption, with a 10-year lag time to disease follow-up (quintile 5 vs. quintile 1 relative risk ¼ 0.41). No associations were observed with total vegetables or with b-carotene-rich or lycopene-rich fruits and vegetables. For current smokers, green leafy vegetables and b-carotene-rich fruits and vegetables showed significant linear trends of increased risk (one additional serving/day relative risk = 1.7). The risk of oral premalignant lesions was significantly reduced with higher consumption of fruits, particularly citrus fruits and juices, while no consistent associations were apparent for vegetables. Such findings of inverse associations with fruit but not vegetables are consistent with a recent meta-analysis of epidemiologic studies of oral cancer, in which the estimated odds ratio for increased fruit consumption was 0.53,

and vegetables had no apparent association with risk. Fruits were found to be significantly protective in many case–control studies of oral premalignancies and malignancies. Although citrus fruits in particular have not been evaluated often, they reduced risk of oral cancer by 50% in a study of 512 Italian male oral cancer patients (additional one serving/day) [102].

Another interesting study was conducted assessing association between terminalia catappa leaves and cancer risk. Terminalia catappa L. is a combretaceous plant broadly distributed on tropical and subtropical beaches. The leaves, bark and fruit of T. catappa have been used for treating dermatitis and for antipyretic and homeostatic purposes in Asian countries. It has been shown that the water extracts of T. catappa leaves could effectively suppress CCl4-induced hepatotoxicity and bleomycin-induced genotoxicity of Chinese hamster ovary cells. Moreover, ethanol extracts of T. catappa leaves (TCE) contains more active components and stronger anti-inflammatory activity, as compared to that of water extracts [103]. As a potential and popular folk medicine, TCE have been proven to possess various biological benefits including anti-cancer activities. Zavras and his colleagues conducted a study in which SCC-4 oral cancer cells were subjected to a treatment with ethanol extracts of TCE and then analyzed for the effect of TCE on the migration and invasion. TCE treatment significantly inhibited the cell migration/invasion capacities of SCC-4 cells. Furthermore, activities and protein levels of MMP-2, MMP-9 and u-PA were all inhibited by TCE. Further studies indicated that TCE may inhibit phosphorylation of ERK1/2, JNK1/2 and Akt while the expression of nuclear protein NF-jB, c-Jun and c-Fos were inhibited as well. DNA-binding activity with AP-1 and NF-αB was also decreased by TCE. This study concluded that TCE may serve as a powerful chemopreventive agent against oral cancer metastasis [103].

31.7 Conclusion

Various studies have demonstrated that genetic susceptibility is involved in the development of head and neck cancer. While there is a significant body of literature on certain markers such as ALDH, ERCC5 and IGF2R, there is currently no clinical tool that utilizes genetic data for risk assessment or diagnosis. As personalized medicine improves, an opportunity exist to develop advanced computational methods that integrate data on behavioral risk factors and environmental exposures with data on genetic variability and epigenetics to personalize the science of head and neck cancer risk assessment and prevention.

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Chapter 32
Biomarkers for Head and Neck Cancer

David Crowe

Contents

Abstract Head and neck squamous cell carcinomas (HNSCC) account for more than 500,000 new cancer cases worldwide each year. Approximately 250,000 people in the United States live with head and neck cancer. In recent years, the incidence of HNSCC has been increasing among individuals without the typical risk factors of tobacco use and age. The 5 year survival rate for HNSCC is low and has not improved in recent years despite the availability of new targeted therapies. Tobacco carcinogens and their

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metabolites can directly damage DNA, inducing DNA repair activity. Defective DNA repair can lead to mutations, genomic instability, and altered gene expression leading to cellular transformation. Molecular changes in HNSCC lead to accumulation of genetic defects and clonal expansion. This review summarizes recent results in HNSCC biomarker research. We review the literature on the tumor suppressor p53 as a biomarker for HNSCC. This review also describes published studies on cytokines in HNSCC. We also review the roles of growth factor receptors as biomarkers in HNSCC. The literature on matrix metalloproteinases as HNSCC biomarkers will be reviewed. The use of DNA methylation as biomarkers will also be examined. Finally, we summarize literature on high throughput methods and other gene products which predict cancer risk, progression, and survival. This review provides a valuable resource for design of future translational and clinical studies aimed at prevention, diagnosis, and treatment of HNSCC.

Keywords Microarray • Proteomics • DNA methylation • Metalloproteinases • Receptors • Growth factors • Cytokines • Tumor suppressor

Abbreviations

AP-1	activator protein 1
DNA	deoxyribonucleic acid
EGFR	epidermal growth factor receptor
ELISA	enzyme linked immunosorbent assay
HNSCC	head and neck squamous cell carcinoma
Grb2	growth factor receptor bound 2
HPV	human papillomavirus
IL	interleukin
JAK	Janus kinase
MMP	matrix metalloproteinase
PCNA	proliferating cell nuclear antigen
PIAS	protein inhibitor of activated STAT
qRT-PCR	quantitative reverse transcription polymerase chain reaction
RANTES	regulated on activation normal T cell expressed and secreted
RTK	receptor tyrosine kinase
SHP	SH2 containing phosphatases
SOCS	suppressor of cytokine signaling
STAT	signal transducer and activator of transcription
TIMP	tissue inhibitor of metalloproteinase

32.1 Introduction

Head and neck squamous cell carcinomas (HNSCC) account for more than 500,000 new cancer cases worldwide each year [1]. Approximately 250,000 people in the United States live with head and neck cancer. In recent years, the

incidence of HNSCC has been increasing among individuals without the typical risk factors of tobacco use and age [2]. Treatment of early stage HNSCC usually involves surgical removal of the tumor with regional lymph node dissection and adjuvant radiation (for review see Ref. [3]). Lymph node metastasis is the most important prognostic factor for HNSCC. Late stage tumors may require neoadjuvant chemoradiation followed by surgery. The 5 year survival rate for HNSCC is low and has not improved in recent years despite the availability of new targeted therapies.

Tobacco carcinogens are primarily responsible for most cases of HNSCC [4]. Tobacco carcinogens and their metabolites can directly damage DNA, inducing DNA repair activity [5]. Defective DNA repair can lead to mutations, genomic instability, and altered gene expression leading to cellular transformation. Molecular changes in HNSCC lead to accumulation of genetic defects and clonal expansion [6]. The major issues in clinical management of HNSCC are tumor recurrence, second primary cancers, and metastatic spread to cervical lymph nodes (for review see Ref. [7]). Detection of genetic changes that predict the development, progression, and clinical outcomes of HNSCC is critical to understanding, prevention, and treatment of this disease. This review summarizes recent results in HNSCC biomarker research. We review the extensive literature on the tumor suppressor p53 as a biomarker for HNSCC. This review also describes published studies on cytokines in HNSCC. We also review the roles of growth factor receptors as biomarkers in HNSCC. The literature on matrix metalloproteinases as HNSCC biomarkers will be reviewed. The use of DNA methylation as biomarkers will also be examined. Finally, we summarize literature on high throughput methods and other gene products which predict cancer risk, progression, and survival. This review provides a valuable resource for design of future translational and clinical studies aimed at prevention, diagnosis, and treatment of HNSCC.

32.2 p53 as a Biomarker for HNSCC

32.2.1 The p53 Tumor Suppressor Protein

p53 is an important tumor suppressor which can block cell cycle progression and induce programmed cell death (for review see Ref. [8]). p53 activation is induced by numerous stress signals such as genotoxic damage, oncogenes, and hypoxia. p53 functions by regulating expression of target genes that halt cell division or induce apoptosis (Fig. 32.1). For example, p53 activates expression of the cyclin dependent kinase inhibitor p21 [9]. This allows cells to survive until damage has been repaired or stress removed. p53 can also induce irreversible cell cycle arrest known as senescence, which keeps precancerous lesions from proliferating. Even in established tumors, reactivation of p53 can induce regression [10]. p53 can also induce autophagy, a lysosomal mediated digestion of cellular components [11].

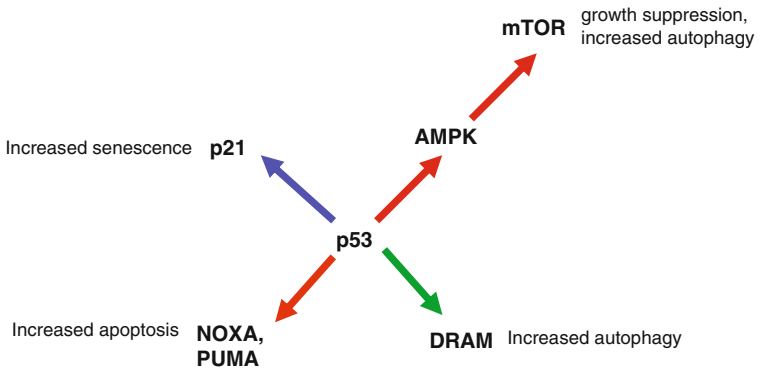

Fig. 32.1 Roles of p53 in head and neck cancer. p53 mediated control of cell survival, proliferation, and death is primarily mediated by regulation of p53 target genes in the nucleus. These p53 mediated responses contribute to tumor suppression. Some of the target genes and pathways by which p53 controls tumor suppression are shown

32.2.2 Inhibition of p53 Function by Human Papillomavirus

p53 is the most commonly mutated gene in human cancers (for review see Ref. [12]). Mutant p53 is frequently defective for sequence specific DNA binding and transactivation of target genes [13]. p53 function can also be compromised by other mechanisms such as interaction with the human papillomavirus (HPV) E6 protein. This interaction results in ubiquitin dependent proteolysis of p53. HPV-16 E6 and E7 seropositivity has been evaluated as a risk marker for head and neck cancer [14]. The study included 204 HNSCC cases and 326 controls which were evaluated for HPV in sera and tumor tissue using enzyme linked immunosorbent assay and polymerase chain reaction. HPV-16 was detected in 33.8% of cancer cases in 22.4% of controls. E6 protein was detected in 20.6% of HNSCC cases and 0.9% of controls. E7 was detected in 18.6% of cancers and 0.6% of controls. HPV-16 DNA was detected in 26.1% of tumors. The adjusted risk of HNSCC was elevated among seropositive patients (odds ratios of 1.7–37.5). E6 and E7 positivity was associated with stage, grade, and nodal status. Anti-E6 or E7 antibodies were detected in 74% of HPV-16 positive cases but only 5% of negative tumors. A subsequent study sequenced DNA from 301 HNSCC patients for HPV types [15]. 27% of HNSCC cases were positive for high risk HPV DNA types, and p16 was expressed in 35% of tumors. p16 positive tumors were significantly associated with high risk HPV. HNSCC that did not express p16 was associated with decreased survival and increased recurrence. HPV negative HNSCC exhibited decreased survival and increased recurrence. This group also examined p53 expression and HPV status in 294 cases of HNSCC [16]. p53 overexpression was detected in 48% of HNSCC, and high risk HPV was found in 27% of cases. p53 positive cancers and HPV negative tumors were associated with decreased survival. When analyzed together, p53 positive/HPV negative HNSCC exhibited significantly worse disease free survival. Analysis of p16 and p53 protein expression in addition to HPV status was subsequently performed in 237 HNSCC cases [17]. p16 and p53 were

expressed in 38 and 48% of cancers. High risk HPV was detected in 28% of tumors. p53 overexpression and lack of high risk HPV were associated with decreased survival, but no correlation with p16 expression was noted. p16 negative/p53 positive/HPV negative tumors exhibited decreased survival. These studies indicate that HPV is an important regulator of p53 function in HNSCC.

32.2.3 p53 Expression in Head and Neck Cancer

p53 mutations resulting from tobacco carcinogens are among the most common genetic changes in head and neck cancer [18]. Some p53 mutants exhibit extended protein half life, resulting in increased expression in HNSCC. An early study examined p53 expression 201 pre-invasive, 209 invasive HNSCC, and 102 normal epithelia samples [19]. Histologically normal epithelium exhibited 5% p53 positive cells, mild dysplasia 28% positive cells, moderate dysplasia 47% positive cells, and severe dysplasia 54% positive cells. A subsequent study found 70% of leukoplakia and HNSCC cases overexpressed p53 protein compared to 5% of normal mucosal samples [20]. p53 and Ki67 expression correlated with histopathologic stage in HNSCC. In cases of leukoplakia, increased p53 expression was associated with non-proliferative features. Another study investigated p53 expression in tumor distant epithelia in 105 cases of HNSCC [21]. p53 overexpression was detected in tumor distant epithelia in 46.7% of cases and was independent of p53 protein status in the primary tumor. Mucosal p53 expression was not associated with recurrence, lymph node or distant metastasis, and survival. However, mucosal p53 expression was associated with increased incidence of second primary tumors. p53 mutation has been associated with acquisition of invasive phenotype [22]. A recent study used p53 immunohistochemistry and fluorescence in situ hybridization to identify microinvasion in HNSCC [23]. Ninety-six percent of 26 archival HNSCC cases showed p53 positive cells at the excision margins. FISH results indicated that 48.9% of HNSCC cases were monoploid for p53 probe signal, 41% were diploid, and 10% were polyploid. There was a statistically significant correlation between p53 expression and ploidy. p53 mutations were associated with high risk of cisplatin and fluorouracil based treatment failure [24]. Additional studies demonstrated that p53 mutations also correlated with greater risk of treatment failure following radiotherapy [25–28]. These studies indicate that p53 mutations dramatically alter p53 function in HNSCC.

32.3 Cytokine Biomarker Studies

32.3.1 The Cytokine Signaling Pathway

Cytokines are secreted proteins that regulate many biological functions by binding to transmembrane cell surface receptors (for review see Ref. [29]). These receptors oligomerize on ligand binding resulting in phosphorylation and activation of associated Janus kinase (JAK) family members (Fig. 32.2). JAKs can phosphorylate tyrosine residues in the cytoplasmic domain of the receptors. This

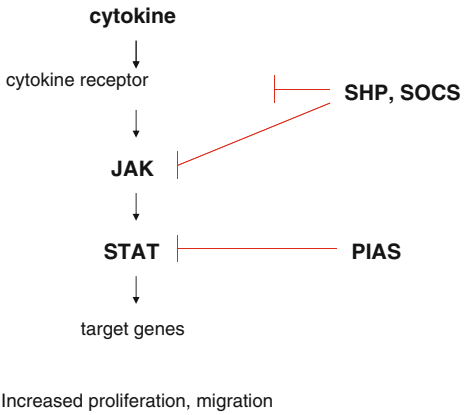

Fig. 32.2 The cytokine signal transduction pathway in head and neck cancer. Cytokines bind to specific receptors on the plasma membrane, resulting in their dimerization and activation of receptor associated JAK proteins. Activated JAKs phosphorylate the receptor which creates binding sites for STAT proteins which are also phosphorylated by JAKs. Phosphorylated STAT proteins can dimerize and translocate to the nucleus to induce transcription of many cytokine regulated genes. SHP, SOCS, and PIAS gene products are inhibitors of cytokine signaling

modification produces recognition sites for signaling proteins with Src homology 2 (SH2) or other phosphotyrosine binding domains. The signal transducer and activator of transcription (STAT) family are SH2 domain transcription factors that are phosphorylated by JAK, enabling STAT proteins to dimerize, enter the nucleus, and regulate target gene transcription (for review see Ref. [30]). Dysregulated cytokine signaling can lead to tumorigenesis; therefore these pathways are controlled at multiple points. SH2 containing phosphatases (SHP) are constitutively expressed and suppress signal transduction by JAK and receptor dephosphorylation. Another gene family known as protein inhibitors of activated STATs (PIAS) is constitutively expressed and inhibits signal transduction by repressing STAT activation. Additionally the suppressor of cytokine signaling (SOCS) family members recognize both cytokine receptors and JAKs. SOCS proteins inhibit cytokine signaling by interference with receptors and JAKs, and by targeting the receptor complex for proteasomal degradation. Head and neck cancer cells must overcome these negative regulatory pathways in order to exploit cytokine signaling for proliferation and invasion.

32.3.2 Cytokine Expression in Head and Neck Cancer

Detection of cytokine biomarkers in saliva of head and neck cancer patients has been an important area of research. Levels of interleukin 1β, IL-6, and IL-8 were measured by ELISA using whole saliva samples from 19 patients with oral cancer

and 20 healthy individuals [31]. Expression of these cytokines was higher in patients with oral cancer than the control individuals, with IL-6 expression significantly higher. A longitudinal prospective study measured pretreatment IL-6 levels in serum of HNSCC patients and correlated these levels with tumor recurrence and survival in 444 untreated patients [32]. Samples were controlled for age, gender, smoking status, cancer site and stage, and comorbidities. Median serum IL-6 level was 13 pg/ml with 2 year recurrence rate of 35%, and 2 year death rate of 26%. Serum IL-6 levels independently predicted recurrence and poor survival in HNSCC patients. A multiplexed analysis also was performed using saliva from HNSCC patients [33]. Mean levels of IL-8 and IL-1β were significantly higher in HNSCC patients, although there was considerable variation between samples. A larger study examined expression of 60 cytokines, chemokines, and other factors in serum from 116 head and neck cancer patients before treatment, 103 successfully treated HNSCC patients, and 117 at risk individuals without cancer [34]. A panel of 25 biomarkers including IL-8, interferon α, interferon γ, interferon inducible protein 10, regulated on activation normal T cell expressed and secreted (RANTES), macrophage inflammatory protein 1α, IL-7, IL-17, IL-1 receptor α, IL-2 receptor, and granulocyte colony stimulating factor was most able to discriminate individuals with active disease. Sensitivity of this panel was 84% with specificity of 98% using a cross validation serum set. A subsequent study identified the chemokine CXCL-9 as a differentially expressed gene in HNSCC [35]. Interferon signaling was identified as one of the most significantly altered pathways in HNSCC [36]. This study compared microdissected HNSCC to adjacent non-tumor epithelia, identifying more than 1,200 unique proteins as differentially expressed in tumor cells. Expression of 80 proteins was classified as dysregulated, with 20% of upregulated proteins belonging to the interferon signaling pathway. These studies demonstrate the importance of deregulated cytokine signaling in progression of HNSCC.

32.4 Receptor Biomarker Studies

32.4.1 Growth Factor Receptor Signaling Pathways

Receptor tyrosine kinases (RTK) are key regulators of diverse cellular processes such as proliferation, differentiation, migration, and survival (for review see Ref. [37]). RTK have similar molecular structure, including extracellular ligand binding domains, a single transmembrane domain, and a cytoplasmic region that contains the protein tyrosine kinase domain. In HNSCC, the epidermal growth factor receptor (EGFR) is frequently overexpressed and contributes to proliferation, survival, and invasion (Fig. 32.3). Activating ligands such as epidermal growth factor (EGF) and transforming growth factor α do not make a direct contribution to receptor dimerization. EGFR does not require transphosphorylation of its activation loop to transduce the signal. The EGFR tyrosine kinase domain forms an asymmetric dimer in which one domain

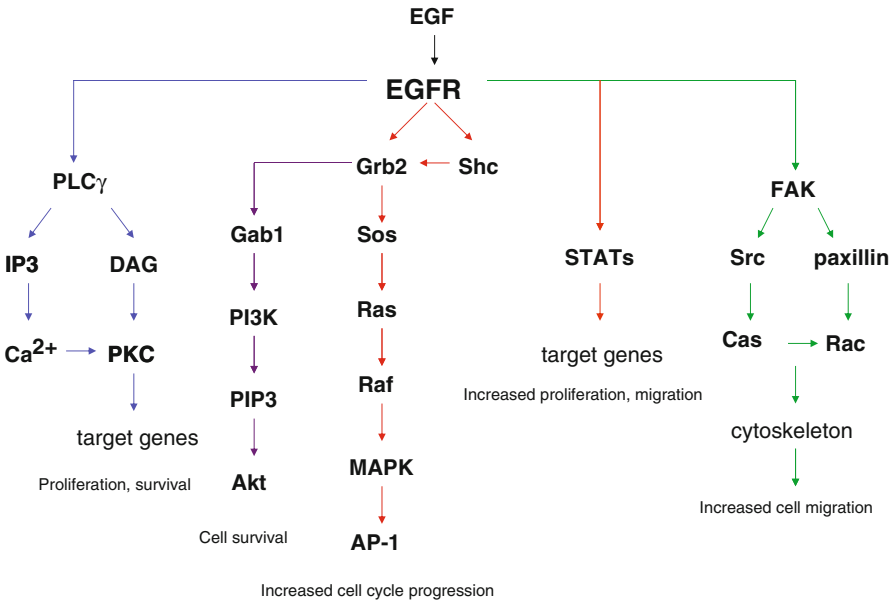

Fig. 32.3 Receptor tyrosine kinase signaling in head and neck cancer. Phosphorylated receptor tyrosine kinases bind docking proteins such as Grb2 which associates with other adaptors such as Shc. These protein interactions activate a variety of pathways such as mitogen activated protein kinase (MAPK), Src, PI3K, PLCγ, STAT, FAK, and Rac to transduce the signals to the nucleus via transcription factors such as AP-1 or via the cytoskeleton to induce cell cycle, survival, and migration related genes

contacts a second that disrupts autoinhibitory interactions observed in the monomer. EGFR can be activated without ligand binding when the monomeric autoinhibitory interactions are disrupted by oncogenic mutations [38]. Receptor activation promotes formation of downstream signaling complexes which transduce the signal to the nucleus. These signaling pathways include Grb2, Shc, Src, Sos, Ras, and the mitogen activated protein kinases. In the nucleus, EGFR signaling induces c-fos which activates AP-1 target genes. Activated EGFR is internalized primarily by clathrin mediated endocytosis, which provides for signaling inhibition. Monoclonal antibodies that bind to the extracellular domain of EGFR have been used to treat HNSCC [39].

32.4.2 Epidermal Growth Factor Receptor Expression in Head and Neck Cancer

EGFR induces expression of proliferation markers such as proliferating cell nuclear antigen (PCNA; [40]). PCNA expression was analyzed by immunohistochemistry in 33 HNSCC cases and adjacent premalignant lesions compared to control samples. Epithelium adjacent to tumors had fourfold to sixfold higher proliferative

activity than controls. PCNA expression increased as tissues progressed from normal to hyperplasia to dysplasia to carcinoma. PCNA expression was observed not only in the basal layer but also in suprabasal cells. EGFR expression was analyzed by immunohistochemistry in 36 HNSCC cases, premalignant lesions, and normal mucosa [41]. Relative staining intensity of EGFR in epithelia adjacent to tumors was twofold higher than in normal controls. EGFR expression was elevated in hyperplastic and dysplastic epithelia and tumors. Expression of the EGFR family member ErbB2 was shown to be upregulated in 69 HNSCC patients [42]. Early local tumor recurrence was associated with strong intracytoplasmic staining for ErbB2. These studies indicate that EGFR signaling are important biomarkers for HNSCC.

32.5 Matrix Metalloproteinase Biomarker Studies

Matrix metalloproteinases (MMP) have been associated with invasion and metastasis in HNSCC. Expression of MMP-2 and MMP-9 was examined in 154 HNSCC patients by immunohistochemistry [43]. Expression of MMP-2 and MMP-9 was found in over 85% of HNSCC cases. Increased MMP-2 expression was associated with greater tumor size. MMP-2 was also correlated with tumor metastasis. MMP-1 overexpression has also been significantly associated with HNSCC [35]. The role of MMP in predicting HNSCC response to chemoradiation was analyzed in 23 patients [44]. MMP-9 expression was significantly associated with objective tumor response. Serum samples collected prospectively from 143 HNSCC patients revealed underexpression of serine protease inhibitor C-1 and serine/cysteine protease inhibitor clade G member 1 [45]. Underexpression of these protease inhibitors was associated with tumor recurrence. MMP expression in saliva has also been evaluated as a potential HNSCC biomarker. Nineteen tongue cancer patients were evaluated for eight salivary biomarkers [46]. MMP-9 expression was significantly increased in saliva from HNSCC patients with high sensitivity and specificity. These results indicate that MMP overexpression is a reliable biomarker for HNSCC.

32.6 Gene Methylation as a Biomarker for Head and Neck Cancer

Methylation of CpG islands in cancer related genes may serve as epigenetic biomarkers for HNSCC diagnosis and prognosis. Eleven genes were prospectively analyzed by methylation specific PCR in primary tumors, histologically normal adjacent mucosa, and saliva from 90 patients at diagnosis and during follow up and 30 saliva specimens from control patients with nonmalignant head and neck pathology [47]. Five additional genes were analyzed on 50 tumors

of the series. Methylation of TIMP3, ECAD, p16, MGMT, DAPK, and RASSF1 was most frequently observed in tumors and paired saliva samples were analyzed at diagnosis. At least one of the six genes was methylated in 75% of the samples. The methylation profile was similar in newly diagnosed and second primary cancers. Aberrant methylation was not associated with worse prognosis. Ninety percent of normal adjacent mucosa and all control saliva samples were negative. Twenty-two patients were followed after treatment. Abnormal methylation was detectable in saliva of five patients before signs of relapse. Saliva samples were negative in the other 17 patients with 16 in remission. A separate study demonstrated p16 promoter hyerpmethylation was associated with shorter disease free survival [48]. A subsequent study analyzed promoter hypermethylation status of MGMT and CDH1 genes by methylation specific PCR in 76 HNSCC cases and 57 normal tissues [49]. MGMT and CDH1 mRNA were analyzed by qRT-PCR. Methylation and mRNA expression profiles were associated with clinical data. Aberrant promoter hypermethylation of CDH1 and MGMT was detected in 61.8 and 73.7% of HNSCC cases with significant differences between tumors and controls for MGMT. CDH1 promoter methylation in tumors and controls was not statistically significant. The mRNA expression levels showed statistically significant differences between tumors and controls for the MGMT gene. CDH1 differences were not statistically significant. These results indicate that specific changes in gene methylation are important biomarkers of HNSCC.

32.7 Microarray Based Biomarker Studies in Head and Neck Cancer

To improve the diagnostic utility of potential biomarkers, HNSCC cases have been analyzed by DNA microarray to determine global changes in gene expression. In one study, 13 paired HNSCC and normal mucosal samples were subjected to microarray analysis [50]. Gene families upregulated in HNSCC included extracellular matrix (collagen, laminin), matrix proteolysis (MMPs, plasminogen activator of urokinase), cell migration (snail homolog 2, myosin, meltrin α, lysyl oxidase like 2). A 25 gene predictor was developed that could distinguish normal from tumor specimens with 87% accuracy. A subsequent study used similar methodology to distinguish HNSCC from normal tissue using 119 tumor samples and 35 controls [51]. The best model included laminin γ2 chain, collagen type IV α1 chain, collagen type I α1 chain, and peptidyl arginine deiminase type 1. These results were validated using an internal independent testing set of 48 HNSCC cases and ten controls with sensitivity and specificity above 95%. The model also was able to distinguish 17 oral epithelial dysplastic lesions from 35 control samples. A separate study by this group validated six potential biomarkers identified by microarray analysis [52]. Quantitative RT-PCR revealed upregulation of CDH11, SPARC, POSTN, and TNC with decreased expression of TGM3. In tissue microarray analysis, SPARC, POSTN,

and TNC exhibited increased protein expression in tumor tissue. TGM3 was found in control tissue and was significantly downregulated in cancer cells. A subsequent study used microarray analysis to predict the response of HNSCC lines to radiotherapy [53]. Fourteen genes were identified (CEBPA, CEBPB, CTNNB1, FN1, MYC, MYCN, PLAU, SDC4, SERPINE1, SP1, TAF4B, THBS1, TP53, VLDLR). Four of these genes were examined by qRT-PCR in a panel of 29 HNSCC lines. FN1 was associated with intrinsic radioresistance, although the mechanism for this association was not identified. These studies demonstrate the utility of using DNA microarrays to identify potential HNSCC biomarkers.

32.8 Proteomic Biomarker Studies in Head and Neck Cancer

Similar to DNA microarray analysis, proteomic techniques have been used to identify differentially expressed proteins in HNSCC. In one study proteomics and qRT-PCR were used to identify overexpressed gene products in HNSCC [54]. Forty-one proteins were identified as overexpressed in HNSCC including αB crystalline, tropomyosin 2, myosin light chain 1, heat shock protein 27, stratifin, thioredoxin dependent peroxide reductase, flavin reductase, vimentin, rho GDP dissociation inhibitor 2, glutathione S transferase π, and superoxide dismutase. Proteomic analysis was used to compare protein expression between matched HNSCC and adjacent non-tumor mucosa [55]. Rho GDP dissociation inhibitor α was differentially expressed in HNSCC. Expression of this gene was selectively upregulated in 78 HNSCC sections which correlated with tumor size and poor overall survival. A subsequent study used mass spectrometry based proteomics of saliva samples to distinguish premalignant lesions and HNSCC in eight samples [56]. Increased myosin and actin expression was detected in HNSCC compared to premalignant oral lesions. Sensitivity was 67–100% and specificity was 75–83% using a validation set of 12 cancer and 12 premalignant lesions. Another study also analyzed pooled saliva samples from patients with HNSCC or control subjects using two dimensional gel electrophoresis and matrix assisted laser desorption/ionization time of flight mass spectrometry [57]. Potential biomarkers were analyzed by western blotting and ELISA. Increased transferrin expression correlated with tumor size and stage. Salivary transferrin was highly specific, sensitive, and accurate for early detection of oral cancer by ELISA. A separate study used global proteomic analysis to compare protein expression in HNSCC lines [58]. Eleven candidate proteins were differentially expressed in the HNSCC lines. Heat shock protein 90 kD β member 1, protein disulfide isomerase precursor, vimentin, tubulin β 2C chain, 78 kD glucose regulated protein precursor (GRP78), and annexin A2 were increased in low grade HNSCC lines. Heat shock protein 90 β, annexin A1, stress induced phosphoprotein 1, elongation factor 2, and integrin α3 precursor were increased in high grade HNSCC. GRP78 expression was confirmed by western blotting and immunohistochemical staining of clinical HNSCC samples showed that GRP78 expression was significantly associated with advanced tumor stage and lymph node metastasis. These studies demonstrate the utility of proteomics technologies in identifying biomarkers for HNSCC.

32.9 Additional Head and Neck Cancer Biomarkers

Studies have quantitated nitrate and nitrite levels in urine as screening markers for HNSCC [59]. Nicotine and cotinine levels were analyzed by high pressure liquid chromatography in 90 healthy individuals and 60 tobacco users. Urinary nicotine and cotinine levels were significantly higher in patients who used tobacco and those diagnosed with HNSCC. A subsequent hospital based case control study evaluated DNA repair capacity in cultured T lymphocytes from 744 HNSCC patients and 753 age, gender, and ethnicity matched healthy controls [60]. Patients with HNSCC had significantly lower DNA repair capacity which accounted for twofold increased risk for HNSCC. There was no significant correlation of DNA repair capacity with tumor stage. A variety of additional gene products have been evaluated as potential biomarkers of HNSCC. Osteopontin levels were examined in serum of HNSCC patients by ELISA and correlated with clinical features [61]. Mean serum osteopontin levels were significantly higher in HNSCC patients than in control subjects (99.5 vs. 55.3 ng/ml). Osteopontin levels were significantly high in patients with advanced stage HNSCC than in those with early stage disease. A subsequent study identified increased haptoglobin expression as a biomarker for HNSCC [62]. Human plasma samples were collected and candidate biomarkers were evaluated by ELISA. Significantly increased haptoglobin levels were detected in serum from 52 HNSCC patients. A retrospective study of HNSCC patients treated with radiotherapy assessed nine biomarkers by immunohistochemistry to predict treatment response [63]. Expression of carbonic anhydrase nine and major vault protein significantly correlated with poor locoregional control. Expression of signaling proteins in the Akt/mTOR pathway has been evaluated in HNSCC compared to normal control mucosa by western blot and immunohistochemistry [64]. Expression of phosphorylated Akt and phosphorylated mTor were significantly higher in HNSCC. Phosphorylated mTor expression was 82% sensitive and 100% specific in differentiating HNSCC from normal mucosa. Another study analyzed ΔNp63 expression in 152 patients with oral preneoplastic lesions [65]. ΔNp63 expression was detected in 27% of patients. δNp63 expression was significantly associated with increased risk of HNSCC (more than threefold higher risk). Another study examined podoplanin and ATP binding cassette G2 subfamily (ABCG2) in 119 patients with oral lichen planus [66]. Podoplanin and ABCG2 expression was observed in 43.6 and 20.9% of cases respectively. Podoplanin and ABCG2 expression was associated with significantly increased risk of HNSCC in oral lichen planus patients. Overexpression of both markers resulted in greater risk of HNSCC. A separate study identified downregulation of tetranectin in serum and saliva samples from HNSCC patients as a risk factor for metastatic disease [67]. Phosphodiesterase levels in serum of HNSCC patients and healthy controls were examined by another study [68]. Increased serum phosphodiesterase levels were associated with advanced HNSCC. Serum biomarkers to predict response to cetuximab containing chemotherapy were assessed by another study [69]. Levels of analytes including MCP1c, IP-10, leptin, IL-5, eotaxin, IL-6,

G-CSF, and CXCL5 changed significantly following chemotherapy. VEGF and IL-6 levels were associated with tumor response and progression free survival.

32.10 Perspectives and Future Directions

Genomic characterization of head and neck cancer has made great strides in detection and revealing new molecular therapeutic targets. These methods have revealed changes in signaling pathways that contribute to the development and progression of head and neck cancer. In addition to analysis of cancer cell pathways, serum and saliva biomarkers have proved important in tumor detection and monitoring of disease progression. Since prognosis and treatment often depends on early diagnosis, determination of these biomarkers is key to improving patient outcomes with fewer therapeutic side effects.

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Chapter 33
The Role of MicroRNA in Head and Neck Cancer

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Abstract Head and neck/oral cancer (HNOC) is the sixth most common cancer in the world. Despite the improvements in surgery, radiotherapy and chemotherapy, the prognosis for HNSCC patients has not significantly improved for the past three decades. Improvement in patient survival requires a better understanding of the disease progression so that HNOC can be detected early in the disease process and targeted with appropriate therapeutic interventions. While substantial advances have been made in defining genomic alterations associated with HNOC, most studies are focused on protein coding genes. Knowledge on genomic aberrations associated with non-coding genes and their contributions to the onset and propagation of HNOC is relatively limited. In this chapter, we will provide an introduction to the different types of non-coding genes and their biological functions in relationship to tumorigenesis. We will then focus our discussion to small non-coding genes (e.g., microRNA) by highlighting the recent advances in small RNA profiling technologies, and surveying the recent studies aimed at deciphering the microRNA signatures of HNOC. The functional relevance of the identified microRNA alterations associated HNOC will be discussed in detail.

Keywords Non-coding RNA • MicroRNA • Long ncRNA • Small ncRNA • Profiling technologies

33.1 Introduction

33.1.1 Head and Neck/Oral Cancer

Head and neck/oral cancer (HNOC) is the sixth most frequent cancer worldwide, accounting for 4% of cancers in men and 2% of cancers in women [1]. Over 90% of oral cancers are classified as oral squamous cell carcinoma (OSCC),

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a cancer that arises from the mucosal epithelium lining the oral cavity. According to the American Cancer Society [2–10], while overall new cancer cases in the US increased about 20% since 2003, the new cases for oral cancer increased over 40%. Furthermore, while deaths associated with all cancers increased slightly (2.8%) since 2003, the deaths associated with oral cancer increased by about 10%. Worldwide the problem is even worse, with over 263,000 new cases being diagnosed each year. In some parts of the world, such as South-Central Asia, home to one fifth of the world's population, oral cancer is a major health problem (the second most common cancer and second leading cause of cancer death in males in South-Central Asia, Global Cancer Facts & Figures, 2nd Edition; ACS, 2011).

HNOC has traditionally been causally associated with heavy smoking and alcohol abuse [11]. Of these, tobacco smoking is well established as a dominant risk factor for OSCC, and this risk is correlated with the intensity and duration of smoking. Nevertheless, the increased incidence of HNOC in nonsmokers and nondrinking patients in recent years suggests that other environmental, immunologic, or genetic factors also contribute to the pathogenesis of HNOC [12]. Human papillomavirus (HPV) is the major etiologic factor in the development of cervical cancer, and has been studied extensively [13]. Results of recent molecular and epidemiologic studies suggested that HPV is also an important etiologic factor in a subset of HNOC [14], particularly those that develop in pharynx, such as oropharyngeal and tonsillar cancers.

33.1.2 Non-Coding RNA: A New Type of Gene

Like other human cancers, HNOC is a disease involving multi-step and multi-gene dynamic changes in the genome. However, most studies on the cancer genome have focused heavily on protein-coding genes, and our knowledge of alterations of the noncoding sequences in cancer is limited. It is worth noting that more than 98% of the human genome does not encode proteins, including most sequences within introns and most intergenic DNA [15]. Many of these noncoding sequences have well-established biological functions in transcription and translation regulation of protein-coding genes, such as transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs). Recently, the biomedical fields have manifested a rapidly expanding interest in a number of newly identified groups of non-coding RNA (ncRNAs) genes (e.g., microRNAs and siRNAs). These ncRNAs play critical roles in various biological functions linked to development and differentiation. Importantly, majority of ncRNAs are expressed in a spatio-temporal manner and often exhibit precise sub-cellular localization. These observations lend support to the contention that transcription of the noncoding portion of the genome contributes to the evolution of complex organisms. Based on their size, ncRNAs can be classified as small and long ncRNAs.

33.1.2.1 Long Non-coding RNA

Long ncRNAs range in size from 300 nucleotides to over several hundred Kb. Long ncRNAs were once thought to be restricted to "housekeeping" functions such as DNA replication, post transcriptional processing and protein synthesis. However, recent studies revealed a much broader functional repertoire of long ncRNAs beyond housekeeping functions, including X chromosome inactivation [16, 17], genomic imprinting [18], telomere [19] and centromere organization [20, 21], and nuclear trafficking [22].

The essential roles of long ncRNAs have been implicated in many developmental events [23]. For example, long ncRNA TUG1 is required for the proper formation of the retina [24], and long ncRNA PINC is involved in the regulation of cell survival and cell cycle progression during mammary gland development [25]. A number of recent studies have focused on the roles of long ncRNAs in various diseases, including cancer [26], and some of the long ncRNAs may serve as biomarkers of cancer detection. For example, de Kok et al., showed that long ncRNA DD3 can be used as a biomarker to detect prostate tumors with high sensitivity and specificity [27].

33.1.2.2 Small Non-coding RNA

Small non-coding RNAs (sncRNAs) are transcripts of fewer than 300 nucleotides that are often involved in a variety of biological functions including direct participation in RNA processing and degradation, and indirect participation in protein synthesis and gene regulation. Because type II RNA polymerases (Pol-II) are inefficient in generating RNAs of this size, the sncRNAs are either transcribed by type III RNA polymerases (Pol-III) or indirectly processed from a large transcript of Pol-II. The following sections provide a general overview of different types of sncRNA and their biological functions.

Transfer RNA

The most prominent example of sncRNA is transfer RNA (tRNA). Transfer RNA is an adaptor molecule composed of RNA, typically 73–93 nucleotides in length, which is involved in translation (i.e., transferring a specific amino acid to a growing polypeptide chain at the ribosomal site of protein synthesis). During this process, tRNAs are delivered to the ribosome by proteins called elongation factors (EF-Tu in bacteria, eEF-1 in eukaryotes), which aid in decoding the message RNA (mRNA) codon sequence. Once delivered, a tRNA already bound to the ribosome transfers the growing polypeptide chain from its 3′ end to the amino acid attached to the 3′ end of the newly-delivered tRNA, a reaction catalyzed by the ribosome.

Small Nucleolar RNA

Small nucleolar RNAs (snoRNAs) are a group of evolutionarily ancient noncoding RNAs. They guide chemical modifications of other RNAs, such as ribosomal RNAs (rRNAs), tRNAs and small nuclear RNAs. There are two major types of RNA modification (methylation and pseudouridylation), which are directed by two different types of snoRNAs, the C/D box snoRNAs which are associated with methylation, and the H/ACA box snoRNAs which are associated with pseudouridylation. Each snoRNA molecule forms an RNA/protein complex with at least four proteins, known as a small nucleolar ribonucleoprotein (snoRNP), to carry out the RNA modification.

Small Nuclear RNA

Small nuclear RNAs (snRNAs) are a class of small RNA molecules that are found within the nucleus of eukaryotic cells. They form RNA/protein complexes known as small nuclear ribonucleoproteins (snRNPs) with specific proteins. snRNPs are involved in a number of essential biological processes such as RNA splicing, regulation of transcription factors (i.e., 7SK RNA) or RNA polymerase II (i.e., B2 RNA), and maintaining telomeres.

Small Interfering RNA

The RNA interference (RNAi) pathway was first described in C. elegans in 1998. It was soon realized that RNAi is conserved in variety of organisms and is a major regulatory mechanism in eukaryotic gene expression. Two types of sncRNAs molecules – microRNA and small interfering RNA (siRNA) – participate in RNAi-mediated gene silencing. SiRNAs are double stranded RNA molecules 20–25 nucleotides in length. Each siRNA is unwound into two single-stranded RNAs, namely the passenger strand and the guiding strand. The passenger strand is degraded, while the guiding strand is incorporated into the RNA-induced silencing complex (RISC). The guiding strand then directs the RISC to bind to specific mRNA by base-pairing with a complementary sequence in the mRNA molecule and induces mRNA degradation.

MicroRNA

MicroRNAs are 21–23 nucleotide single stranded RNA molecules found in eukaryotic cells. Similar to siRNA, microRNA also utilize the RNAi pathway to regulate gene expression at the post-transcriptional level. Mature microRNAs form stable

complexes with Argonaute proteins (such as Ago2), the core of the RNAi-induced silencing complex (RISC). The microRNA then directs RISC to bind to the mRNA molecules containing specific targeting sequences and results in translational repression and/or enhanced mRNA degradation. MicroRNAs show very different characteristics between plants and animals. In plant cells the microRNA complementary to its mRNA target is nearly perfect, with no or few mismatched bases. In animal cells, on the other hand, microRNA complementarity typically encompasses the 5′ bases 2–7 of the microRNA (known as the seed region), and one microRNA can target many different sites on the same mRNA or on many different mRNAs. Another difference is the location of target sites on the mRNAs. In animal cells, the microRNA target sites are often located in the 3′-untranslated regions (3′-UTR) of the mRNA. In plant cells, target sites can be located in the 3′-UTR but are more often in the coding region. MicroRNAs are well conserved in eukaryotic organisms and are thought to be a vital and evolutionarily ancient component of genetic regulation.

Piwi-Interacting RNA

Piwi-interacting RNAs (piRNAs) are poorly conserved at the primary sequence level, and distinct from microRNA and siRNA in size (26–31 nucleotides). These piRNAs are specifically expressed in spermatogenic cells in the testes of mammals. While still not well-characterized, it appears that the piRNA biogenesis pathway is distinct from miRNA and siRNA biogenesis. PiRNAs form RNA/protein complexes through interactions with a subfamily of Argonaute (Ago) proteins known as P-element induced wimpy testis proteins (piwi-proteins). These complexes have been implicated in epigenetic and post-transcriptional gene silencing, and are responsible for maintaining incomplete differentiation in stem cells and maintaining the stability of cell division rate in germ line cells.

In the following sections, we will focus our discussion on small non-coding RNAs (sncRNAs; transcripts fewer than 300 nucleotide in size) that participate directly in RNA processing and degradation, but indirectly in protein synthesis and gene regulation. This chapter provides a simple and general view of sncRNA-mediated regulation of gene expression, with particular attention to the recent advances in microRNAs in head and neck cancer.

33.2 MicroRNA and Cancer

33.2.1 MicroRNA Biogenesis and Functions

MicroRNAs are newly recognized, non-coding, regulatory RNA molecules, about 22 nucleotides in length, and found in all metazoans studied thus far. It is estimated that the human genome may have approximately 1,000 microRNAs [28]. Although they account for only a very small fraction of the expressed genome, microRNAs

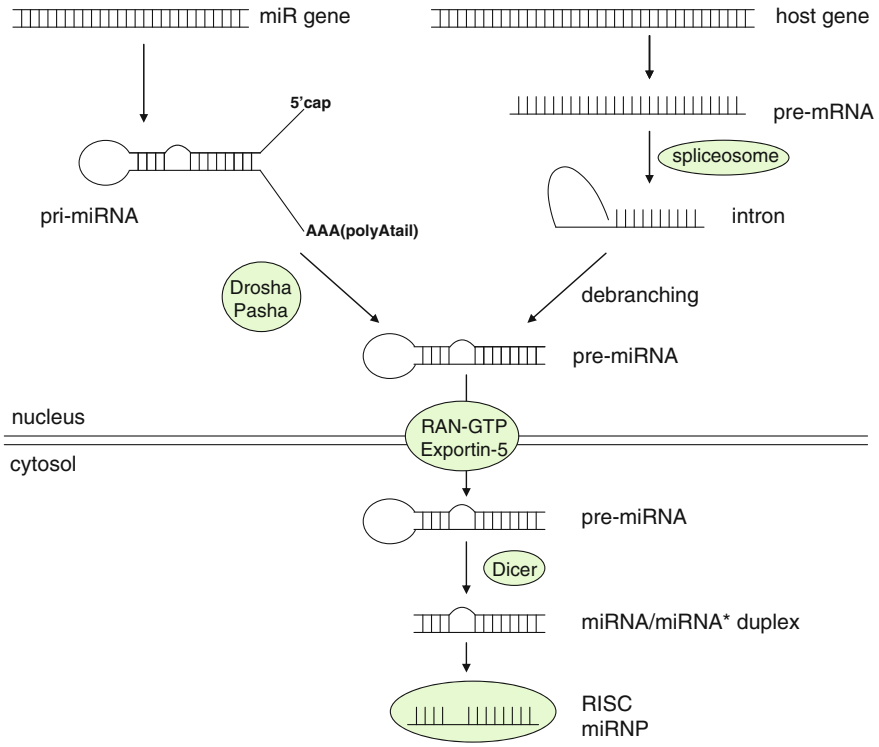

Fig. 33.1 MicroRNA biogenesis (Adopted from Dai and Zhou [29])

are pivotal regulators of development and cellular homeostasis through their control of diverse cellular processes including proliferation, differentiation, apoptosis, survival, motility and morphogenesis.

MicroRNA biogenesis has been well characterized (Fig. 33.1). The genes encoding microRNAs are much longer than the processed mature microRNA molecules. MicroRNAs are first transcribed as primary transcripts (pri-miRNA) with a cap and poly-A tail. They are then processed into short, 70-nucleotide stem-loop structures known as pre-miRNA in the cell nucleus. In animal cells, this processing is performed by a protein complex consisting of the nuclease Drosha and the double-stranded RNA binding protein Pasha. The pre-microRNAs are then transported to the cytoplasm by Exportin-5 (Exp5; a member of the Ran transport receptor family). Once in the cytoplasm, pre-microRNAs are further cleaved by Dicer (a second RNase III endonuclease) to form a short double strand microRNA:microRNA* duplex. Finally, the microRNA:microRNA* duplex is unwound into mature microRNA and microRNA* by a helicase. The mature microRNAs are then incorporated into the RNA-induced silencing complex (RISC). RISC, also known as a microRNA ribonucleoprotein complex (miRNP), is responsible for the gene silencing induced by both microRNA and siRNA. The pathway is different for microRNAs derived from intronic stem-loops which are processed by Dicer. No Drosha activity

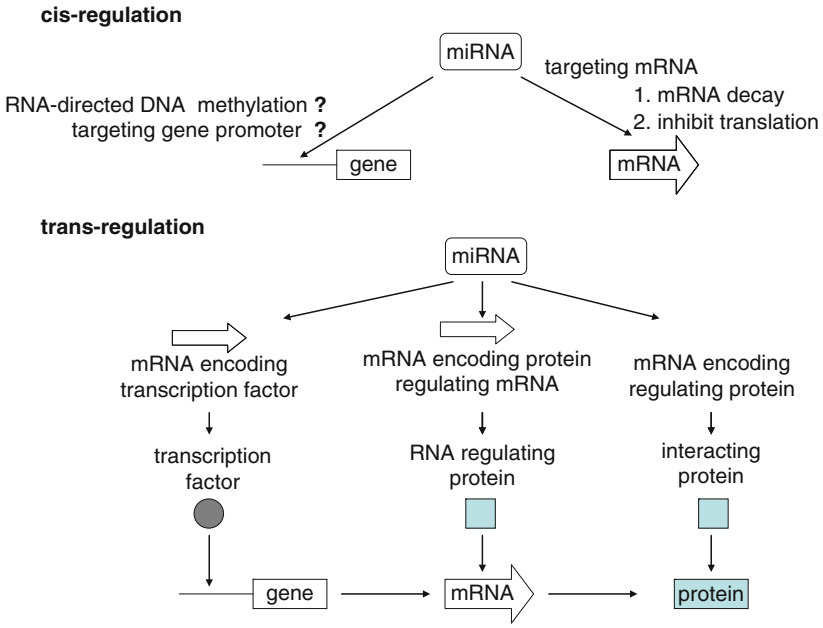

Fig. 33.2 Potential microRNA regulation mechanisms (Adopted from Liu et al. [35])

is needed for their maturation. In plant cells, the pathway also varies slightly due to their lack of Drosha homologs; instead, Dicer homologs are responsible for both pri-miRNA and pre-miRNA processing steps. For detailed discussion on microRNA biogenesis, we refer you to earlier reviews [30, 31].

MicroRNAs are not involved directly in protein synthesis, but are believed to control the expression of more than one-third of the protein-coding genes in human genome [32–34]. Each microRNA can target many mRNA transcripts and regulate hundreds of genes downstream. One microRNA can have multiple target sites in the mRNA transcript of a downstream gene. Therefore, microRNAs contribute a newly recognized level of gene expression regulation. As illustrated in Fig. 33.2, the potential mechanisms of microRNA-mediated gene regulation are multifactorial and encompass interaction(s) among different mechanisms. It has been demonstrated that microRNA binds to the target mRNA and regulates gene expression at the post-transcriptional levels (e.g., enhance mRNA degradation and inhibit translation). This cis-regulation occurs by binding of the ~21 nucleotide mature microRNA to an imperfectly matched sequence in the target mRNA. Following the expression changes of specific microRNA-targeted genes (e.g., genes coding for transcription factors and genes coding for RNA regulating proteins), subsequent effects may alter the levels of other mRNAs (or protein interactions), and thus microRNA may exert its effects on the expressed genome through trans-regulatory mechanism(s). For more details on microRNA biogenesis, basic functions, and their roles in normal physiology and diseases, numerous excellent reviews are recommended [30, 36–41].

33.2.2 The Functional Role of MicroRNA in Cancer

MicroRNAs play important roles in cell fate determination, proliferation and cell death. In addition to these vital processes, microRNAs are implicated in diverse cellular activities, such as immune response [42–44], insulin secretion [45], neurotransmitter synthesis [46], and circadian rhythm [47], to name a few. The microRNA gene family is continuously growing with novel members discovered in association with rapid advances in genomic technologies. Three important observations early in the history of microRNA suggested its critical role in human cancer. Firstly, the earliest microRNAs discovered in *C. elegans* and Drosophila were shown to control cell proliferation and apoptosis [48, 49]. Their deregulation may therefore contribute to proliferative diseases such as cancer. Secondly, when human microRNAs were discovered, it was noticed that many microRNA genes were located at fragile sites in the genome regions that are commonly amplified or deleted in human cancer [50]. Thirdly, cancer cells were found to have widespread deregulations in microRNA expression compared to normal cells [51, 52].

Since these early studies, an extensive literature has been accumulated on microRNAs and their roles in carcinogenesis, with more evidence on specific roles of these molecules and their involvement in pathways known to be altered in this complex disease process. Although they account for only a minor fraction of the expressed genome, microRNAs are pivotal regulators of diverse cellular processes including proliferation, differentiation, apoptosis, survival, motility and morphogenesis. Several microRNAs have been functionally classified as proto-oncogenes or tumor suppressors and are aberrantly expressed in different cancer types including leukemia [53, 54], lymphoma [55], breast cancer [56, 57], bladder cancers [58], cervical cancer [59–61], pancreatic tumors [62], thyroid cancer [63, 64], colorectal cancer [65], lung cancer [66, 67], liver cancer [68, 69], and HNOC [70–73]. Dysregulation (e.g., overexpression or loss of expression) of these cancer-related microRNAs contributes to tumor initiation and progression by promoting uncontrolled proliferation, favoring survival, inhibiting differentiation and/or enhancing invasive behavior [51, 74].

33.3 MicroRNA in Head and Neck/Oral Cancer

Accumulating evidences suggest that microRNAs play important roles in many human cancers, including HNOC. MicroRNA expression patterns may become powerful biomarkers for the diagnosis and prognosis of HNOC. In addition, microRNA therapy could be a novel strategy for HNOC prevention and therapeutics. Recent advances in microRNA expression profiling have led to a better understanding of the cancer pathogenesis. In the following, we will survey recent technological advances in microRNA profiling and their applications in HNOC. We will also highlight the identified microRNAs that play major roles in HNOC.

33.3.1 MicroRNA Profiling in Head and Neck/Oral Cancer

High-throughput microRNA gene expression analysis is a technical challenge. The short length and uniqueness of each microRNA render many conventional tools ineffective; very small RNAs are difficult to reliably amplify or label without introducing bias. Earlier attempts for the detection and identification of microRNA included three basic approaches: hybridization based methods (e.g., Northern blots and microarrays), PCR-based detection, and cloning methods. Based on these initial approaches, higher-throughput technologies have been developed to obtain comprehensive microRNA profiles at the genome-wide scale.

33.3.1.1 Hybridization Based MicroRNA Profiling – Microarray

Most of the early microRNA profiling studies were based on different types of microarrays. The differences in these microarrays are mainly in the probe design, probe immobilization chemistry, sample labeling, and signal detection methods (see [35, 75] for reviews on microarray-based microRNA profiling). Similar to the evolution of mRNA microarrays, during the early stage of microRNA array development, most of the arrays were custom made. For example, using a custom-made microRNA microarray [76], Tran and co-workers presented the first microarray-based microRNA profile of HNOC based on 9 HNOC cell lines [72]. This study provided the largest genome-wide survey of mature microRNA transcripts in head and neck cancer cell lines at the time. With the introduction of several commercially available microRNA array platforms, the study design and data analysis became more streamlined. For example, using GenoExplorer microRNA array from GenoSensor Corporation (Tempe, AZ), Chang and co-workers screened for alterations of microRNA expression in HNOC primary tissue samples, HNOC cell lines, and normal control samples [77]. Their study identified 8 up-regulated microRNAs (including miR-21, let-7, miR-18, miR-29c, miR-142-3p, miR-155, and miR-146b) and 1 down-regulated microRNA (miR-494) in HNOC. More recently, a number of innovative microarray platforms have been adapted for microRNA profiling, including the locked nucleic acid (LNA)-based microRNA array (miRCURY LNA arrays from Exiqon, Inc). LNA is a conformational analogue of RNA, and exhibits unprecedented binding affinity to its target RNA molecule. A number of recent studies have been reported using this platform for microRNA profiling on several types of malignancies, including chronic myeloid leukemia, cutaneous T-cell lymphoma, adrenocortical cancer and breast cancer [78–81].

33.3.1.2 qRT-PCR Based MicroRNA Profiling

While the microarray-based profiling methods described above provide excellent throughput and coverage, these methods do not amplify the microRNA and this often compromises their sensitivity. Real-time quantitative PCR based approaches

have unparalleled sensitivity and specificity. However, it is technically challenging to amplify and quantify mature microRNA because the mature microRNA is only about 21–23 nucleotides long, roughly the length of a standard PCR primer. As such, earlier versions of qRT-PCR assays were often designed to quantify microRNA precursors (pre-microRNAs). For example, the expression of 222 microRNA precursors were profiled in 32 human cancer cell lines (including 5 HNOC cell lines) using TaqMan assays designed for detecting hairpin-containing microRNA precursors [82]. Interestingly, unsupervised clustering analysis based on the expression values of these 222 microRNA precursors was able to cluster most of the cancer cell lines into tissue specific groups. This suggested that the existence of a tissue-specific microRNA expression signature for cancers originating from various tissues. It should be emphasized that this profile is for the pre-microRNAs, not the mature microRNAs. While the relative levels of most mature microRNAs are correlated with the levels of corresponding precursors, additional tests will be needed to ensure that the levels of the mature microRNAs are reflected by the precursors.

Recently, a new TaqMan-based approach has been developed directly quantify the mature microRNA. This assay incorporates a target specific stem-loop and a reverse transcription primer. The innovative design overcomes a fundamental challenge in microRNA quantification: the short length of mature microRNAs (~22 nucleotides) prohibits the conventional design of a specific quantitative real-time PCR assay. The stem-loop structure provides specificity for only the mature microRNA target and forms a RT primer/mature microRNA-chimera that extend the 3′ end of the microRNA. The resulting longer RT product presents a template amenable to standard real-time PCR using TaqMan Assays. These latest qPCR assays are commercially available (e.g., TaqMan MicroRNA Assay from Applied Biosystems). These assays can be packed into a convenient, pre-configured micro fluidic card that contains up to 384 unique TaqMan assays and is compatible with most of the common qPCR instruments. A number of recent microRNA profiling studies have been performed using this new TaqMan assay on either HNOC cell lines or clinical tissue samples from HNOC (as described in later sections).

33.3.1.3 Cloning and Sequencing Based MicroRNA Profiling

This approach is developed by combining aspects of microRNA cloning and serial analysis of gene expression (SAGE) method, which leads to its name miRAGE [83]. Similar to traditional SAGE experiments, miRAGE starts with the isolation of 18- to 26-base RNA molecules to which specialized linkers are ligated, and which are reverse-transcribed into cDNAs. The subsequent steps (including PCR amplification of the cDNAs mixture, purification, concatenation, and sequencing) are performed with procedures optimized for small RNA molecules. SAGE was originally designed to characterize gene expression profiles. It has the potential to be a high-throughput gene expression profiling tool. Over the years, much improvement has been made to increase sequencing efficiency; high-throughput deep sequencing

platforms (e.g., Genome Analyzer from Illumina) are now available for the profiling of small RNAs [84], which allows both the detection and identification of the microRNA species at high speed and sensitivity. Although it is not as popular as microarrays and qRT-PCR due to technological and economical challenges, this technology has the unique advantage of combining discovery and quantification.

33.3.2 MicroRNA Alterations Associated with Head and Neck/Oral Cancer

MicroRNA deregulation is a critical event in HNOC. As described above, as the microRNA profiling technologies advance rapidly, a number of microRNA profiling studies on HNOC have been reported. However, there tends to be poor agreement among these profiling studies. A number of potential factors may contribute to the observed inconsistency, such as the heterogeneity in the tissue samples, variations in genetic and environmental backgrounds of the subjects, and the differences in profiling technologies. Although reanalysis of the profiling data as a whole remains a challenge, meta-analysis of multiple studies is a reasonable approach for identifying consistently-reported, differentially-expressed microRNAs in HNOC. We recently performed a meta-analysis based on 13 independent microRNA profiling studies on HNOC (Table 33.1) [96]. Studies were included in the systematic review if: (1) they were microRNA profiling studies in patients with HNSCC; (2) they used HNSCC and adjacent non-cancerous tissues for comparison; (3) they used large-scale microRNA profiling techniques (e.g., microarrays or qRT-PCR arrays); (4) they were published as full articles in English. Studies using HNSCC cell lines, serum or saliva samples, or focused on specific disease stages, or using other microRNA techniques were not included. Review articles were also excluded. A total of 432 differentially expressed microRNAs were reported in these studies, including 264 up-regulated and 168 down-regulated microRNAs. Among the reported differentially expressed microRNAs, 90 were reported by at least two studies; 67 (74.4%) with a consistent direction of change, and 23 (25.6%) with an inconsistent direction. Among the 67 microRNAs with consistent directions, 46 (68.7%) were reported to be up-regulated, and 21 (31.3%) were reported to be down-regulated in HNOC. As shown in Table 33.2, 11 differentially expressed microRNAs were reported in at least 4 studies with consistent direction, including seven consistently up-regulated microRNAs (miR-21, miR-155, miR-130b, miR-31, miR-223, miR-34b, miR-7), and four consistently down-regulated microRNAs (miR-100, miR-99a, miR-125b, miR-375) in HNOC. Detailed discussions on these consistently up- and down-regulated microRNAs in HNOC are provided below.

MiR-21: The up-regulation of miR-21 is the most consistently observed microRNA deregulation (reported in 11 out of 13 studies we surveyed). The human miR-21 gene is located on the plus strand of chromosome 17q23.2 within a coding gene TMEM49. Despite being located in the intronic region of a coding gene in the

Table 33.1 Thirteen microRNA profiling studies used in the meta-analysis[a]

References	Sample size		Site	Profiling platform
	HNSCC	Normal		
Wong TS, 2008 Clin Cancer Res, [70]	4	4	Tongue	TaqMan microRNA assay (Applied Biosystems)
Chang SS, 2008 Int J Cancer, [77]	4	4	2 base of tongue, 1 laryngeal, 1 tonsillar	MicroRNA array (Genesensor)
Li J, 2009 Clin Cancer Res, [85][b]	10	10	Tongue	MicroRNA array (probe set from Invitrogen)
Avissar M, 2009 Clin Cancer Res, [86]	16	5	Not specified	MicroRNA array (Ambion)
Ramdas L, 2009 Head Neck, [87]	5	5	2 tongue, 1 base of tongue, 1 laryngopharynx, 1 FOM	MicroRNA array (Ambion)
Childs G, 2009 Am J Pathol, [88]	8	8	Not specified	MicroRNA array (probes from Ambion)
Cervigne NK, 2009 Hum Mol Genet, [89]	12	7	8 tongue, 2 lateral tongue, 1 buccal mucosa, 1 FOM	TaqMan microRNA assay (Applied Biosystems)
Liu CJ, 2010 Cancer Res, [90]	10	10	Not specified	TaqMan microRNA assay (Applied Biosystems)
Hui AB, 2010 Clin Cancer Res, [91]	54	4	20 Larynx, 24 oropharynx, 10 hypopharynx	TaqMan microRNA assay (Applied Biosystems)
Kikkawa N, 2010 Br J Cancer, [92]	10	10	Hypopharyngeal	TaqMan microRNA assay (Applied Biosystems)
Scapoli L, 2010 Int J Immunopathol Pharmacol, [93]	15	11	8 jaw, 5 tongue, 1 cheek, 1 FOM	MicroRNA array (Invitrogen)
Lajer CB, 2011 Br J Cancer, [94][c]	49	39	30 oral cavity, 19 oro- or hypopharynx	MicroRNA array (Affymetrix)
Rentoft M, 2011 Int J Oncol, [95]	21	8	Tongue	MicroRNA array (Exiqon)

[a] Adapted from Chen et al. [96]. The meta-analysis included published studies on HNOC from oral cavity and laryngopharynx. HNOC from other anatomical sites (e.g., nasal cavity, external ear) were not included

[b] Differentially expressed microRNAs identified from both early-stage and advanced-stage patients with HNOC of the tongue from Li et al. [85] study were included in the analysis

[c] Differentially expressed microRNAs identified from patients with HNOC from oral cavity and HNOC from pharynx from Lajer et al. [94] study were included in the analysis

Table 33.2 Differentially expressed microRNAs that were consistently reported in HNSCC (by at least four studies)[a]

MicroRNA	Chromosomal Location	Mature miR sequence	Up-/Down-Regulation	References	No. of Refs.	Sample Size (SCC/ctrl)
miR-21	17q23.1	uagcuuaucagacugauguuga	Up	[70, 77, 85, 86, 88–94]	11	192/112
miR-155	21q21.3	uuaaugcuaaucgugauaggggu	Up	[70, 77, 89–91, 94]	6	133/68
miR-130b	22	cagugcaaugaugaaagggcau	Up	[86, 90, 91, 94]	4	129/58
miR-223	Xq12	ugucaguuugucaaauacccca	Up	[89–91, 94]	4	125/60
miR-31	9p21.3	aggcaagaugcuggcauagcu	Up	[70, 85, 90, 94]	4	73/63
miR-7	9q21.32 or 15q26.1 or 19p13.3	uggaagacuagugauuuuguugu	Up	[87, 89, 92, 95]	4	48/30
miR-34b	11q23.1	caaucacuaacuccacugccau	Up	[70, 87, 89, 90]	4	31/26
miR-100	11q24.1	aacccguagauccgaacuugug	Down	[70, 90–92, 94]	5	127/67
miR-99a	21q21.1	aacccguagauccgaucuugug	Down	[70, 90–92, 94]	5	127/67
miR-375	2q35	uuuguucguucggcucgcguga	Down	[86, 91, 92, 94]	4	129/58
miR-125b	11q24.1 or 21q21.1	ucccugagacccuaacuuguga	Down	[70, 91, 92, 94]	4	117/57

[a]Adapted from Chen et al. [96]

direction of transcription, it has its own gene promoter which independently transcribes a 3,433-nucleotide primary transcript of miR-21 (pri-miR-21). The pri-miR-21 is processed into pre-miR-21 and then into mature miR-21, which directs the RISC-mediated silencing of its target genes. MiR-21 is one of the most well-established oncogenic microRNAs. A large number of target genes for miR-21 have been identified and experimentally confirmed, and most of them are tumor suppressors. Notable targets include PTEN [97], PDCD4 [98], Tropomyosin [99], Sprouty 1 and 2 [100, 101], Bcl2 [102], RECK [103], JAG1 [104], HNRPK [99], TGFBRII [105], P12/CDK2AP1 [106], MEF2C [107], RhoB [108], and hMSH2 [109]. Over-expression of miR-21 is frequently observed in a wide variety of solid tumors, including that of breast [110], ovaries [111], cervix [59], colon [98], liver [97], brain [112], and esophagus [113]. The up-regulation of miR-21 has been linked with poor prognosis in HNOC and may act as an apoptosis inhibitor [85, 114].

MiR-155: MiR-155 has been suggested previously as an oncogenic microRNA [115], and has been implicated in the regulation of cell survival, growth, and chemosensitivity [116–118]. Over-expression of the miR-155 gene has also be observed in several solid tumors, such as thyroid carcinoma [119], breast cancer [110], cervical cancer [120], pancreatic cancer [121, 122], lung cancer [67], and HNOC. The expression of miR-155 is regulated by the transforming growth factor beta/Smad pathway [116], which is frequently elevated in HNOC [123]. MiR-155 has also been shown to be involved in mammalian innate and adaptive immunity and viral infection [44, 124].

MiR-130b: In addition to HNOC, miR-130b has also been shown to promote liver tumor-initiating cell growth and self-renewal [125], and to target tumor suppressor RUNX3 in gastric cancer [126]. Up-regulation of miR-130b has also been suggested to contribute to the human T-cell lymphotrophic virus 1 (HTLV-1)-mediated cellular transformation by targeting TP53INP1 and promoting cell proliferation and survival [127]. A recent study demonstrated that miR-130b also plays a role in keratinocyte senescence [128].

MiR-223: MiR-223 is a hematopoietic specific microRNA with crucial functions in myeloid lineage development [129, 130]. The level of miR-223 is often reduced in chronic lymphocytic leukemia [131], acute lymphoblastic leukemia [132], and acute myeloid leukemia [133, 134]. Enhanced expression of miR-223 is observed in several types of solid tumors, including esophageal cancer [135] and HNOC. MiR-223 functions as an oncogene in gastric cancer [136], and promotes gastric cancer invasion and metastasis [137]. Elevated serum miR-223 may serve as a biomarker for hepatocellular carcinoma [138].

MiR-31: While miR-31 up-regulation has been consistently observed in HNOC, its role in tumorigenesis is not entirely clear, and may be cancer type specific. The up-regulation of miR-31 has also been observed in colorectal cancer [139, 140] and hepatocellular carcinoma [141], but reduced expression of miR-31 was observed in breast cancer [142], and frequent homozygous deletion of miR-31 gene was reported in urothelial carcinomas [143]. While miR-31 inhibits metastasis in breast cancer [144], up-regulation of miR-31 is essential to the TGF-beta-induced invasion and metastasis of colon cancer cells [145]. For pancreatic cancer, both inhibition and

enhanced expression of miR-31 lead to reduced migration and invasion in different pancreatic cancer cell lines [146]. More studies will be needed to define the role of miR-31 in tumorigenesis. As shown in our meta-analysis, up-regulation of miR-31 is frequently observed in HNOC. Increases in plasma miR-31 have recently been suggested as a potential marker of oral cancer [147].

MiR-7: Knowledge on miR-7 and its role in tumorigenesis are still elusive. While up-regulation of miR-7 was reported in HNOC by several studies [87, 89, 92, 95], down-regulation of miR-7 has been reported in other cancer types [148–150], and also reported in tongue squamous cell carcinoma cell lines [151, 152]. It is worth noting that there are 3 predicted miR-7 genes in human genome (located at 9q21.32, 15q26.1, and 19p13.3). Therefore, tissue specific (or cell specific) differential regulation of these 3 miR-7 genes may contribute to the inconsistent miR-7 expression observed in different cancer types. Additional studies focus on individual miR-7 genes will be needed to resolve this apparent contradiction. MiR-7 has been suggested to function as tumor suppresser based on its confirmed target genes, which include several proto-oncogenes such as insulin receptor substrate 1 (IRS1), insulin receptor substrate 2 (IRS2), epidermoid growth factor receptor (EGFR), v-raf-1 murine leukemia viral oncogene homolog 1 (RAF1) and p21/CDC42/RAC1-activated kinase 1 (PAK1) [148–150]. Jiang et al. in 2010 demonstrated that insulin-like growth factor1 receptor (IGF1R) is a novel target of microRNA-7 in oral tongue squamous cell carcinoma cell lines [153]. It was further shown that down-regulation of IGF1R, that in turn attenuated the insulin growth factor 1 (IGF1)-induced activation of protein kinase B, was mediated by microRNA-7. The activation of protein kinase B leads to reduced cell proliferation and cell cycle arrest and an increased apoptosis rate. The function of microRNA-7 on several key signaling molecules in several human cancers indicates a contribution to tumorigenesis via multiple pathways and at various levels [153].

MiR-34b: MiR-34b involves in a number of important molecular mechanisms that contribute to tumorigenesis, including epithelial-mesenchymal-transition (EMT) [154]. MiR-34b gene is located around CpG islands and is regulated through aberrant DNA methylation in a number of cancer types, including HNOC [71], esophageal squamous cell carcinoma (ESCC) [155], and non-small cell lung cancer (NSCLC) [156]. The expression of miR-34b appears to be further regulated by p53 at gene promoter level [157–159].

MiR-99a and miR-100: MiR-99a and miR-100 are members of miR-99 family (miR-99b is the third member of the miR-99 family). In addition to HNOC, deregulation of the miR-99 family has also been reported in several cancer types [160, 161]. A number of recent functional studies suggested that members of the miR-99 family target insulin-like growth factor 1 receptor (IGF1R) and mechanistic target of rapamycin (mTOR) signaling pathways [96, 162–164].

MiR-375: Reduced level of miR-375 has been correlated with poor outcome and metastasis in HNOC [165]. It may function as a tumor suppressor by suppressing the tumor's invasive properties in HNOC [165]. Frequent down-regulation of miR-375 has also been reported in gastric cancer, and has been shown to inhibit cell proliferation and regulate cell survival [166–168].

MiR-125b: The down-regulation of miR-125b appears to play an important role in the development and/or progression of HNOC [169, 170], and may contribute to resistance to ionizing radiation [170]. There are two predicted genes for miR-125b in the human genome (located at 11q24.1 or 21q21.1). One of the gene for miR-125b is closely localized with the gene for miR-100 (11q24.1; one of the most frequently deleted genomic region in OSCC), and concurrent down-regulation of miR-125b and miR-100 is often observed in OSCC [170].

33.3.3 Other Functionally Relevant MicroRNAs in Head and Neck/Oral Cancer

MiR-138: MiR-138 is one of the most frequently down-regulated microRNAs in HNOC and the down-regulation of miR-138 is associated with enhanced cell migration, cell invasion and reduced apoptosis [151]. There are two predicted miR-138 genes in human genome (located at 3p21.33 and 16q13). Loss of heterozygosity (LOH) at both chromosome loci have been observed in HNOC and appears to correlate with tumor progression (i.e., cervical lymph node metastasis) [171–173]. The deregulation of miR-138 has also been implied in other cancers, including thyroid cancer [63], lung cancer [174], liver cancer [175], and leukemia [176]. In addition to its role(s) in tumorigenesis, miR-138 has also been thought to play a role in keratinocyte senescence [128], mammary gland development [177], regulating dendritic spine morphogenesis [178], and modulating cardiac patterning during embryonic development [179]. The precise regulation of these diverse biological processes is dependent on the ability of miR-138 to regulate multiple target genes in specific physiological/pathological settings. Our recent functional analysis demonstrated that miR-138 regulates cell migration and invasion by concurrently targeting RhoC and ROCK2, which leads to the down-regulation of the Rho GTPase signaling pathway that is essential for actin cytoskeleton remodeling [180]. It has become evident that cancer cells can dedifferentiate through activation of specific biological pathways associated with EMT, thereby gaining the ability to migrate and invade. EMT is characterized by loss of epithelial-cell markers (e.g., E-cadherin) and gain of mesenchymal-cell markers (e.g., Vimentin). Previous studies suggested that the miR-200 family and miR-205 regulate EMT by targeting the Zinc finger E-box-binding homeobox (ZEB) family transcription repressors (ZEB1 and ZEB2) which control E-cadherin expression [181]. Similarly, deregulation of miR-101 leads to the overexpression of polycomb group protein EZH2 [182, 183], which also acts as a transcription suppresser to inhibit the expression of E-cadherin and induce EMT [184]. Our bioinformatics analysis and the preliminary experimental results indicated that miR-138 targets both ZEB and EZH repressors, and also targets additional molecular regulators that control E-cadherin expression, such as FOSL1. Furthermore, our preliminary results also demonstrated that miR-138 controls Vim expression by interacting with its targeting sequences located in both the 3′-UTR and coding region of the Vim gene. These results suggested that miR-138 is a

powerful EMT regulator that controls EMT through multiple pathways. Taken together, these observations suggested that miR-138 is a multi-functional molecular regulator, and the down-regulation of miR-138 in OSCC plays essential roles in the progression of OSCC in terms of enhancing the metastatic potential of the OSCC cells by promoting EMT and enhancing cell migration and invasion.

MiR-137 and miR-193a: It has been suggested that both miR-137 and miR-193a are silenced by DNA hypermethylation in HNOC [71]. This epigenetic event has also been observed in glioblastoma for silencing miR-137 [185]. The ectopic transfection of miR-137 or miR-193a into a HNOC cell line led to significant down-regulation of cyclin-dependent kinase 6 or E2F transcription factor 6, respectively, as well as reduced cell growth [71]. These observations are consistent with previous findings in which tumor suppressing roles have been suggested for miR-137 in glioblastoma [185] and melanoma [186], and for miR-193a in hepatocarcinoma, lung epithelial carcinoma and cervical adenocarcinoma cell lines [187].

MiR-133a/b: In the human genome, there are two known miR-133a genes (miR-133a-1 and miR-133a-2, found on chromosome 18 and 20, respectively) and one miR-133b gene (found on chromosomes 6). Down-regulation of miR-133a and miR-133b has been consistently observed in HNOC [70, 71], and functional studies further demonstrated the tumor-suppresser functions of miR-133a/133b in HNOC cell lines, including inhibiting proliferation and inducing apoptosis [188]. The down-regulation of miR-133b has also been observed in colorectal cancer [139]. In addition to their apparent tumor-suppresser function, miR133a/b have also been associated with various functional roles in cardiomyocytes [189–191], osteoblasts [192], and neurons [193]. The miR-133 family, together with miR-1 and miR-206, have previously been considered as muscle specific microRNAs and are essential for proper skeletal and cardiac muscle development and function [194].

MiR-98: The ability of tumor cells to adapt to microenvironment alterations is a key element for their survival and tumor progression. Ability to survive under hypoxia conditions or in the presence of chemotherapeutic agents by developing resistance is major contributor to treatment failures and yet still poorly understood. Studies have shown that microRNA deregulation contributes to these adaptations of cancer cells. Partial regulation of the High Mobility Group A2 (HMGA2) protein, a member of the HMGA family, was identified to be controlled at least in part by miR-98 in cancer cell lines from the head and neck studied in hypoxia conditions [73]. HMGA2 expression occurs predominately during embryogenesis. However, proteins from the HMGA family are implicated in differentiation, neoplastic transformation, and integration and expression of viral genome. In oral squamous cell carcinoma the same protein has been implicated in acquisition of mesenchymal characteristics by the epithelial cells. It is worth noting that MiR-98 is one of the members of the let-7 family, one of the first microRNAs to be identified. Let-7 has been shown to act as a master regulator for cell cycle exit [195].

MiR-15a: Using a human tumor xenograft model, Cohen et al. demonstrated that miR-15a is involved in DNA synthesis control and cell cycle progression [196]. Protein kinase C alpha (PKCa) was identified as a key mediator of squamous cell carcinoma proliferation via activation of MAPK and negative regulation of miR-15a.

MiR-15a inhibits cyclin E expression and DNA synthesis. This feed-forward loop involves PKCa which inhibits miR-15a that allows uninhibited cyclin E expression and thus promotes DNA synthesis [196].

33.4 Conclusions and Future Directions

Despite advances in diagnosis and treatment, mortality rates of HNOC have not improved significantly over the past three decades, which points to the immediate need for a better understanding of this disease. Accumulating evidence suggests that microRNAs play important roles in many human cancers, including HNOC. They are pivotal regulators of diverse cellular processes including proliferation, differentiation, apoptosis, survival, motility and morphogenesis. Recent advances in microRNA expression profiling have led to a better understanding of HNOC pathogenesis. This information will lead to the identification of specific microRNA expression patterns that may become powerful biomarkers for the diagnosis and prognosis of HNOC. In addition, the expanding knowledge of specific roles of certain microRNAs will further contribute to our understanding of the complexity of tumor progression and behavior. Consideration of this information and incorporation into treatment modalities through targeted therapy could potentially enhance our abilities to improve outcomes especially when other established therapies have failed.

It is important to note that HNOCs are a group of diverse cancers that develop from many different anatomical sites and are associated with different risk factors [197], genetic characteristics [198], and different clinical outcomes [199, 200]. Currently, most of the existing microRNA profiling studies on HNOC include cases from multiple anatomical sites. Ideally, site specific microRNA signatures for various HNOCs should be identified, which will lead to substantial translational outcomes that will advance the management of these diverse HNOC types. This has been realized to some extent already, and a few studies have been devoted to the identification of site specific microRNA signature for HNOC, including a study by [94], to identify microRNAs alterations associated specifically with HNOCs of the oral cavity, and the HNOCs of the oro- or hypopharynx [94].

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Chapter 34
Detection of Oral Cancer Using Salivary Diagnostics

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Contents

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Abstract Saliva is a non-invasive and accessible biofluid that provides accurate readouts for the detection of oral cancers. Recent technological advances have uncovered oral cancer specific salivary biomarkers. The availability of highly sensitive and high-throughput assays such as microarray, mass spectrometry, quantitative reverse transcriptase polymerase chain reaction (RT-PCR) and nano-scale sensors can measure proteins and nucleic acids despite the low concentrations in saliva. This chapter will discuss these proteomic and transcriptomic salivary biomarkers development for oral cancer, and the translational applications of these markers for the detection of the disease.

Keywords Oral cancer • Saliva • Biomarkers • Salivary diagnostics

Abbreviations

2-DE	2-dimensional gel electrophoresis
AUC	area under curve
cDNA	complimentary DNA
cRNA	complimentary RNA
ELISA	enzyme-linked immunosorbent assay
IVT	in vitro transcription
LC-MS/MS	liquid chromatography
miRNA	micro RNA
mRNA	messenger RNA
MS/MS	multidimensional chromatography with tandem mass spectrometry
OSCC	oral squamous cell carcinoma
PCR	polymerase chain reaction
POC	point of care platform
q-PCR	quantitative PCR
RNA	ribonucleic acid
ROC	receiver operating characteristic value
RT-PCR	quantitative reverse transcriptase polymerase chain reaction
SIR	saliva internal reference genes

34.1 Introduction

Oral cancers include cancers of the mouth and the pharynx and accounts for roughly 6% of all cancers diagnosed annually in the United States. Moreover, approximately 35,000 people will be diagnosed annually in the United States and about 7,600 will die from the disease [1]. Despite significant therapeutic and surgical advances for oral cancers, overall survival rate still remains low (~60% in 5 years) due to the lack of effective early detection technologies. Detection of oral cancers is currently based

on the expert visual and tactile examination of the oral cavity. However, since clinical screening for oral lesions are often neglected in routine healthcare, frequently oral cancers developed and progressed undetected.

As highlighted in the review by Lingen et al. [2] there are present screening and early detection techniques and devices available for oral cancer. Currently the gold standard for oral cancer is the scalpel biopsy [3]. Other methods include brush biopsy, toluidine blue staining, and light-based detection systems including tissue reflectance systems, and narrow-emission tissue fluorescence systems. Despite their availability, there is no hard data to promote these technology are capable of identify premalignant lesions before they are detectable by conventional oral exam.

A conventional oral examination (COE) using standard incandescent light has been the standard method for oral cancer screening. However, even though many believe COE can be an effective screening test, studies show that it does not identify all potentially premalignant lesions and other biologically relevant lesions that may potentially lead to cancer [4]. Thus, the development of the brush biopsy by CDx Laboratories in 1999, a screening device meant for examination of low-level lesions in regards to suspicion for carcinoma [5]. However, even though this technique appeared promising, the lack of concrete data of its screening efficacy for non-suspicious lesions undermines its clinical credibility.

Toluidine blue staining is another oral cancer screening technique that is widely used. Although not FDA approved in the United States, it is widely used in other parts of the world for the identification of abnormal lesions in the oral mucosa [6]. Toluidine blue is a dye that stains nucleic acids and abnormal tissues. However, problematic issues regarding the specificity of toluidine blue staining warrants reservation towards the use of this compound for oral cancer screening. For instance, Onofre et al. found that even though that all carcinomas stained positively, only 50% of lesions with dysplasia stained positive while 35% of benign lesions also stained [7].

More recently, light-based oral cancer detection systems have emerged. There are two types of light-based oral cancer detection systems marketed, tissue reflectance systems, and narrow-emission tissue fluorescence systems. Tissue reflectance systems utilizes an acetic acid rinse, where normal epithelium will appear lightly bluish under blue-white illumination, while abnormal epithelium appears distinctly white. Narrow-emission tissue fluorescence on the other hand, performs upon the principle of tissue auto-fluorescence for the detection of oral cancer. Upon excitation using lights of a specific wavelength range (400–600 nm), normal oral mucosa emits a pale green auto-fluorescence through a handheld filter. In contrast, abnormal or suspicious tissues will not auto-flouresce and appear dark by comparison to surrounding healthy tissues. However, despite evidence that support the use of these light-based systems, just as the previous mentioned techniques, studies that definitively demonstrate that these systems can reliably detect oral premalignant lesion are absent. For instance, several studies showed that post-acetic acid tissue reflectance oral cancer screening resulted in false positives upon confirmation via scalpel biopsies [8, 9]. Also, even though preliminary results are promising for narrow-emission tissue fluorescence system for oral cancer screening [10, 11], additional well-designed clinical trials are still necessary to determine whether the device can reliably detect premalignant lesions.

Thus, with the shortcomings of the present detection systems, biomarkers provide new avenues for oral cancer detection where saliva is an ideal non-invasive source. Utilizing both transcriptomic and proteomic high throughput technologies, it has been demonstrated that oral squamous cell carcinoma (OSCC) could be detected using salivary biomarkers with great clinical discrimination. Four validated mRNA salivary biomarkers discriminatory for OSCC yielded a receiver operating characteristic value (ROC) of 95%, with 91% sensitivity and 91% specificity [12]. Moreover, five validated protein biomarkers discriminatory for OSCC yielded a ROC of 93%, with 90% sensitivity and 83% specificity in detecting OSCC. These findings demonstrated that saliva is a credible bio-fluid for the detection of OSCC [13].

34.2 Salivary Biomarkers for Oral Cancer

34.2.1 Introduction

This chapter will address the early detection technology of oral cancers through salivary biomarkers. Additionally, insights will be provided in regards to how significant advances in transcriptomic and proteomic high throughput technologies have allowed salivary biomarkers to be utilized for the detection of OSCC with significant clinical discrimination. Moreover, a comprehensive overview will be provided in regards to the implementation strategy for the discriminatory oral cancers specific salivary biomarkers and introduce a point of care technology that is capable of detecting salivary oral cancer biomarkers in real time. Lastly, this chapter will provide a summary for the intended clinical context for salivary biomarkers for oral cancer detection.

34.2.2 Transcriptomic Analysis of Saliva

Messenger RNAs (mRNA) and micro RNAs (miRNA) are important for the translational application in disease detection as discriminatory biomarkers. Due to the low concentration of RNAs in saliva, detection of oral cancer using saliva became readily available upon the emergence of the microarray technology for discovery and quantitative RT-PCR validation (qPCR) of oral cancer discriminatory salivary biomarkers.

34.2.3 Discovery of mRNA Salivary Biomarkers for Oral Cancer [14]

Discovery of mRNA salivary biomarkers for oral cancer was achieved by RNA extraction, amplification and gene expression profiling using microarray and basic polymerase chain reaction (PCR) techniques. RNA extraction from cell free saliva (both

non-cancer and cancer samples) was achieved using Qiagen's RNA Easy Mini Kit. Further, to achieve sufficient amount of RNA for discovery using microarray analysis, the extracted salivary RNA is amplified twice using RiboAmp® Plus. The first round of RNA amplification reverse transcribed the isolated RNA into cDNA, followed by in vitro transcription (IVT). A second round of amplification was subsequently carried out using the cDNA (totaling 1.5 rounds of RNA amplification). Next, using the Affymetrix RNA Labeling kit, the cRNA product was biotinylated. The biotinylated cRNA was purified with Genechip Cleanup Module and RT-PCR and Bioanalyzer were used to assess the quality of the cRNA post isolation and amplification. Affymetrix Human Genome U133 plus 2.0 Array (54,000 probe sets representing approximately 38,500 genes) was then used for gene profiling. Any probe set with a P value <.0001 and intensity value of >200 is an indication that the matching gene transcript is reliably detected. The resulting microarray data was then processed and analyzed according to methods established by Warnes and Liu to generate statistically significant candidate genes for salivary biomarkers indicative of oral cancer [15].

34.2.4 Quantitative Gene Expression by Quantitative PCR [14]

Quantitative PCR (q-PCR) was performed using ABI 7500 real-time PCR System. Isolated salivary RNA that was not amplified was reversed transcribed into cDNA by using MuLV Reverse Transcriptase. The resulting cDNA was then used for PCR amplification using Power SYBR Green PCR mix. Primers were appropriately designed based on the oral cancer discovery microarray analysis as previously mentioned, and synthesized by Sigma-Geonosys. All reactions were performed in triplicates, and all transcripts were normalized to three saliva internal reference genes (SIR) Glyceraldehyde 3-phosphate dehydrogenase (GAPDH), Actin-Beta (ACTB) and Ribosomal Protein S9 (RPS9).

34.2.5 Oral Cancer Specific Salivary mRNA Biomarkers (United States Cohort) [12]

To test for the hypothesis that distinct mRNA expression patterns can be identified in saliva from OSCC patients in the US, 32 patients with primary T1 or T2 OSCC were included in this study, along with the same number of age-, sex-matched subjects with comparable smoking histories, without OSCC as the control group. On average, 54.2 ± 20.1 ng ($n = 64$) of total RNA was extracted from 560 uL of saliva supernatant. The RNA quantity between OSCC and matched control samples were not found to be significantly different (t-test, $P = 0.29$, $n = 64$). HG U133A microarrays identified difference in salivary RNA profiles between cancer patients and matched normal subjects where 836 transcripts were significantly up regulated and 843 transcripts were significantly down regulated in OSCC patients ($p < 0.05$; $n = 20$). To narrow down the candidates, only those transcripts, 17 in all, that had a

Table 34.1 Quantitative PCR validation of selected nine transcripts in saliva [12]

Gene symbol	Primer sequence (5′–3′)	Validated*	P value	Mean fold increase
DUSP1	F: CCTACCAGTATTATTCCCGACG R: TTGTGAAGGCAGACACCTACAC	Yes	0.039	2.60
H3F3A	F: AAAGCACCCAGGAAGCAAC R: GCGAATCAGAAGTTCAGTGGAC	Yes	0.011	5.61
IL1B	F: GTGCTGAATGTGGACTCAATCC R: ACCCTAAGGCAGGCAGTTG	Yes	0.005	5.48
IL8	F: GAGGGTTGTGGAGAAGTTTTTG R: CTGGCATCTTCACTGATTCTTG	Yes	0.000	24.3
OAZ1	F: AGAGAGAGTCTTCGGGAGAGG R: AGATGAGCGAGTCTACGGTTC	Yes	0.009	2.82
S100P	F: GAGTTCATCGTGTTCGTGGCTG R: CTCCAGGGCATCATTTGAGTCC	Yes	0.003	4.88
SAT	F: CCAGTGAAGAGGGTTGGAGAC R: TGGAGGTTGTCATCTACAGCAG	Yes	0.005	2.98
GADD45B	F: TGATGAATGTGGACCCAGAC R: GAGCGTGAAGTGGATTTGC	No	0.116	
RGS2	F: CCTGCCATAAAGACTGACCTTG R: GCTTCCTGATTCACTACCCAAC	No	0.149	

Table 34.2 ROC curve analysis of OSCC-associated salivary mRNA biomarkers [12]

Biomarker	Area under ROC curve	Threshold/cutoff (M)	Sensitivity (%)	Specificity (%)
DUSP1	0.65	8.35E-17	59	75
H3F3A	0.68	1.58E-15	53	81
IL1B	0.70	4.34E-16	63	72
IL8	0.85	3.19E-18	88	81
OAZ1	0.69	7.42E-17	100	38
S100P	0.71	2.11E-15	72	63
SAT	0.70	1.56E-15	81	56

change in regulation >threefold in all 10 OSCC saliva specimens, and a more stringent cutoff with $p<0.01$ were selected (B2M, DUSP1, FTH1, G0S2, GADD45B, H3F3A, HSPC016, IER3, IL1B, IL8, MAP2K3, OAZ1, PRG1, RGS2, S100P, SAT). Nine out of the 17 candidates were selected for validation based on their cancer association and 7 out of the 9 candidate transcriptomic markers were validated in OSCC patients while 2 transcripts did not (Table 34.1).

Receiver Operator characteristic (ROC) curve analysis of the nine validated OSCC-associated salivary mRNA biomarkers determined the predictive power of each transcript as shown in Table 34.2. The analysis revealed that IL8 mRNA was the optimal performer amongst the seven validated mRNA biomarkers for OSCC, with a calculated area under the ROC curve (AUC) of 0.85, yielding a sensitivity of 88% and specificity of 81% to distinguish OSCC from the normal. Moreover, by

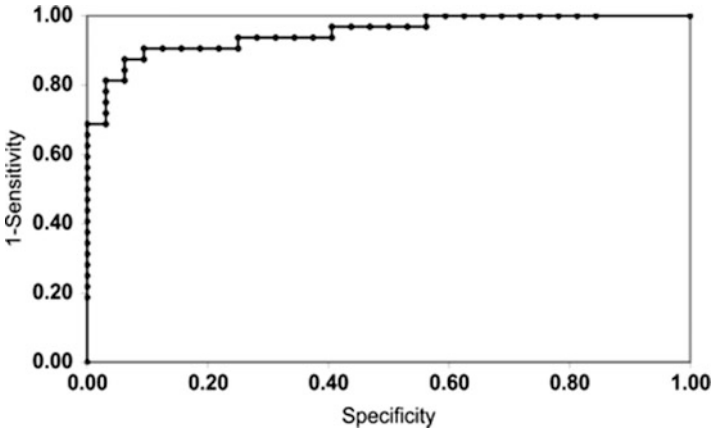

Fig. 34.1 ROC curve analysis for the OSCC combinatorial predictive power of IL1B, OAZ1, SAT, and IL8 [12]

combining four mRNA biomarkers (IL1B, OAZ1, SAT, and IL8), ROC curve analysis for the predictive power of the mRNA biomarkers were at an astounding 91% for both sensitivity and specificity, with an AUC of 0.95 (Fig. 34.1).

34.2.6 Oral Cancer Specific Salivary miRNA Biomarkers (United States Cohort) [16]

Park et al. conducted a study to determine the presence of miRNA in saliva and their potential as discriminatory OSCC salivary biomarkers. It was determined that 314 of the 708 known human miRNAs (from miRBase version 12.0) were present in both whole and supernatant saliva of healthy controls. Moreover, two salivary miRNA biomarkers, miR-125a and miR-200a were found significantly down regulated in OSCC patients. These findings suggest that saliva miRNA biomarkers are discriminatory and are useful for oral cancer detection.

34.3 Proteomic Analysis of Saliva

The Human saliva contains a large number of proteins that plays a pivotal role in maintaining oral and general health, and also is found to be a source of biomarkers for the assessment of oral cancer. Upon the availability of Shotgun proteomics based on multidimensional chromatography with tandem mass spectrometry (MS/MS), a total of 1,939 unique proteins have been compiled from 19,474 unique peptide sequences, where 597 of the 1,939 unique proteins identified in the human saliva are also present

in the human plasma proteome [13]. Moreover, using subtractive proteomics, discriminatory protein biomarkers for OSCC patients were successfully discovered and validated. The following sections will address the methods utilized by Hu et al. for the discovery and validation of protein biomarkers discriminatory against OSCC patients. However, since multiple groups have discovered distinct protein biomarkers for OSCC, we will address the findings of the other groups as well.

34.3.1 Discovery of Protein Biomarkers for Oral Cancer, 2-Dimensional Gel Electrophoresis (2D-DE) [13]

For the discovery of oral cancer specific protein biomarkers using 2D-DE, pooled OSCC and control saliva samples were used, where concentration in each sample was measured using a 2D Quant kit (GE Healthcare). The pooled samples of OSCC (n = 16) and control (n = 16) were profiled using 2D-DE with Sypro-Ruby staining. The proteins for both samples were precipitated by cold ethanol and stored in the −20°C overnight. Equal amount of proteins from both samples were used for comparative 2D-DE analysis. Gel images were then acquired via PDQuest software from Bio-Rad, and upon normalization of the samples via gel density, the proteins spots were automatically detected and matched and subsequently manually reviewed. Finally, the relative levels of protein spots between the disease and control patients were determined. Trypsin digestion and liquid chromatography MS/MS (LC-MS/MS) identified the candidate proteins for OSCC and control samples upon search using Mascot database.

34.3.2 Validation of Protein Biomarkers for Oral Cancer, Immunoassays (ELISA and Immunoblotting) [13]

ELISAs and immunoblotting were used to validate the candidate proteins listed in Table 34.3. ELISAs were conducted to determine the levels of Mac-2 binding proteins, Histone H1, S100A9, and S100P in saliva samples from OSCC and matched control samples. These samples were then quantitatively analyzed and the protein levels were determined. Immunoblotting was also done to compare the protein levels between OSCC and matched control subjects. The proteins that were validated via immunoblotting included MRP14, profilin, CD59, catalase, Rab-7, hemapoetic lineage cell-specific protein and moesin. The western blotting (WB) data for MRP, CD59, profilin, and catalase were normalized against actin levels from the same samples. The bands were quantified using Scion Imaging software. The reported P values were based on non-parametric test using the Wilcoxon rank sum test to determine significant differences between OSCC

Table 34.3 Immunoassay validation of salivary proteins differentially abundant in OSCC and healthy control [15]

Protein	Fold change (mean level)	*P*	Validation method
M2BP	1.99	0.006	ELISA
Profilin	1.93	0.0003	Immunoblotting
CD59	2.45	0.00001	Immunoblotting
MRP14	2.15	0.000002	Immunoblotting
Catalase	2.07	0.0000005	Immunoblotting
Histone H1	1.10	0.92	ELISA
S100A12	1.01	0.82	ELISA
Ras-related protein Rab-7	1.12	0.61	Immunoblotting
Moesin	1.19	0.32	Immunoblotting
Involucrin	1.67	0.11	ELISA
S100P	1.24	0.05	ELISA
Hematopoietic lineage cell-specific protein	1.43	0.002	Immunoblotting

and control salivary protein biomarkers. ROC curve analysis of the proteomic biomarkers was built to determine the overall OSCC predictive power of the combine five-candidate protein biomarkers (M2BP, MRP14, CD59, profilin, and catalase).

34.3.3 Oral Cancer Specific Salivary Protein Biomarkers (United States Cohort) [17–19]

Hu et al., St. John et al., and Arellano-Garcia et al. reported discriminatory protein biomarkers for OSCC. Hu et al. reported that LC-MS/MS and Mascot database search identified a total of 461 proteins from OSCC and 438 proteins from matched control subjects. 409 of the proteins overlapped between OSCC and control subjects, whereas 52 proteins were only identified in OSCC subjects, and 29 proteins were only identified in control samples. Twelve candidates showing up regulated levels in OSCC were chosen for ELISA and immunoblot assays due to the availability commercially of antibodies and ELISA assays for these proteins. Of the 12 candidate proteins, five proteins (M2BP, profilin, CD59, MRP14, and catalase) were found to be significantly different between OSCC and matched healthy groups. ROC analysis based on the five proteins (M2BP, MRP14, CD59, catalase and profilin) yielded an AUC value of 0.93, with a sensitivity of 90% and specificity of 83% (Fig. 34.2).

St. John et al. reported in 2004 that interleukin-8 (IL-8) were significantly up regulated in saliva in OSCC patients (n = 32) in comparison to control samples (n = 32). Moreover, Arrellano-Garcia et al. confirmed that the up-regulation of

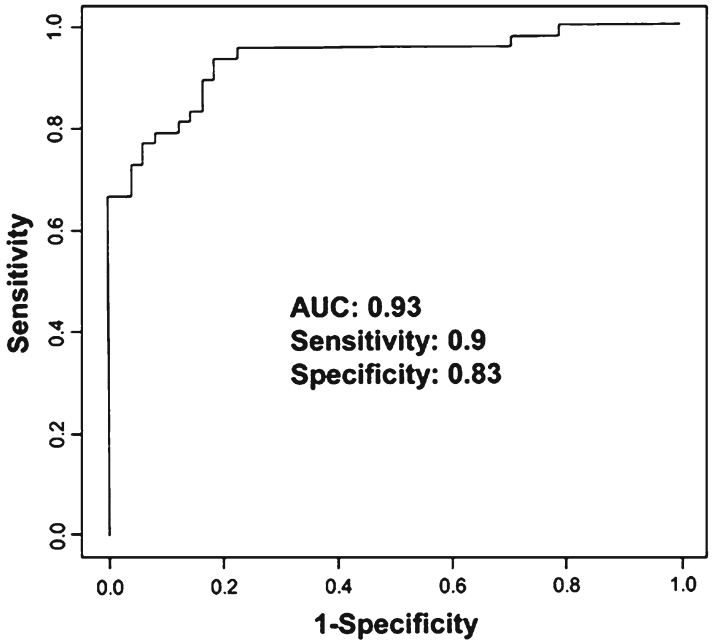

Fig. 34.2 ROC analysis based on combination of five validated protein markers (M2BP, MRP14, CD59, catalase and profiling) [15]

salivary IL-8 in OSCC patients, and also report significant higher levels of IL-1β proteins in OSCC saliva samples.

34.3.4 OSCC Detection by Salivary Biomarkers in a Serbian Population [20]

One of the biggest challenges in the field of biomarker research is the ability to not only discover and validate the initial excellent biomarkers, however, to also reproduce the findings in other ethnic groups. Brinkmann et al. conducted a comprehensive study in attempt to validate both salivary transcriptomic and proteomic biomarkers for OSCC found in the US cohort, within a Serbian cohort. 6 salivary transcriptomic biomarkers (IL1B, IL8, SA1, S100P, DUSP1, and OAZ1) and 3 salivary proteomic biomarkers (IL1B, IL8 and M2BP) that were previously reported as highly discriminatory for OSCC were investigated. All three salivary protein markers validated, and 4 out of 6 salivary transcriptomic biomarkers validated using 35 Serbian OSCC and 51 control subjects. However,

Table 34.4 Validation of saliva biomarkers in a Serbian population in OSCC/T1-T2/T3-T4 versus healthy control subjects [19]

Marker performance	p-Value (OSCC total/T1–T2/T3–T4)	Mean fold increase (OSCC total/T1–T2/T3–T4)
Protein markers		
IL1B	<0.0001/0.0002/<0.0001	3.96/3.20/4.76
IL8	<0.0001/0.004/<0.0001	3.09/2.66/3.55
M2BP	0.03/0.008/0.49	1.89/2.20/1.56
RNA markers		
IL8	0.0001/0.006/0.0008	2.85/2.45/3.34
S100P	0.001/0.003/0.02	3.24/5.10/2.01
SAT1	0.002/0.01/0.02	2.61/2.32/2.95
OAZ1	0.11/0.30/0.14	1.28/1.29/1.27
IL1B[a]	0.21/0.82/0.02	0.80/0.34/1.99
DUSP1	0.17/0.21/0.36	0.62/0.88/0.43

with further analysis, this study showed that the salivary protein biomarker M2BP performed as a highly significant marker for early stage oral cancer (T1/T2), however, not significant for late stage oral cancer (T3/T4). Moreover, interesting IL1B mRNA salivary biomarker behaved in the opposite manner, by being discriminatory for early stage OSCC, while, not significantly discriminatory for late stage OSCC. These findings are summarized in Table 34.4.

34.4 Clinical Implications for Oral Cancer Specific Salivary Biomarkers

34.4.1 Point of Care Platform for Detection of Oral Cancer Using Saliva

An important goal of salivary diagnostics for effective early detection of oral cancer is to advance a platform so that dentists are able to engage in chair-side screening of oral cancers using saliva. As previously mentioned in this chapter, salivary biomarkers for the detection of oral cancer are well established and highly discriminatory. However, it is just as important to establish a proper platform for the clinical application of these biomarkers. The UCLA Oral Fluid NanoSensor Test (OFNASET) POC device is an electrochemical platform integrated sensitive and specific multiplexing assay, sample collection, sample procession for proteomic and transcriptomic biomarkers in saliva (Fig. 34.3). This POC platform has been examined within an Indian cohort of oral cancer saliva samples and proven to be comparable with ELISA and qPCR assays for the proteins and RNA biomarkers respectively. The UCLA Salivary Diagnostic POC device showed significant clinical discrimination

Fig. 34.3 The ***UCLA Oral Fluid NanoSensor Test (OFNASET) POC*** device is an electrochemical platform integrated sensitive and specific multiplexing assay, sample collection, sample procession for proteomic and transcriptomic biomarkers in saliva

for OSCC (n = 28) versus control (n = 28) using two biomarkers, IL8 mRNA and IL8 protein. This demonstrated not only the POC device can effectively discern oral cancer, but also, multiplexible by utilizing both mRNA and protein biomarker.

34.4.2 Intended Clinical Context for Salivary Biomarkers for Oral Cancer Detection

Figure 34.4 outlines the current clinical triage map of patients with suspicious persistent oral lesions. In current clinical practice, suspicious persistent oral mucosal lesions detected by general practitioners are referred to oral medicine or oral surgery clinics for scalpel biopsies. Current literature indicates that 10% of these oral mucosal lesions will eventually diagnosed as oral squamous cell carcinoma (OSCC) and/or epithelial dysplasia. Clinical practice for both oral cancer and dysplasia is the same, total lesion excision. If one could develop salivary biomarkers to have performance of 98% sensitivity and at least 50% specificity for oral cancer/dysplasia detection, this will permit at least half of the referral subjects with suspicious persistent oral mucosal lesions not to have a biopsy, a significant clinical impact. Should the hypothesis be validated, future goals will include the evaluation of salivary diagnostic markers for oral cancer and dysplasia detection in primary referral clinics, where clinical impact can be more significant. In addition to significantly reducing the number of biopsies, the reduced mortalities and morbidities associated with early detection of oral cancer as well as the reduction in health care costs are significant and impactful.

34.5 Conclusion

This chapter examined both transcriptomic and proteomic biomarkers established to discern oral cancer utilizing saliva. Also, an efficient, multiplexible POC device was also introduced here as well as an overview in regards to the intended clinical context for salivary biomarkers for oral cancer detection. The ultimate goal of salivary diagnostics of oral cancer is for dentists to have the ability to conduct chair-side screenings of the disease using saliva. Hence, with these established findings and rapid progression for the POC technology, the universal usage of saliva for the detection of oral cancer appears imminent.

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Index

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