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Non-melanoma Skin Cancer of the Head and Neck

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Non-melanoma Skin Cancer of the Head and Neck

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A Note on the Series

Head and neck cancer (HNC) is a major public health challenge. Its management involves a multidisciplinary team approach, which varies depending upon the subtle differences in the location of the tumor, stage and biology of disease, and availability of resources. In the wake of rapidly evolving diagnostic technologies and management techniques, and advances in the basic sciences related to HNC, it is important for both clinicians and basic scientists to be up to date in their knowledge of new diagnostic and management protocols.

This series aims to cover the entire range of HNC-related issues through independent volumes on specific topics. Each volume focuses on a single topic relevant to the current practice of HNC and contains comprehensive chapters written by experts in the field. The reviews in each volume provide vast information on key clinical advances and novel approaches to enable a better understanding of relevant aspects in HNC.

Individual volumes present different perspectives and have the potential to serve as stand-alone reference guides. We believe these volumes will prove useful for the practice of head and neck surgery and oncology. Medical students, residents, clinicians, and general practitioners seeking to develop their knowledge of HNC will benefit from them.

Rehan Kazi
Raghav C. Dwivedi

Foreword

Randal S. Weber

Non-melanoma skin cancer is a significant public health problem for the populations of North America, Australia, and parts of Europe. The disease is rising in incidence and has a significant economic impact on healthcare expenditures in these regions. Noneconomic cost is significant and includes disturbance of body image, function, and quality of life.

Non-melanoma Skin Cancer of the Head and Neck edited by Riffat, Palme, and Veness is a concise volume devoted to the biology, pathology, and clinical characteristics of non-melanoma skin cancer. Current and future therapeutic modalities are addressed in the setting of multidisciplinary care. The editors are recognized clinical experts in the field of cutaneous malignancy management and bring their knowledge and practical experience to bear in the creation of this text. Their focus on both cutaneous and adnexal cancers of the skin is useful and will serve as a ready resource

for both these common and uncommon malignancies. The theme of the text on multidisciplinary intervention and care for the patient is both current and timely. The authors are to be commended for providing a succinct source of current knowledge that will inform evidence-based decisions in the management of patients with cutaneous malignancies of the head and neck.

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Preface

Non-melanoma skin cancer is a global public health issue. With an ever-increasing, and aging, world population coupled with the increasing number of immunosuppressed individuals, the number of patients continues to rise. The head and neck is overwhelmingly the most frequent location for the development of a non-melanoma skin cancer and as such challenges the clinician with its complex anatomy. The importance of maintaining the aesthetics of the face and the function of the anatomy cannot be overstated, yet ultimately it is always the aim of curing a patient with the minimum of morbidity that clinicians strive for. However, the spectrum of presentations and subsequent management varies widely, ranging from patients with the ubiquitous low-risk midface basal cell carcinoma to those diagnosed with relatively uncommon but potentially life-threatening high-risk squamous cell carcinomas (e.g., involving metastatic lymph nodes or with perineural invasion present) and Merkel cell carcinomas.

The concept of a multidisciplinary team approach is now the gold standard paradigm for most patients diagnosed with cancer, and this applies no less to patients diagnosed with non-melanoma skin cancer. While many patients with superficial and small lesions are cured by relatively simple often non-morbid treatment, others with more advanced cancers require a multidisciplinary team approach and often the institution of morbid treatment.

Australians experience the highest incidence of skin cancer in the world, and Australian clinicians are highly experienced in the management of these patients. It is the drawing from this local experience that is the impetus behind the writing of this book. As only one example, the requirement for extensive surgery often involving complex reconstruction and the important role of radiotherapy are expanded on in relevant chapters by authors widely published in their respective specialties. Many of the contributors are internationally recognized experts in their particular field at the cutting edge of clinical research and in treating patients—it is this knowledge and skill base that forms the basis of this book. The aim of writing this book is to provide busy clinicians with easily readable information and in most cases practical advice on managing patients with non-melanoma skin cancer. More comprehensive textbooks are available but few offer the concise, informative, and up-to-date approach that we hope this book provides to the reader.

Faruque Riffat
Carsten Palme
Michael Veness

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Abbreviations

AACR	Australian Association of Cancer Registries
ACE	Adult comorbidity evaluation
AEC	Airway exchange catheter
AIHW	Australian Institute of Health and Welfare
AJCC	American Joint Committee on Cancer
AK	Actinic keratosis
ASA	American Society of Anesthesiologists
BCC	Basal cell carcinoma
CAM-ICU	Confusion assessment method for ICU
CI	Charlson index
CIRS	Cumulative illness rating scale
CK	Cytokeratin
CLL	Chronic lymphocytic leukemia
CNI	Calcineurin inhibitor
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
COSA	Clinical Oncological Society of Australia
cSCC	Cutaneous squamous cell carcinoma
CT	Computed tomography
DAS	Difficult Airway Society
DFS	Disease-free survival
DFSP	Dermatofibrosarcoma protuberans
DSS	Disease-specific survival
DVT	Deep vein thrombosis
EAC	External auditory canal
EAM	External auditory meatus
EBV	Epstein–Barr virus
ECS	Extracapsular spread
EGFR	Epidermal growth factor receptor
ENS	Extranodal spread
ENT-HNS	Otorhinolaryngology and head and neck surgeon
ETT	Endotracheal tube
FAMM	Facial artery musculomucosal
FDG-PET	$^{[18F]}$Fluorodeoxyglucose positron emission tomography

HIV	Human immunodeficiency virus
HN	Head and neck
HNC	Head and neck cancer
HNcSCC	Head and neck cutaneous squamous cell carcinoma
HNMDT	Head and neck multidisciplinary team
HPV	Human papillomavirus
HR	Hazard ratio
ICU	Intensive care unit
IMRT	Intensity-modulated radiation therapy
ITEM score	Immunosuppression, treatment, extranodal spread, and margin status score
LMWH	Low molecular weight heparin
LOS	Length of stay
LTBR	Lateral temporal bone resection
LVI	Lymphovascular invasion
MAC	Microcystic adnexal carcinoma
MCC	Merkel cell carcinoma
MCT	Medial canthal tendon
MCV	Merkel cell polyomavirus
MMS	Mohs micrographic surgery
MRI	Magnetic resonance imaging
mSCC	Mucosal squamous cell carcinoma
mTOR	Mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Clinical Excellence
NMSC	Non-melanoma skin cancer
OMF	Oral and maxillofacial surgeon
OS	Overall survival
OSA	Obstructive sleep apnea
PCA	Patient-controlled analgesia
PDGFB	Platelet-derived growth factor band
PDT	Photodynamic therapy
PE	Pulmonary embolism
PET	Positron emission tomography
PN	Parenteral nutrition
PNI	Perineural invasion
PNS	Perineural spread
PRS	Plastic and reconstructive surgeon
PUVA	Psoralen and ultraviolet A
RASS	Richmond agitation–sedation scale
RCRI	Revised cardiac risk index
RCT	Randomized controlled trial
RSTL	Relaxed skin tension line
RT	Radiotherapy
SCC	Squamous cell carcinoma

SHNCI	Sydney Head and Neck Cancer Institute
SLN	Sentinel lymph node
SMAS	Superficial musculoaponeurotic system
SNB	Sentinel node biopsy
SNLB	Sentinel lymph node biopsy
SSI	Surgical site infection
STBR	Subtotal temporal bone resection
STM	Soft tissue metastases
STSG	Split-thickness skin graft
TKI	Tyrosine kinase inhibitor
TLR7	Toll-like receptor 7
TMJ	Temporomandibular joint
TROG	Trans-Tasman Radiation Oncology Group
TTBR	Total temporal bone resection
UFH	Unfractionated heparin
US	Ultrasound
UVA	Ultraviolet A
VAP	Ventilator-associated pneumonia
VTE	Venous thromboembolism
XP	Xeroderma pigmentosum

Epidemiology and Aetiology of Non-melanoma Skin Cancer

1

Zubair Hasan and Faruque Riffat

Introduction

Skin cancer can be categorized broadly into cutaneous melanoma and nonmelanoma skin cancer (NMSC). Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) are the most common types of NMSC. Apart from these, rarer cutaneous malignancies, such as Merkel cell carcinoma (MCC) and malignancies of the adnexal structures, also occur. NMSC is by far the most common malignancy encountered in the human body, and is found frequently in primary care settings, which makes it an important public health consideration. It is managed by a variety of medical practitioners, being of multidisciplinary interest to otolaryngologists, head and neck surgeons, plastic surgeons, dermatologists, radiation oncologists, and primary care physicians.

When detected early, NMSC usually is easily amenable to treatment in low-risk outpatient settings; it is associated with low mortality. As such, most cancer registries the world over do not collect information pertaining to NMSC routinely, and therefore, precise epidemiological data are difficult to ascertain. Nonetheless, because of its overall high incidence, NMSC is associated with significant burden of disease and economic cost, particularly in the setting of advanced disease. Accordingly, the epidemiology of NMSC is important to define, as it establishes the magnitude of the problem and can dictate future planning and research priorities.

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The head and neck is the region most frequently affected by NMSC. This is not surprising, given that this is an area of maximal sun exposure, and UV radiation has long been known to be the most important aetiological factor in the pathogenesis of NMSC. However, a myriad of other genetic and environmental factors also contribute to the development of NMSC.

Epidemiology

Although a common disease, in particular in fair-skinned populations across Europe, North America and Australia, the epidemiology of NMSC shows marked geographical variations [1]. NMSC is more common than any other malignancy and BCC is more than two times as common as SCC [2]. In Australia, a country with the highest worldwide incidence, the prevalence of both SCC and BCC is on the rise [2–4]. This trend has occurred despite significant public health campaigns in recent decades, such as 'SunSmart', which advocates protective clothing, SPF 30+ sunscreen and avoidance of excessive sunlight, in particular during peak sunlight hours [5]. Generally considered to be easily amenable to treatment, NMSC nevertheless incurs a significant burden upon individuals and the healthcare system on account of its high incidence. With the average age of the Australian population increasing, it is anticipated that this burden will rise in coming years [4].

While cancer registries usually do not record epidemiological data, a series of cross-sectional studies in 1985, 1990, 1995 and, most recently, in 2002 has provided periodic estimates of the incidence of NMSC in Australia [2]. In the most recent survey from 2002, the age-standardized incidence of NMSC was estimated to be 1170 per 100,000 [2]. By comparison, the estimated incidence of cutaneous melanoma in 2012 was 62.7 in males and 39.9 in females per 100,000, respectively [6]. NMSC affects all age groups, although it is uncommon in individuals <40 years of age who otherwise have no other risk factors. Incidence rises markedly with age, with a significant increase in risk in those over the age of 70 years [2].

The 2002 survey also indicated roughly 1.8 % of the population were treated for NMSC in the preceding year, and confirmed rates of both BCC and SCC were higher in the northern latitudes of Australia, which are areas of greater sunlight exposure, in Australia-born residents and in poor skin tanners [2]. The median age in Denmark was found recently to be 68 years for BCC and 78 years for SCC [7]. Males are typically affected more commonly than females, especially in older age groups. Multiple tumours are common, and occur in ~25 % of patients with both BCC and SCC.

In contrast, NMSC is a rare disease in darker skinned populations. In India, for example, the estimated incidence is between 0.5 and 2 per 100,000 [8]. In Asian and black races, SCC occurs more frequently than BCC, is a more aggressive disease, occurring preferentially in sun-protected rather than sun-exposed areas and in areas of chronic scarring and ulceration [8–11].

Mortality associated with NMSC is relatively low compared with other cancers. Between 1998 and 2005 there was an average of 382 deaths per year in Australia, i.e. approximately 1–3 per 100,000, a figure representing <1 % of total cancer

deaths in this period [3]. This is not to say that NMSC does not contribute to significant morbidity and mortality. The overall high incidence of disease translates into significant healthcare costs [12]. Morbidity related to NMSC is in terms of lost productivity and perceived loss of quality of life. As an aesthetically important region of the body, surgery involving the head and neck may impact negatively upon patients' quality of life because of cosmetic disfigurement [13]. Furthermore, a recent systematic review of the literature examining the morbidity and mortality costs of NMSC found substantial costs arose because of premature death and lost productivity, which could have been averted with early detection and preventive strategies [14].

Increasing Incidence

Notwithstanding that NMSC is already the most common cancer in fair-skinned populations globally, data accumulated over the past two to three decades indicate that the incidence of NMSC is further on the rise. In Australia, between the 1985 and 2002 surveys, a statistically significant ($p < 0.0005$) rise in the age-standardized incidence was observed in both SCC and BCC—2.1 and 1.3 times the 1985 rates, respectively [2]. Furthermore, data obtained from Medicare Australia for items billed for treatment of NMSC by excision, curettage, laser, or cyrotherapy also indicate a steady annual rise in the number of NMSC cases treated by these methods between 1997 and 2010, with a more significant rise in the older age groups (>55 years of age) [4]. Suggested explanations for this phenomenon include (1) an ageing population, (2) increased detection, (3) changes in recreational outdoor activities, (4) clothing style, and (5) ozone depletion [12, 15].

Similar trends have been observed in Europe and North America, with a suggested 'epidemic' of NMSC. Nevertheless, the magnitude of NMSC in these continents pales in comparison to the absolute figures in Australia [15]. Exact figures are difficult to ascertain because of similar challenges in obtaining epidemiological data. In the USA, data collected between 1994 and 2006 on the basis of Medicare claims show an almost doubling of the incidence of NMSC [16]. In Northern Ireland, the incidence of SCC and BCC was 23–46 per 100,000 and 72–94 per 100,000 between 1993 and 2004, with a rise of 62 % in the number of skin cancer specimens handled by pathology laboratories during this period [17]. Examination of data in a number of other European nations has also shown increased incidence [12].

The implications of the increase in NMSC incidence will be felt over the coming decades and policy-makers will have to respond to the changing needs in treating a cancer that already incurs significant economic burden upon healthcare systems globally. The expense associated with treating individual NMSC cases is not substantial; Medicare data from the USA indicate that the cost of treating NMSC per case is 5–10 % of the cost for other cancers, but overall, it is the fifth most expensive cancer to treat [18]. In Australia it has been estimated that the costs are ~$700 per case. Given the high incidence of NMSC in Australia, it is not surprising that it is the most expensive cancer to treat overall, costing the healthcare system $264 million, or 9 % of total cancer expenditure [19]. Whereas the bulk of NMSC is treated

in outpatient settings, it is important to note that this cancer also incurs significant inpatient costs, with approximately 95,000 hospital admissions in Australia in 2010–11, a figure that is greater than that for any other type of cancer [6].

Aetiology

Risk Factors

The single most important aetiological factor in the pathogenesis of NMSC is UV-induced DNA damage [1]. NMSC is rare in dark-skinned races because of the protective role of melanin in UV-induced damage of skin cells [20]. The pathogenesis of SCC strongly correlates with cumulative exposure of UV radiation, in particular, UV-B (290–320 nm). In contrast, intermittent exposure is more significant in the development of BCC. Consequently, the distribution of NMSC is predominantly in the head and neck and in other areas of maximal sun exposure, such as the arms and back [21]. In Australia, factors shown consistently to be associated with an increased risk of NMSC are: (1) living in northern latitudes where exposure to the sun is maximal, (2) being fair-skinned with poor skin-tanning, and (3) high cumulative sun exposure. In addition, the male gender is affected more commonly than the female gender, as are fair-skinned races over Blacks or Asians. The risk of developing NMSC increases markedly with age [2].

Other risk factors include infection with human papillomavirus (HPV), chemical carcinogens, as well as acquired or inherited immunosuppression [22]. Tobacco smoking is an established risk factor for SCC but not for BCC [23]. Arsenic is a chemical carcinogen, which with chronic exposure is associated strongly with the development of a variety of dermatological manifestations and malignancies, including SCC and BCC [24]. Areas of chronic irritation and scarring also predispose to SCC, which is known to arise in the setting of chronic ‘Marjolin’ ulcers, sinus tracts and scars [25].

Immunosuppression and NMSC

NMSC is associated with significant morbidity in post-transplantation patients and in patients with autoimmune disorders who are on immunosuppressive agents, with increasing risk associated with an increasing duration of immunosuppression [26, 27]. The risk of cutaneous as well as systemic cancers is increased in this group of patients. The risk of developing SCC is particularly high in this group of patients. Recipients of solid organ transplants have an approximate 100-fold increase in the risk of developing SCC compared with a 10–16-fold increase in risk of developing BCC [28]. In a series of Australian heart transplant recipients, the cumulative incidence of NMSC was 43 % over 10 years [29], while in a series of Italian heart transplant recipients the corresponding figure was 35 % [30]. NMSC in this cohort of patients may be particularly aggressive, manifest as recurrent, multifocal, or

metastatic disease, and is therefore far more difficult to manage when compared to the non-immunosuppressed patient [31]. Risk of mortality is approximately 5 % in patients who develop SCC after a renal transplant [32]. With increasing numbers of transplant recipients and longer survival times of such patients, the burden of disease represented by this cohort of patients is likely to increase over the coming years.

Gene Mutations

As with all malignancies, acquired and inherited mutations in genetic code play a role in the pathogenesis of NMSC. The *p53* gene is a tumour-suppressor gene located on chromosome 17, mutations of which strongly correlate with an array of cancers, including SCC and BCC. The *p53* gene plays an important regulatory role in the cell cycle, in DNA repair, and in apoptosis [21]. Alterations in pyrimidine dimers, induced by UV radiation, may inactivate the gene, subsequently causing dysregulation of the cell cycle, failure of apoptosis and tumour formation [33].

Another relevant gene in the pathogenesis of BCC is patched (*PTCH1*). The *PTCH1* gene located on chromosome 9 is involved in the sonic hedgehog signalling cascade. Its involvement in disease was first identified in individuals with the nevoid BCC syndrome, an autosomal-dominant syndrome [25]. Patients with this syndrome have associated defects in the sonic hedgehog pathway and present with multiple BCCs, odontogenic cysts, skeletal defects, palmar and plantar pits, and calcification of the falx cerebri [25]. Mutations, however, also occur in sporadic cases of BCC. *PTCH1* is a tumour suppressor gene that binds to and inhibits smoothened (SMOH), a transmembrane protein that promotes cellular growth. Mutations in the *PTCH1* gene leads to failure of this inhibition and aberrant cellular growth [34].

Other inherited conditions, such as xerodermapigmentosum, also predispose individuals to NMSC. Xerodermapigmentosum is an autosomal-recessive condition wherein cells have a reduced capacity to repair UV-induced damage, leading to multiple SCC and other skin cancers. The mutation involved in xerodermapigmentosum disrupts the nucleotide excision repair, which enzymatically repairs UV-induced DNA damage [21]. Epidermodysplasiaverruciformis is another autosomal-recessive condition, wherein increased susceptibility to viral oncogenesis secondary to HPV leads to widespread wart formation followed by the emergence of cutaneous SCC [35].

Other Cutaneous Malignancies of the Head and Neck

Merkel Cell Carcinoma

MCC is a rare but highly malignant neuroendocrine tumour. Aetiology is also thought to be sunlight-related, although recently additional links have been made with polyomavirus and immunosuppression [36]. As with other types of NMSC,

the head and neck is the most commonly affected region of the body [37]. Data pertaining to the epidemiology of MCC have not been studied extensively. However, a cancer registry from Western Australia between 1993 and 2007 indicated that this region had the highest reported incidence of MCC in the world [38]. Males were found to be affected more commonly than females—1 per 100,000 in males compared to 0.63 per 100,000 in females, with the median age being 77 years [38]. MCC can also often occur in patients with pre-existing SCC or BCC. Prognosis is generally poor, particularly in metastatic disease, with a 5-year survival of 75 %, 59 %, and 25 % for local, regional, and distant disease, respectively [37].

Appendigeal Malignancies

Malignancies arising from the adnexal structures of the skin with apocrine, eccrine, follicular, or sebaceous differentiation are rare, representing <1 % of cutaneous head and neck malignancies [25, 39]. Although sebaceous carcinoma is rare, it is a highly malignant appendigeal neoplasm, with an incidence of ~1 case per million of the population [40]. Although it may occur outside the eyelid, an ocular distribution is more likely usually from a meibomian gland or from the glands of Zeis. The tumour most commonly occurs in patients aged 60–80 years, and affects Asian people more than other races [41]. Women are generally reported to have a higher incidence than men. However, this distribution is questionable, as in a series of 1349 patients, 54 % were men [42]. The presence of other aetiological factors is unclear, although Muir–Torre syndrome, an autosomal-dominant inherited condition, is characterized by sebaceous tumours and visceral neoplasms, and previous irradiation [41, 42].

Dermatofibrosarcoma protuberans: Dermatofibrosarcoma protuberans (DFSP) is a mesenchymal neoplasm of intermediate malignant potential. Although a rare skin tumour overall, it is the most common cutaneous sarcoma. The tumour demonstrates aggressive local growth with a high propensity for recurrence, despite surgical excision [43]. On the basis of population-based cancer registry data, the incidence of DFSP in the USA was found to be ~4 per million, with a small but statistically significant higher incidence in women than in men (4.4 vs. 4.2) [44].

DFSP occurs most commonly on the trunk. However, 10–15 % of cases occur in the head and neck, where it commonly affects the scalp and supraclavicular fossa [43, 44]. Aetiological factors are unclear, although recent advances in the molecular pathogenesis of DFSP have indicated that >90 % of cases are caused by reciprocal translocations between chromosomes 17 and 22. The resultant gene is a fusion between platelet-derived growth factor band (PDGFB) collagen 1A1, which leads to upregulation of the PDGFB protein. This is thought to underlie the pathogenesis of DFSP [45, 46]. Imatinib, an inhibitor of PDGFB, has recently been used to show demonstrable efficacy against DFSP [47, 48]. An association with antecedent trauma to the affected area has also been reported [43].

Angiosarcoma

Angiosarcoma of the head and neck is an exceedingly rare yet extremely aggressive malignancy of vascular origin. Data relating to head and neck angiosarcoma are sparse. Approximately half of all angiosarcomas occur in the head and neck and the scalp has been found to be affected more commonly than any other part of the body [49]. The male gender is affected more than two times than the female gender [50, 51]. One of the largest series of patients with head and neck angiosarcoma reported in the literature is from the Connecticut Tumour Registry between 1980 and 2001 [52]. Of 54 patients studied over a 21-year period, 29 patients had angiosarcoma of the head and neck, with a mean age at diagnosis of 71 years. The authors found a 1-year mortality of 48 % and a 5-year mortality of 28 %. This series also contained one instance of familial angiosarcoma of the head and neck. Documented risk factors include chemical exposure (vinyl chloride, thorium, arsenic) and radiation [53–55].

Summary

Precise epidemiological data pertaining to NMSC of the head and neck are unavailable. Nevertheless, it is clear that the burden of NMSC is increasing globally and that this burden can be significant in terms of personal and societal costs. While a variety of aetiological factors have been associated with NMSC, UV exposure remains the single most important factor for the development of NMSC, particularly in males of fair skin who live in equatorial longitudes.

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Pathology Reporting of Non-melanoma Skin Cancer at the ICPMR, Westmead Hospital

2

Hedley Coleman and Jeanne Tomlinson

Introduction

It is well known that Australia has the highest skin cancer incidence in the world [1] and approximately two-thirds of Australians will be diagnosed with skin cancer before the age of 70 years [2]. Non-melanoma skin cancers (NMSC) are the most commonly diagnosed form of cancer in Australia, with approximately 430,000 new cases estimated to have been diagnosed in 2008 [3].

It is vital that our head and neck pathology reports contain all of the relevant information in the form of minimum datasets. Information obtained from these pathology reports has a key role in the rational planning of patient management, which is then used to guide clinical decisions [4, 5]. Structured reporting of cancer, including NMSC, by pathologists aims to improve the standardization, completeness and usability of pathology reports for clinicians, and thereby improves decision support for cancer treatment [6–8]. The reporting of the grade, pathological stage, as well as other relevant information should provide the clinicians in the multidisciplinary setting with accurate staging and prognostic information in a consistent manner, thereby resulting in a high standard of care and appropriate management [4, 5]. Clinicians will thus be able to make suitable adjuvant therapy recommendations and provide accurate information on prognosis [5].

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Laboratory Considerations for the Skin Resection Specimen

The preparation in the laboratory of all skin specimens that are suspected of being malignant neoplasms should be standardized for the required consistency in reporting. The cut-up protocol that is followed in the Department of Tissue Pathology and Diagnostic Oncology at the Institute for Clinical Pathology and Medical Research (ICPMR), Westmead Hospital (the department), is based upon the standards and datasets for reporting of cancers of the Royal College of Pathologists, and is outlined below [6–8].

When preparing skin specimens in the laboratory, the overall size of the specimen should be measured and, particularly with excision specimens, this should incorporate three dimensions. The presence of the surface lesion or abnormality must be recorded and measurements should include the maximum diameter and elevation, if possible [6–8].

It is desirable and useful for multidisciplinary meetings that complex gross specimens suspected of harbouring a malignant lesion be photographed before dissection. The overall conformation of the tumour, its relation to the resection margins and how the tumour and margins have been sampled can be presented and assessed [5].

The surgical margin must be inked. Inking of the excised skin specimen assists in obtaining an accurate assessment of the surgical margins and thereby allows the determination of the adequacy of tumour excision and clearance from the margins (Fig. 2.1). The potential for dye to track and spread, which gives rise to false margins, should always be taken into account in the final histopathological assessment of the specimen [6–8].

When the lesion is clearly identified on the skin surface, sampling the polar margins of the skin ellipse should be discretionary and based predominantly on whether the lesion is close to the margin (<1–2 mm) or is less than that in the short/transverse axes [6–8].

When the lesion cannot be identified, or if there is uncertainty, the whole of the specimen should be sampled. In this situation, the polar ends from the long axis of a skin ellipse should also be examined. In certain very large specimens, in addition to sampling the lesion, the cruciate margins at 3, 6, 9 and 12 o'clock can be sampled, although the limitation in assessing margin clearance in these situations should be appreciated by the treating clinicians [6–8].

It is not possible usually to ink small and fragmented curetted or shave specimens. For these small specimens it is recommended that at least three levels be examined to reduce the possibility of sampling error [6–8].

Histopathology Reporting Protocol

The AJCC 7th edition divides NMSC into the following two separate chapters, each of which has a different staging system: [9]

- Cutaneous squamous cell carcinoma (SCC) and other cutaneous carcinomas (including basal cell carcinoma)
- Merkel cell carcinoma (MCC)

Fig. 2.1 Skin resection specimen that has been inked with attached sutures which allow for correct orientation and assessment of the surgical margin

This review of the pathological reporting of NMSC as practised within the department will, therefore, briefly address NMSC under these two broad headings. In addition, the standardized protocol for neck dissections for cases of head and neck NMSC is discussed briefly, as these tumours may present with regional lymph node metastases.

The minimum datasets produced as a result are based upon the Royal College of Pathologists [6–8, 10] and the Royal College of Pathologists of Australasia standards, as well as datasets for reporting cancers [5].

Cutaneous SCC and Other Cutaneous Carcinomas

Of the 430,000 newly diagnosed cases in Australia, basal cell carcinoma (BCC) accounts for at least two-thirds of NMSC, with most other NMSC being SCC [11]. In 2010, there were 445 reported deaths resulting from NMSC [12]. BCC rarely metastasizes to other organs, but it may be highly invasive and cause significant destruction of local tissues. SCC is also invasive but has a greater potential than BCC to metastasize. The true incidence of BCC and SCC is, however, not known in Australia as NMSCs are not reportable by law to the relevant state and national

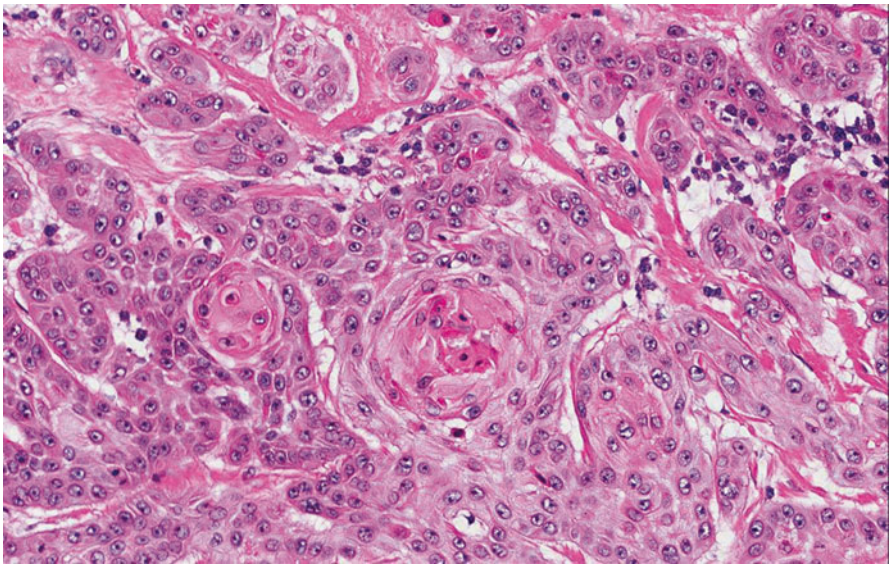

Fig. 2.2 Moderately differentiated squamous cell carcinoma showing vesicular nuclei and keratin eddies (H&E)

cancer registries [11]. The total numbers of cases of BCC and SCC that involve the skin of the scalp, face and neck is therefore unknown; however, it is believed that they would be fewer in number than the total number of estimated cases.

Cutaneous SCC

Most cutaneous SCCs arise in the skin of the sun-damaged head and neck and frequently involve the lower lip [13, 14]. Patients with rare genetically inherited disorders, such as albinism and xeroderma pigmentosum, as well as patients with systemic immunosuppression also have a high incidence of SCC [14]. Pathologists should separate neoplasms of the hair-bearing lip from those involving the vermilion zone, as these are staged according to the Head and Neck TNM staging system for the lip and oral cavity [9]. The AJCC 7th edition also excludes the eyelid from cutaneous SCC staging [9]. In the department, 80 cases of primary SCC of the skin of the face and neck, excluding the scalp and metastatic tumours to the parotid gland, were reported between 2007 and 2009 (unpublished data).

Histologically, SCC is composed of islands of squamous epithelial cells that arise from the epidermis in sun-damaged skin or within a pre-existing solar keratosis, and invade into the underlying dermis. The individual tumour cells have eosinophilic cytoplasm with large pleomorphic vesicular nuclei that exhibit mitotic figures. Individual cell keratinization and keratin pearls may be observed (Fig. 2.2). The degree of pleomorphism and deviation from normal squamous epithelium have

been used historically to subjectively grade SCC into well, moderately and poorly differentiated categories [13, 14]. The tumour islands and strands may be surrounded by a desmoplastic stromal reaction with a variable inflammatory response that may include eosinophils. The tumour cells may also infiltrate along nerves and invade lymphovascular channels [13, 14].

Immunohistochemical stains are of limited practical importance except in the spindle cell variant of SCC in which a broad-spectrum cytokeratin cocktail, such as MNF116, may be requested to confirm carcinoma; *p63* may also be useful [15]. In addition, staining for Ber-EP4 is uniformly negative, which allows distinction from keratotic BCC, as BCC demonstrates diffuse positive staining [15].

The World Health Organization's *Pathology and Genetics of Skin Tumours* (2006) outlines several histological variants of SCC [13].

- *Acantholytic SCC*. This variant is found often involving the head and neck. The islands of tumour cells demonstrate central acantholysis resulting in a pattern that appears gland-like [13, 15].
- *Spindle cell SCC* is rare and usually arises in sun-damaged or previously irradiated skin. These spindle-shaped tumour cells have large vesicular nuclei with numerous mitoses and minimal eosinophilc cytoplasm [13, 15]. Immunohistochemical stains are usually employed to exclude other spindle cell malignancies such as spindle cell melanoma and atypical fibroxanthoma.
- *Verrucous carcinoma* is a distinctive and well-differentiated variant of SCC that may occur on the skin of the head and neck but more commonly involves the oral cavity [13, 15].
- *Pseudovascular SCC* is an aggressive variant with prominent acantholysis [13, 15].
- *Adenosquamous carcinoma* is a rare variant that is characterized by the formation of mucin-secreting glands [13, 15].
- *Other variants:* Clear cell, signet-ring, infiltrating and rhabdoid (Table 2.1) [13, 15].

Basal Cell Carcinoma (BCC)

BCC is the most common variety of NMSC that usually arises in sun-damaged skin [13]. The tumour rarely occurs in black and oriental people [14]. Additionally, BCC that is indistinguishable from acquired types may be associated with the Gorlin Goltz syndrome (naevoid BCC syndrome) in younger patients [13]. In the head and neck region, BCCs are usually located in the central mid-face region; however, they may also rarely involve the external auditory canal. In our department, 246 cases of BCC of the skin of the face and neck, excluding the scalp, were reported between 2007 and 2009 (unpublished data).

Histologically, the tumours are composed of islands and nests of basaloid cells that exhibit palisading of cells at the periphery. The overlying epidermis may also show features of a solar keratosis. The cells have hyperchromatic nuclei with scanty, pale cytoplasm. Intercellular bridges are not observed. Numerous mitotic figures are seen with prominent numbers of apoptotic tumour cells (Fig. 2.3a) [13–15]. Surface

Table 2.1 Diagnostic summary: squamous cell carcinoma (SCC)

Macroscopy	
Site, type and size of specimen	Exclude vermilion of the lip and eyelid
Maximum diameter of lesion	
Microscopy	
Histological subtype	High-risk variants – invasive SCC associated with *in situ* SCC (Bowen disease), acantholytic, desmoplastic and spindle cell variants
Grade (according to most poorly differentiated area)	Well; moderately; poorly Poorly differentiated contributes to upstaging from pT1 to pT2
Tumour thickness (measured from the granular cell layer)	<2 mm; 2–4 mm; >4 mm <2 mm low risk for metastasis >10 mm high risk for metastasis
Level of invasion	Invasion of fat, facial/cranial bones and muscle – pT3 Invasion of skull base – pT4
Perineural invasion	Into skull base – pT4 High risk of local recurrence and mortality
Lymphovascular invasion	Document presence
Margins	0 mm – involved; <1 mm – close; >1 mm – clear
Immunohistochemistry	Cytokeratin, such as MNF116, positive in spindle cell variant
	Ber-EP4 negative
Lymph nodes	
Level and number of nodes involved	Primary pN staging determinant
Maximum size of metastatic deposit	pN staging determinant Tumour deposits >30 and >60 mm
Extracapsular extension	Widely regarded as a manifestation of potential biological aggression, considered to be associated with a worse prognosis

Adapted from RCP dataset for histopathology reporting of primary cutaneous squamous cell carcinoma, 2012 [6]

ulceration may be observed in larger lesions [15]. More aggressive tumours usually extend into the subcutis, with involvement of underlying cartilage in the nose and ears being relatively uncommon [15]. Perineural invasion might be observed; however, it is also relatively uncommon and is described more frequently in the infiltrating, morphoeic and basosquamous subtypes [15]. The tumour islands are surrounded by newly formed stroma, with retraction artefact or clefting at the tumourstromal interface being observed (Fig. 2.3b) [13–15]. The surrounding stroma may also show loss of appendages, amyloid deposition and contain a variable chronic inflammatory cell infiltrate. Calcification may also be observed within the centre of keratin eddies [15].

Immunohistochemical stains are of limited practical importance; however, diffuse positive staining for Ber-EP4 may be useful in separating BCC from SCC, as outlined previously [15].

The World Health Organization's *Pathology and Genetics of Skin Tumours* (2006) outlines several histological variants of BCC and any single lesion may demonstrate the features of more than one of these subtypes [13].

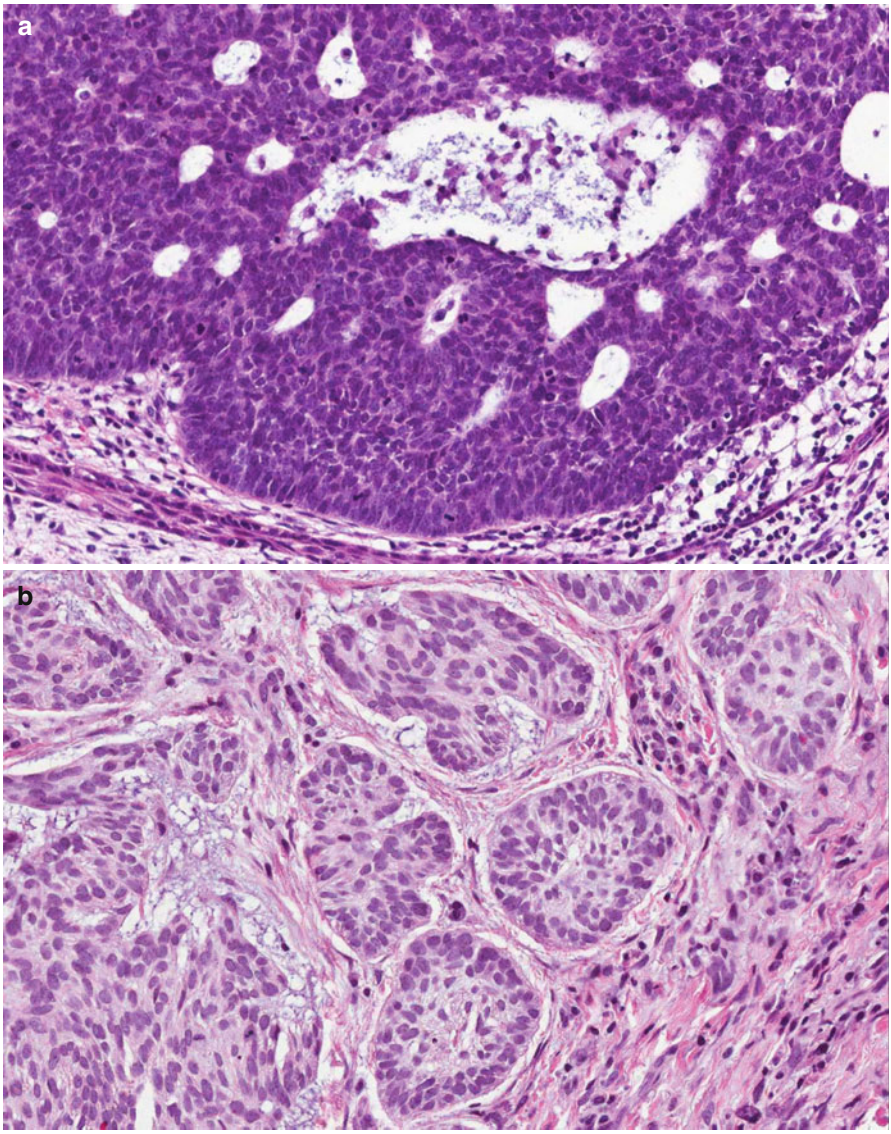

Fig. 2.3 (**a**) Nodular basal cell carcinoma with central necrosis and peripherally palisaded basaloid cells. (**b**) Micronodular basal cell carcinoma showing 'retraction artefact' around the tumour islands (H&E)

- *The superficial* (*multifocal*) variant usually presents clinically as an erythematous, scaly plaque and histologically is composed of multiple foci of budding basaloid cells arising from multiple points along the under-surface of the epidermis. This pattern accounts for 10–15 % of all lesions [13, 15].
- *Solid or nodular:* The clinical noduloulcerative lesion or rodent ulcer translates to a solid or nodular histological subtype. This accounts for almost 70 % of BCC

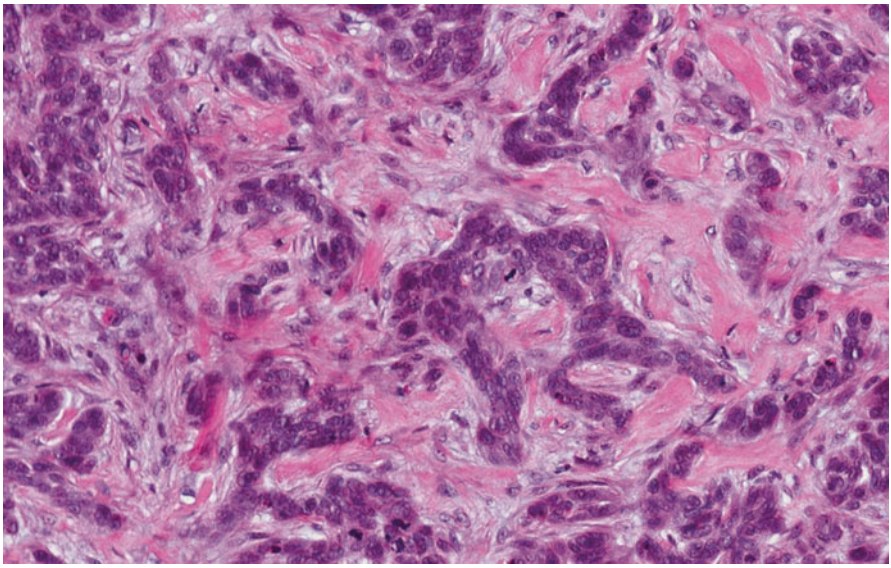

Fig. 2.4 Infiltrative basal cell carcinoma with irregular strands of basaloid cells surrounded by hyalinized collagen (H&E)

and is composed of islands of basaloid cells that exhibit apoptosis, focal necrosis and increased numbers of mitoses. Peripherally palisaded cells are present with retraction of the surrounding stroma being observed (Fig. 2.3a) [13, 15].

- The *micronodular* subtype resembles the solid type. However, the tumour islands are smaller with less pronounced peripheral palisading. The tumour also has a higher propensity for recurrence (Fig. 2.3b) [13, 15].
- The *infiltrating* type has an infiltrative pattern of growth without associated stromal fibrosis. This subtype accounts for about 5 % of cases and the tumour is composed of elongated strands of tumour cells that infiltrate between the collagen fibres (Fig. 2.4) [15].
- The *fibroepithelial* type is characterized by a unique clinicopathological presentation and an indolent behaviour [13].
- *BCC with adnexal differentiation* [13].
- The *metatypical* or *basosquamous* types are rare variants that are composed of islands of basaloid cells which mature into larger and paler cells [13, 15].
- *Keratotic BCC* is similar to the solid type. The centre of the tumour islands, however, demonstrates squamous differentiation and keratinization [13, 15].
- Other variants account for less than 10 % of all BCCs [13].
  - *Cystic* subtype is found most commonly on the face as a small well circumscribed tumour with little stroma and interspersed small cystlike structures containing keratinous debris and melanin pigment.
  - *Adenoid BCC* consists of thin strands of basaloid cells arranged in a reticular pattern. These may occur in association with the solid type.

Table 2.2 Diagnostic summary: basal cell carcinoma

Macroscopy	
Site, type and size of specimen	Exclude vermilion of the lip and eyelid
Microscopy	
Histological subtype	Infiltrating, morphoeic, micronodular and basosquamous are clinical high-risk variants
Level of invasion	Invasion of fat, facial/cranial bones and muscle – pT3 Invasion of skull base – pT4
Perineural invasion	Below the dermis, within tumour or advancing front Perineural invasion of skull base – pT4
Lymphovascular invasion	Particularly basosquamous
Margins	0 mm – involved; <1 mm – close; >1 mm – clear
Maximum diameter of lesion	T1 < 20 mm; T2 > 20 mm squamous cell carcinoma
Immunohistochemistry	Ber-EP4 positive – to differentiate from squamous cell carcinoma
Lymph nodes	Rare (if present follow cutaneous SCC nodal reporting proforma)

Adapted from RCP dataset for histopathology reporting of primary cutaneous basal cell carcinoma, 2012 [7]

- *Morphoeic* or *sclerosing BCC* is composed of thin, elongated strands of tumour cells within a surrounding dense, fibrous stroma.
- *Pigmented BCC* shows melanin pigment being formed within tumour cells. It is seen in several BCC variants, and can be clinically mistaken for melanoma (Table 2.2).

Merkel Cell Carcinoma (MCC)

MCC is a rare and aggressive cutaneous tumour with a high mortality rate that tends to occur in sun-exposed skin of elderly people, particularly on the head and neck. It occurs rarely in children. MCC exhibits both epithelial and neuroendocrine differentiation [13, 14, 16]. Only four cases involving the skin of the face and neck, excluding the scalp, were reported in the department between 2007 and 2009 (unpublished data).

MCC is presumed to be derived from Merkel cells that are located within the basal cell layer of the epidermis where they are concentrated in the touch-sensitive areas [13, 14, 16]. MCC produces ectopic peptides; however, the levels appear to be insufficient to result in a paraneoplastic syndrome, which is rare [16]. Merkel cell polyomavirus (MCV) is the first polyomavirus directly linked to human cancer [17]. MCV is clonally integrated into MCC tumour cells, which then require continued MCV oncoprotein expression to survive. Identification of this tumour virus has led to possible new opportunities for early diagnosis and targeted treatment of MCC. It has been suggested that there may, therefore, be two independent pathways for the development of MCC—one driven by UV irradiation and the other by the presence of MCV [17].

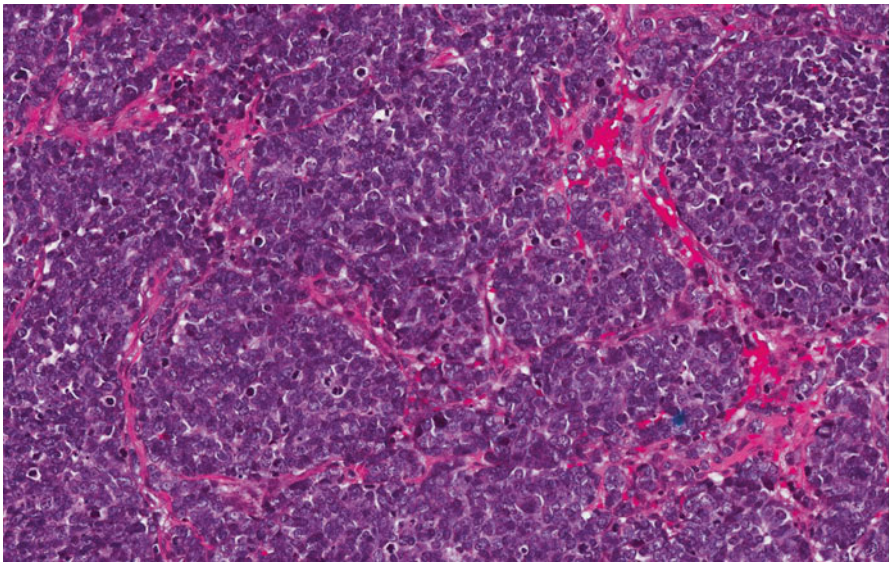

Fig. 2.5 Merkel cell carcinoma comprising nests of pleomorphic 'small blue cells' with hyperchromatic nuclei, small nucleoli and numerous mitoses (H&E)

Histologically, MCC is composed of 'small round-to-oval blue cells' which have hyperchromatic nuclei and scant cytoplasm, located within the dermis and subcutaneous fat [13, 14, 16]. The epidermis generally is not involved and it is separated from the tumour by a 'grenz zone' of normal papillary dermis. Rarely, tumour cells might invade the epidermis. The tumour cell nuclei typically have an evenly dispersed 'salt-and-pepper' type of chromatin pattern with two or three inconspicuous nucleoli and numerous mitotic figures (Fig. 2.5) [13, 14, 16]. The scanty cytoplasm is amphophilic and the cell borders are ill-defined. The tumour cells are arranged in densely packed sheets, cords and small nests. Extensive apoptosis and focal areas of necrosis are observed frequently within the tumour. Adverse histopathological features include small cell size, lymphovascular invasion and more than ten mitoses per high-power field [13].

Intermediate, small cell, trabecular and combined subtypes have been described [16]. The histological growth pattern of the intermediate variant is composed of a diffuse, sheet-like growth with relatively large cells. The small cell variant has small, round and dyscohesive groups of cells, whereas the trabecular variant has columns of tumour cells. The prognostic significance of the subtypes is not certain at this time. However, the small cell type may have some survival advantage. The surrounding stroma contains a variable inflammatory cell infiltrate. Occasionally, extensive infiltration into underlying muscle and lymphovascular spaces is identified. The differential diagnosis includes BCC, melanoma, lymphoma and metastatic neuroendocrine carcinomas, particularly small cell lung carcinoma (Table 2.3) [13].

Table 2.3 Diagnostic summary: merkel cell carcinoma

Macroscopy	
Site, type and size of specimen	
Maximum diameter of lesion	T1, T2, T3
Microscopy	
Level of invasion	Invasion of fat, bone, fascia cartilage and muscle – pT4
Lymphovascular invasion	
Margins	Involved – <1 mm, 1–5 mm, >5 mm
Maximum diameter of lesion	pT1 < 20 mm; pT2 20–50 mm; pT3 > 50 mm
Immunohistochemistry	CK-20, AE1/AE3, TTF-1, S-100, melan-A, desmin, leucocyte common antigen
Lymph nodes	
Level and number of nodes involved	pN0, pN1, pN2
Extracapsular extension and margin	

Adapted from RCP dataset for histopathology reporting of primary cutaneous Merkel cell carcinoma, 2012 [8]
CK cytokeratin, *TTF-1* thyroid transcription factor-1

MCC expresses both epithelial and neuroendocrine features. The immunohistochemical profile of the tumours include positive 'paranuclear dot' staining with cytokeratin, such as AE1/AE3 or Cam 5.2 (Fig. 2.6). Neuron-specific enolase, synaptophysin, chromogranin A, neurofilament protein and CD117 are also positive [13, 16]. Cytokeratin 20 (CK-20), a stain for low molecular weight keratin filaments, is a highly sensitive marker for MCC. The tumour is negative for cytokeratin 7 (CK-7) and thyroid transcription factor-1 (TTF-1), both of which usually are positive in small cell carcinoma of the lung [13, 16]. MCC is also negative for S-100, melan-A, leucocyte common antigen and desmin; excluding melanoma, lymphoma and rhabdomyosarcoma, respectively.

The tumour exhibits frequent locoregional recurrence and distant metastases.

Lymph Node Dissection of the Head and Neck for Metastatic NMSC

Seven major anatomical levels or groups of lymph nodes are described in the drainage of the head and neck. Neck dissection specimens should either be orientated by the surgeon and pinned or sutured to a cork/polystyrene board, or separated into the various nodal groups by marking the superior margin of each group with a suture, or by placing each group in a separately labelled container [5, 10].

These nodal levels should be designated as follows: Level I—nodes of the submandibular (IB) and submental (IA) triangles; Levels II, III and IV—nodes of the upper, middle and lower deep cervical chain; Level V—nodes of the posterior triangle; Level VI—nodes of the anterior compartment, around the midline structures

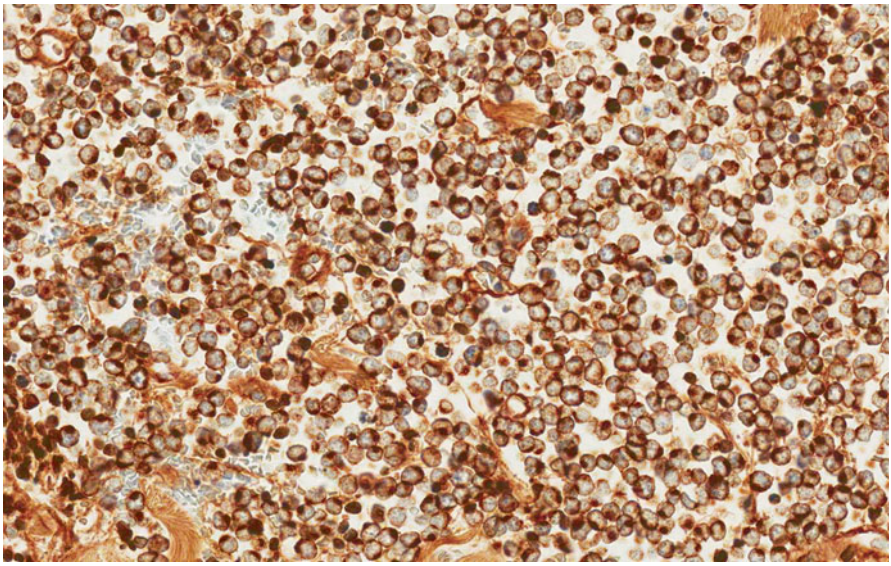

Fig. 2.6 Merkel cells exhibiting 'paranuclear dot' positive staining for keratin (AE1/AE3)

of the neck from the hyoid bone to the suprasternal notch; and Level VII—nodes that are located in the superior mediastinum [5, 10].

At present, the AJCC does not contain any specific advice on sentinel lymph node protocol for cutaneous SCC [6, 9]. Sentinel lymph node protocols, as performed for breast cancer, may however be undertaken for MCC, as requested [8].

Laboratory Considerations for Neck Dissection

For each anatomical level, when dissecting the specimen, the total number of nodes identified and number of nodes involved by carcinoma must be documented (Table 2.4). Record the size of the largest metastatic deposit in mm, which is a determinant in the TNM staging [5, 10]. The presence or absence of extracapsular spread (ECS) should also be documented as this is a manifestation of the biological aggression of the carcinoma and is associated with a poorer prognosis [10]. If ECS is present, the nodal levels showing this feature should be documented [5, 10]. The extent of ECS may be recorded by direct measurement (in mm) from the edge of the residual node when present, or as 'extensive' if residual node is not identified. If histological evidence of ECS is equivocal, it should rather be documented as being 'present' and this should prompt the use of adjuvant radiotherapy [10].

Table 2.4 Diagnostic summary: neck dissection

Neck dissection: left/right			
Levels submitted	I □ IIA □ IIB □ III □ IV □ V □ VI □ Other □		
Nodal level	No. nodes present	No. positive nodes	Extracapsular spread present
IA			Yes □ No □
IB			Yes □ No □
IIA			Yes □ No □
IIB			Yes □ No □
III			Yes □ No □
IV			Yes □ No □
V			Yes □ No □
VI			Yes □ No □
Other			Yes □ No □
Size of deposit(s)	……mm, level □		
Margins clear	Yes □ No □		

Adapted from RCP dataset for histopathology reporting of nodal excisions and neck dissection specimens associated with head and neck carcinomas, 2013 [10]

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Evaluation, Staging and Prognostication

3

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Initial Evaluation

The majority of non-melanoma skin cancers (NMSCs), particularly those encountered in primary care settings, will be identified and are easily amenable to local therapy. The most common types of NMSC are basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and rarer tumours, including Merkel cell cancer (MCC) and sarcoma. Metastatic SCC is a rare entity (<5 % of cases); metastatic BCC even more so [1]. However, it is important to identify high-risk patients because of the significant morbidity and mortality experienced by this subgroup of patients. Optimal management of these patients requires multidisciplinary input. Considerable research has been conducted into early identification of such high-risk patients. The initial approach involves a thorough clinical assessment, including detailed history and evaluation of any relevant systemic disease, risk factors and comorbidities, followed by histological analysis. Advanced lesions will require more detailed investigations, including cross-sectional imaging in the form of computed tomography (CT) and or magnetic resonance imaging (MRI). The investigation should not only

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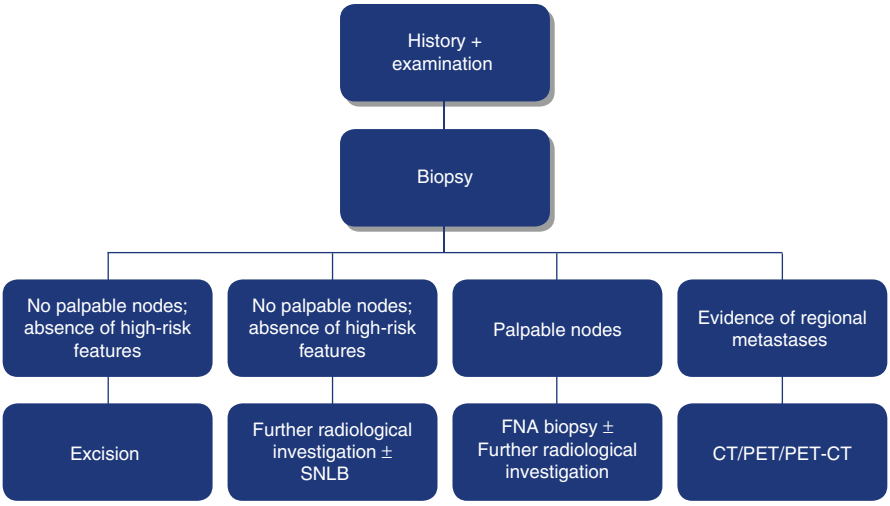

Fig. 3.1 Algorithm for initial evaluation of a patient with suspected NMSC. *CT* computed tomography, *PET* positron emission tomography, *SNLB* sentinel lymph node biopsy, *FNA* fine-needle aspiration

focus on the primary lesion but also on any potential regional and distant metastatic disease. One approach to the initial assessment of NMSC is shown in Fig. 3.1.

Basal Cell Carcinoma (BCC)

In contrast to SCC, there are no known precursor lesions for BCC. The classic presentation described for nodular BCC is a 'pearly' telangiectatic nodule with rolled borders. Central ulceration or crusting may occur. The nodular subtype accounts for approximately 60 % of BCC, but it can also be superficial or morpheaform. Superficial BCC may be a plaque or a papule and is pink/red in colour. Morpheaform lesions are smooth, flesh-coloured plaques or papules resembling scars with ill-defined borders [2].

In the head and neck, the nose is most commonly affected, followed by other sun-exposed areas, such as the scalp and ear [3, 4]. Prospectively acquired data in an Australian setting examining site-specific distribution of BCC has shown that 57 % (379 out of 663) of BCCs were in the head and neck, with the nose, cheek, forehead and ears most commonly affected (Table 3.1) [5].

Growth of BCC is slow and usually occurs over a number of years. BCC typically remains a local disease. Metastatic spread is extremely rare and usually occurs via the draining lymphatics. Recurrence is associated with anatomical location, with midfacial BCC associated with the highest recurrence rate. Local invasion may occur, with growth into the adjacent and underlying structures, leading to the description of the 'rodent ulcer'.

Table 3.1 Distribution of basal cell carcinoma in the head and neck in Queensland, Australia, 1997–2006 [5]

Anatomical site	No. of tumours
Nose	110
Cheek/perioral	64
Forehead/temple	61
Neck	47
Ears	38
Eyes	31
Chin/jaw	14
Scalp	5

Squamous Cell Carcinoma (SCC)

Actinic keratosis is the most common precursor lesion leading to SCC. Sometimes multiple, these lesions typically are rough, scaly and macular. Few actinic keratoses eventually will develop into SCC and the majority of these lesions will rescind, in particular in the event of withdrawal of sunlight exposure [6]. Bowen disease, or intraepithelial SCC, presents as well demarcated, erythematous scaly keratotic papules and plaques. The natural history of Bowen disease is not entirely clear, and it is thought the lesion may persist for years before invasion [7]. Verrucous carcinoma is a subtype of SCC, which in the head and neck most commonly affects the face and oral cavity. It presents as florid exophytic lesions. These lesions rarely metastasize; however, they may be locally invasive [8].

Morphologically, the appearance of SCC exhibits a range of phenotypic variability. Similar to BCC, sun-exposed areas of the head and neck are most commonly affected, with involvement of the lip or ear associated with poorer prognosis and increased metastatic potential. Patients with SCC may have a history of numerous premalignant lesions, which may be visible on examination or have been self-reported. Invasive SCC may also occur in the absence of a history of premalignant lesions. In such patients, SCC presents as a firm, hyperkeratotic lesion, although larger tumours may be associated with induration, ulceration, haemorrhage and necrotic areas. Local symptoms and signs—numbness, pain, trismus, immobility, paraesthesia, dysaesthesia, cranial nerve palsy—may indicate deep tissue invasion and/or underlying perineural spread, which is a poor prognostic factor [9].

SCC may metastasize to regional lymph nodes found within the parotid gland and lateral deep cervical chain. The presence of such metastases has a significant potential adverse impact on prognosis in terms of morbidity, mortality and quality of life [10].

Distant spread is rare but may occur in more advanced and/or recurrent disease and involve the lung, liver, brain and bone [9]. Dermal metastases are rare and may occur in the immunocompromised patient, often in the terminal phase of their illness, and are similar in appearance to primary SCC.

Table 3.2 High-risk features of non-melanoma skin cancer according to the *American Joint Committee on Cancer Staging Manual, 7th Edition* [13]

Depth
>2 mm thickness
Clark level >IV
Perineural invasion
Location
Primary site ear
Primary site non-glabrous lip
Differentiation
Poorly differentiated
Undifferentiated

Histopathological Evaluation

Histopathological investigation must be carried out for any lesion suspected to be an NMSC; it is important for definitive diagnosis, treatment selection and prognostication. Tissue sampling may be carried out as excision or punch biopsies. Care should be taken in cosmetically sensitive areas of the face where punch biopsy may be preferred. Whereas punch biopsy is often carried out, a proportion of cases will be missed using this modality. In one study punch biopsy was successful in diagnosing BCC in 81 % of cases [11].

Histologically, BCC is characterized by collections of cells resembling the basal layer of the epithelium. Retraction between the stroma and tumour may be present as an artefact and helps to differentiate BCC from appendageal tumours of similar appearance [12].

SCC and its precursor lesions—actinic keratosis and Bowen disease— are characterized by sheets and ridges of squamous cells. Actinic keratosis involves only part of the epidermis, Bowen disease involves the full thickness of the epidermis, and invasive SCC invades past the basement membrane. The degree of differentiation can be categorized as mild, moderate or severe and is related to prognosis. The degree of differentiation correlates with the extent of keratinization, nuclear hyperchromasia and increased mitotic activity [12].

Histological subtype is not the only means of firmly establishing a diagnosis, but it further permits identification of high-risk features, such as perineural invasion, degree of tumour differentiation and tumour depth. Histological subtype may also predict disease behaviour. Poor tumour differentiation, increasing tumour depth (Clark stage≥IV) and perineural spread collectively predict a poor prognosis (Table 3.2) [13].

Clinical or Histological Features Predictive of Advanced Disease

In addition to the features listed by the American Joint Committee on Cancer (AJCC), risk of advanced disease in SCC has been associated with a variety of clinical and histological patient and tumour factors, summarized in Table 3.3.

Table 3.3 Patient and tumour risk factors for metastatic squamous cell carcinoma

Patient	Tumour
Male gender	Size Diameter >2 cm
Immunosuppression Organ transplantation Haematological cancers AIDS	Depth Depth >4 mm Clark level >IV
Late presentation	Anatomical location Ear Non-hair bearing lip Cheek
	Perineural or lymphovascular invasion
	Grade Poor differentiation Undifferentiated
	Recurrent or poorly excised tumour

Previous editions of the AJCC staging manual have emphasized that horizontal tumour depth is an important prognostic factor. In reality, it is likely to be associated weakly with disease prognosis and risk of metastatic disease. In a series of 266 patients with nodal metastatic disease reported by Veness et al., 70 % of lesions were <2 cm in size [14]. In these patients who had primary T1 lesions (<2 cm), tumour thickness was found to be >4 mm in 60 % of them. The authors found a significant correlation in these patients between increasing tumour thickness and lesion size and nodal metastasis, suggesting that these tumours had a propensity for both vertical and horizontal growth. However, not all large SCCs were found to metastasize, suggesting that horizontally large tumours (2–3 cm) with minimal thickness (2–3 mm) may lack the propensity to metastasize.

Kraus et al. also showed that both tumour thickness and diameter are important for predicting metastatic disease. In their cohort of 45 patients with metastatic cutaneous SCC, 81 % had tumours of >2 cm in diameter, while 83 % had tumours with a depth of invasion of >3 mm [15]. Poorly differentiated SCC is more likely to be associated with the development of regional metastases. Breuninger and colleagues reported a significant difference in the rate of nodal metastasis between high-and low-grade SCC (17 % vs. 4 %) [16].

Perineural invasion is a relatively uncommon yet important finding on histological evaluation and is associated with larger primary tumours, a higher risk of local recurrence, and metastatic disease. Geist et al. report a 2.5–14 % incidence of perineural invasion in SCC and 3 % in BCC [17]. In a large series of patients with 967 cutaneous SCCs, Goepfert et al. found a 14 % prevalence of perineural invasion and a 47 % local recurrence rate, and a metastatic rate of 34.8 % in patients with perineural invasion treated surgically [18]. Lymphovascular invasion, at least in one study, has also been reported to increase the risk of developing nodal metastatic disease. In this study, Moore and colleagues documented 40 % of patients with nodal metastasis having lymphovascular invasion compared with only 8 % of node-negative subjects [19].

Anatomically, high-risk lesions include those draining to the parotid basin—lateral scalp, temple, forehead, ear or cheek. A study of 295 patients who underwent neck dissection for metastatic disease in the setting of primary cutaneous SCC revealed that 38 % of lesions originated in the anterior face, 15.2 % were from the external ear, and 22.4 % were from the posterior head; the primary site was not identifiable in 25 % of cases [20].

Incomplete resection margins and failure to consider re-excision or adjuvant external beam radiotherapy with subsequent persistent disease or the development of local recurrence are important treatment factors to bear in mind. Patients developing local recurrence are at a much higher risk of nodal metastases [14, 21, 22].

Further Evaluation in Advanced NMSC

Regional or distant metastases occur in a small, but prognostically significant, number of NMSCs. While SCC and BCC of the head and neck region are often considered to be associated with relatively good prognosis, the group that develop regional disease are at an increased risk of morbidity and mortality. These patients require expert assessment and evaluation within a multidisciplinary setting [23].

Clinical examination should be performed in all patients with suspicious skin lesions to assess for palpable lymph nodes (Fig. 3.2). A complete skin examination should also be performed to assess for other skin lesions, in particular for 'in-transit' metastases in close proximity to the primary lesion [2]. Palpation, however, is not an entirely accurate method for diagnosis of neck disease. Haberal et al. conducted a prospective study of 48 patients with head and neck cancer undergoing neck dissection, and compared the modalities of palpation, ultrasound and CT findings to the gold standard of histopathology of lymph nodes [25]. They found palpation had a positive predictive value and negative predictive value of 78 % and 74 %, respectively.

In comparison, the corresponding values for ultrasound were 94 and 80 %, and for CT 90 and 85 %. Similar data specific to cutaneous NMSC are lacking.

In patients with palpable lymph nodes, radiological evaluation is required to ascertain further locoregional and distal metastasis [26]. The most superior imaging modality of radiological investigation has yet to be identified in the context of NMSC; modalities available include ultrasonography, CT, MRI and positron emission tomography (PET) scanning [27]. If clinical or radiological suspicion of metastatic disease is raised, further assessment and cytological confirmation via fine-needle aspiration biopsy should be performed. If this subsequent analysis is positive for metastatic disease, the patient then undergoes therapeutic neck lymph node dissection to remove metastatic disease. The addition of adjuvant external beam radiotherapy increases the 5-year disease-specific survival (DSS) rate from 54 % for those patients treated with surgery alone, to 73 % in patients treated with a dual modality. The disease-free interval is also improved [28].

Low-risk patients with no palpable lymph nodes typically do not require further evaluation. The presence of high-risk clinical or histological features—large or neglected tumours, recurrent disease, suspected or documented cranial nerve involvement, including the facial and/or trigeminal nerves, the immunocompromized host, or extracutaneous involvement—may indicate a need for further

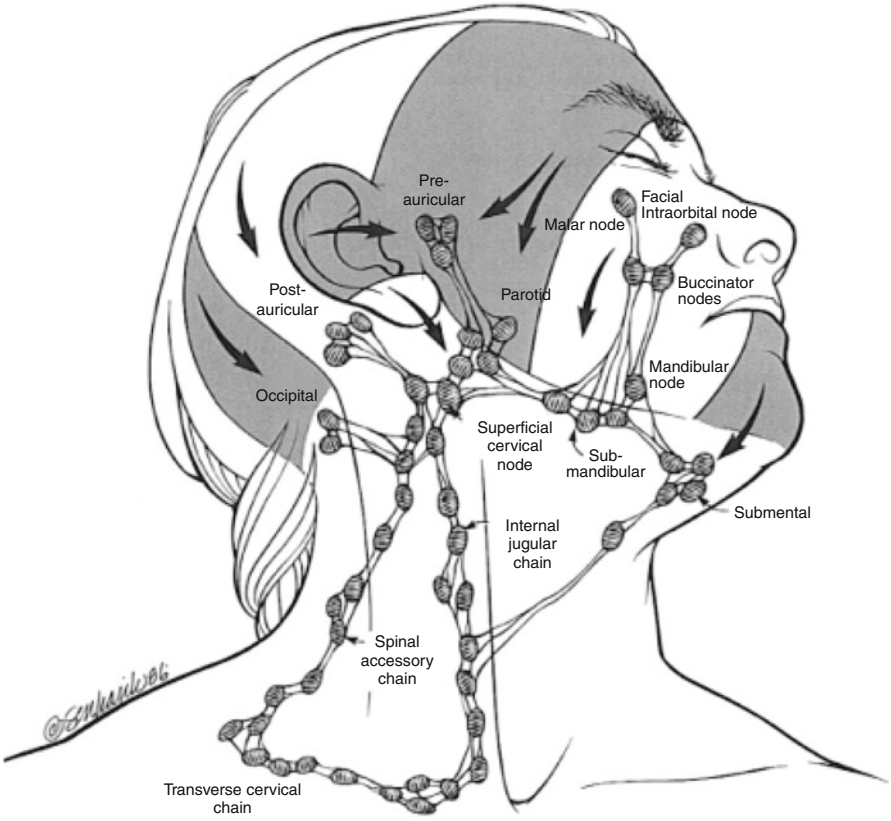

Fig. 3.2 Lymph node drainage of the head and neck [24]

radiological evaluation [24]. The value of sentinel lymph node biopsy is currently uncertain, although it has been advocated by some authors [29, 30].

Metastatic BCC represents a rare entity, and is reported to occur in as little as 0.0028–0.55 % of cases [1]. BCC is more likely to cause deep local invasion rather than metastatic spread. As such, reliable data are lacking on further evaluation and management of patients with metastatic disease. Locoregional lymph nodes, lung, bone and liver are most commonly affected. Metastases are more likely to occur with large, deeply invasive tumours and in tumours with perineural involvement. Data are limited regarding how best to evaluate such patients, but indicate the potential need for early aggressive treatment in selected patients [31].

Staging

The AJCC TNM (T, tumour; N, node; M, distant metastasis) system is used for staging of NMSC. Previous editions of the TNM staging, importantly, failed to separate NMSC accurately on the basis of histology and disease extent. This had a significant adverse impact on treatment allocation and prognostication. In 2002, O'Brien et al. proposed an alternative staging system (i.e. PN staging system), which sought to

Table 3.4 TNM staging for cutaneous squamous cell carcinoma and other cutaneous carcinomas[a] based on the *American Joint Committee on Cancer Staging Manual*, *7th edition* [13]

Tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
T1	Tumour ≤2 cm in greatest dimension with fewer than two high-risk features[b]
T2	Tumour >2 cm in greatest dimension or tumour any size with two or more high-risk features
T3	Tumour with invasion of maxilla, mandible, orbit or temporal bone
T4	Tumour with invasion of skeleton (axial or appendicular) or perineural invasion of skull base
Node (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, >3 cm but not >6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, >3 cm but not >6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
N3	Metastasis in a lymph node, >6 cm in greatest dimension
Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

[a]Excludes cutaneous squamous cell carcinoma of the eyelid

[b]High-risk features for the primary tumour (T) staging: (1) Depth/invasion: >2 mm thickness, Clark level >IV, or perineural invasion; (2) anatomical location: primary site ear, or primary site non-hair bearing lip; (3) differentiation: poorly differentiated or undifferentiated

separate patients into prognostic groups on the basis of disease extent and involvement of parotid and/or cervical nodal regions (Table 3.4) [32]. Some of the suggested changes have been adopted into the current edition of the AJCC staging manual, as well as omission of MCC from staging of NMSC, in favour of its own unique staging system. The P classification, although subsequently shown to be a significant prognostic factor in patients with cutaneous SCC of the head and neck [33], has been omitted from the current TNM staging system, which has been devised for NMSC of the entire body.

The current T system classifies patients on the basis of size of primary tumour, as well as presence or absence of high-risk features, and invasion into underlying structures. The N classification examines size and number of lymph node metastases in the ipsilateral and contralateral sides to the site of primary disease. The M classification indicates the presence or absence of distant metastatic disease.

Table 3.5 The O'Brien et al. system for clinical staging of metastatic cutaneous SCC involving the parotid gland and neck [32]

Parotid	Neck
P1 – Metastatic node ≤3 cm	N0 – No clinical neck disease
P2 – Metastatic node >3 cm but ≤6 cm OR Multiple parotid nodes	N1 – single ipsilateral neck node ≤3 cm
P3 – Metastatic node >6 cm OR disease involving facial nerve or skull base	N2 – Single node >3 cm OR Multiple nodes or contralateral neck nodes

Prognostication

The O'Brien et al. [32] classification (Table 3.5) has been tested by Palme et al. [33] on a cohort of 126 patients with cutaneous SCC with parotid or neck disease. Patients were retrospectively re-stratified into groups on the basis of the O'Brien classification system. The results of multivariate analysis showed a statistically significant decrease in 5-year DSS, which ranged from 66 % for P0 to 33 % in patients with P3 disease. They did not, however, find that the status of neck disease significantly altered survival. Subsequent multicentre analysis involving 322 patients from 3 Australian and 3 North American centres showed statistically significant ($p = 0.027$) differences in survival between patients with pathological N-positive and P-positive disease when compared with N0 and P0 patients, without showing the value of subgroupings within the N and P stages [34].

The Immunosuppression, Treatment, Extranodal spread and Margin status (ITEM) score is a useful tool in prognostication of patients with metastatic cutaneous SCC. A study conducted by the Westmead Hospital Group (Sydney, Australia) involved a cohort of 250 patients to identify prognostic markers in patients with metastatic cutaneous SCC [35]. Multivariate analysis showed the following four important factors of strong prognostic significance: (1) immunosuppression, which was associated with negative outcome (HR 0.32, 95 % CI 0.16–0.66), (2) absence of extranodal spread (HR 9.92, 95 % CI 1.28–77.09), (3) surgery and radiotherapy over surgery only (HR 0.32, 95 % CI 0.16–0.66) and (4) clear resection margins (HR 1.85, 95 % CI 1.85–3.37). Presence of extranodal spread, therefore, is the strongest predictor of poor prognosis. Other factors studied, which apparently were not prognostic of statistical significance, included (1) presence of parotid disease, (2) lymph node size and number and, importantly, (3) the P or N stage of the O'Brien staging system [32], which was found not to provide a significant difference in outcome.

Ch'ng et al. have also found recently that epidermal growth factor receptor (EGFR) expression in cutaneous SCC is associated with poorer prognosis [36]. They discovered that EGFR was expressed in 79 % of lesions that originate as primary lesions and subsequently metastasize, although only 43 % of tumours that had metastasized expressed EGFR [36]. However, further research is warranted to more accurately define the impact of EGFR expression upon prognosis in patients with NMSC.

Prognostic factors in NMSC can thus be summarized on the basis of the following patient, tumour and treatment factors:

- Patient factors
  - Immunosuppression (in particular in the context of solid organ transplantation)
  - Recurrent NMSC
- Tumour factors
  - Tumour size
  - Tumour location
  - Metastasis
- Treatment factors
  - Degree of completion of resection
  - Use of radiotherapy

Summary

Evaluation of NMSC includes an accurate and systematic history and examination. Assessment must include the primary skin lesion as well as draining lymph nodes. Tissue sampling is crucial for histological evaluation and to assess the presence of high-risk features of NMSC. A number of imaging modalities are available; however, the optimal modality is yet to be clarified. Patients with complex or metastatic disease or those with high-risk features, in particular, will require further imaging. Such patients should be managed in a multidisciplinary setting with input from a variety of clinicians. A number of strong prognostic factors have been identified for predicting outcome in patients with NMSC; nevertheless, further research is essential to develop a precise prognostic model.

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Non-melanoma Skin Cancer: Primary Non-surgical Therapies and Prevention Strategies

4

Malcolm A. Buchanan, Brett Levin, and Michael Veness

Introduction

Patients with non-melanoma skin cancer (NMSC) may be managed non-surgically on the basis of relevant tumour and patient factors. This chapter presents non-surgical treatment options for the two most common NMSCs—basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). The management of Merkel cell carcinoma (often non-surgically) is discussed in Chap. 6. Excision, although considered the gold standard, is not always possible or considered the best option (Box 4.1). Numerous topical (e.g. 5-fluorouracil [5-FU], imiquimod) and intralesional (e.g. methotrexate, interferon) [1] options, as well as other modalities are widely available, often with ill-defined criteria for using them. Additionally, because the evidence to support these treatments is predominantly low-level with long-term follow-up (≤5 years) lacking, clinicians need to consider various issues before using any recommendation.

An efficacious non-surgical modality for invasive NMSC available to the clinician is radiotherapy (RT), which has a well-established and documented role in the definitive treatment of NMSC [2]. The outcome, with regard to cure for small (<2 cm) NMSCs treated with RT, is similar to surgery and provides the clinician with an alternative option in appropriate circumstances [3]. The role of adjuvant

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Box 4.1 Non-surgical Options
- Excision remains the treatment of choice in select patients.
- Patient and tumour factors may better suit a non-surgical approach.
- Clinicians have numerous topical, intralesional and destructive options available.
- Superficial lesions can often be treated non-surgically.
- Radiotherapy plays a greater role in invasive NMSC.
- The supportive evidence for most options is often low level.

Box 4.2 Role of Radiotherapy
- Radiotherapy is an efficacious non-surgical treatment option for select patients with NMSC.
- The cosmetic outcome of radiotherapy compares favourably with surgery, especially if surgical defects require graft or flap reconstruction.
- Adjuvant radiotherapy decreases the risk of local recurrence where surgical margins are inadequate and re-excision may compromise form or function.
- Patients with NMSC located on the mid-face may particularly benefit from an opinion on the role of radiotherapy, in appropriate circumstances.

RT in treating microscopic cancer following excision is not as well documented but recommended in circumstances in which the risk of recurrence is present (close/positive margins) and re-excision is not possible [4].

Radiotherapy

RT (or external beam RT) may be recommended as definitive treatment when surgery is not optimal or possible, and also in the adjuvant setting, to reduce the risk of recurrence (Box 4.2). A recommendation of definitive RT may be determined by the site or size of a tumour and when the functional and/or cosmetic outcome may be better achieved non-surgically by RT. Adjuvant RT aims to reduce the risk of locoregional recurrence, usually when close or positive excision margins are present. Palliative RT is useful in symptom control in patients with advanced disease, typically in the presence of advanced ulcerative lesions in patients with poor performance status who are often well palliated with 1–5 fractions of RT.

Advantages of RT

RT avoids the need for an operation and the associated surgical morbidity, scarring and the requirement for reconstruction. It has the benefit of being able to treat tissue extensively and deeply (5–30+ mm margins) that may otherwise require excision

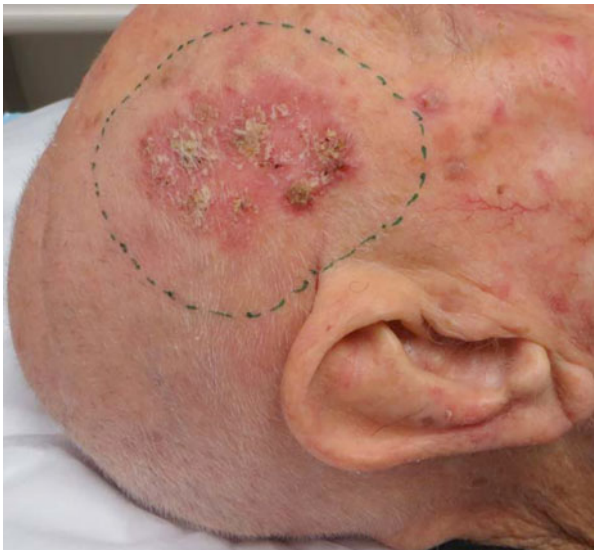

Fig. 4.1 Elderly man with a large area of *in situ* SCC (Bowen disease) treated with widefield local radiotherapy, as opposed to wide excision and graft reconstruction. Note the *marks* delineating the planned radiotherapy field

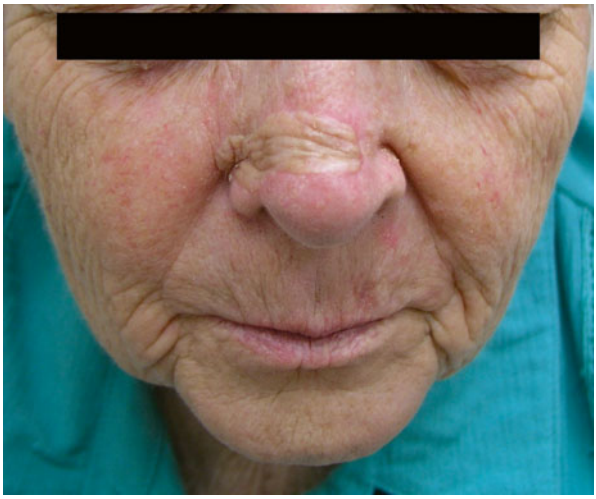

Fig. 4.2 Woman having previously undergone wide excision of a mid-nasal BCC and repair with a skin graft. The difference in skin colour and elasticity from the donor site compared with the nose is obvious. The patient may have been better treated, or at least offered the option, non-surgically, with radiotherapy with the likelihood of achieving a better cosmetic result

(+/− reconstruction) (Fig. 4.1). An obvious benefit is improved cosmesis, especially in situations in which a flap or graft is required (Fig. 4.2) [5]. RT is particularly beneficial in areas of the mid-face where excision and reconstruction could have a greater impact on form and function (e.g. the periorbital region—especially the medial canthus—lower eyelid, nose [in particular the ala and tip], nasolabial fold, and lip and chin) (Fig. 4.3a, b) [6]. Elderly patients with co-morbid conditions are also often better approached with RT.

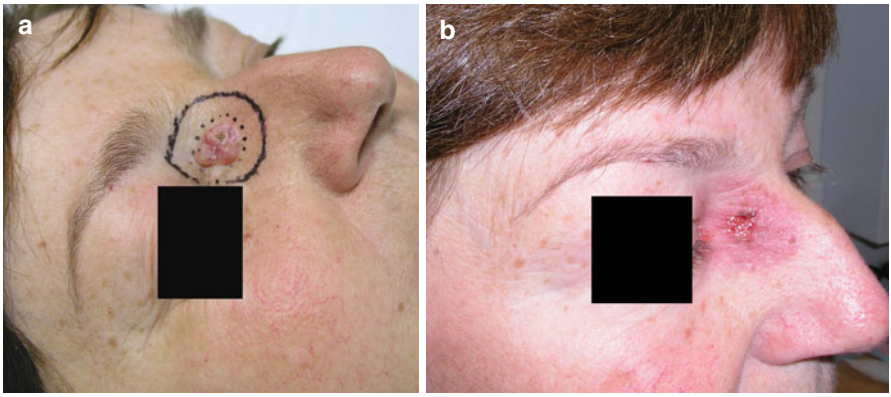

Fig. 4.3 (**a**, **b**) Patient with a moderately large nodular BCC located on the medial canthus. Excision with appropriate margins and reconstruction may result in suboptimal cosmesis. The patient proceeded to definitive radiotherapy (55 Gy in 25 daily fractions). The patient had an internal eye shield inserted to protect the orbital contents. She had an excellent response to radiotherapy and at 4 weeks post-completion had complete regression of her BCC and a resolving radiotherapy reaction

Disadvantages of RT

The time required to undergo a course of RT is a disadvantage compared with day-case surgery. A typical course of fractionated RT ranges from 10 to 25 once a day (minus weekends) with 10-min outpatient treatments (or fractions). However, in older, sicker patients fewer (3–5) fractions can be used. On account of the risk of potential late complications, such as soft tissue/cartilage necrosis, RT cannot be delivered a second time to the same site. Younger patients (<50 years) can still receive RT, but the late (>5 years) in-field cosmetic outcome (i.e. hypopigmentation, telangiectasia, epidermal atrophy), especially with continued unprotected sun exposure, may not be ideal (Fig. 4.4). The risk of an in-field radiation-induced malignancy many years after small-field cutaneous RT is theoretically possible, but rare, and should not be a reason to avoid RT in younger patients.

Patients with xerodermapigmentosum (XP) should not undergo RT because of the risk of inducing skin cancers, especially at a younger age. Similarly, lower limb lesions, especially in older patients suffering from diabetes and peripheral vascular disease, should not be irradiated if possible, because of the risk of delayed wound healing [7].

Basal Cell Carcinoma (BCC)

BCCs are the most common NMSC diagnosed, with the majority located on the head and neck. They are often excised (with margin assessment); typically with a margin of 3–5 mm. Surgery can also be performed under real-time margin control

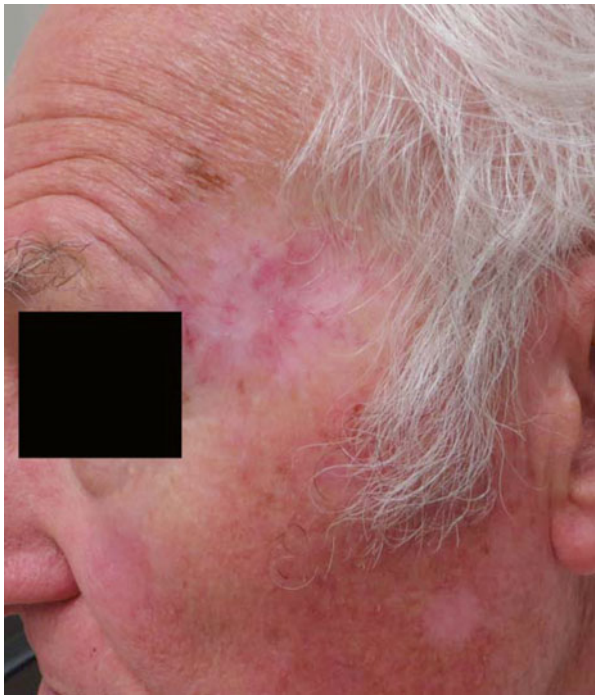

Fig. 4.4 Elderly man 5 years after receiving adjuvant radiotherapy to his left temple. Note the well delineated in-field hypopigmentation, scattered telangiectasia and epidermal atrophy (or smoothness). Late cosmetic changes in older patients, even midface, are usually of little concern to the patient. Women will often apply foundation makeup with good effect

with frozen sections to determine the extent of clearance (Mohs micrographic surgery). However, a variety of non-surgical options are available to the clinician, including RT, cryosurgery, photodynamic therapy (PDT), curettage and cautery, topical treatment, and intralesional injection.

Radiotherapy (RT)

Only a few randomized controlled trials have reported on the outcome of RT on patients with BCC. A Cochrane review of seven treatment modalities suggested that either RT or surgery results in the lowest recurrence rates [8].

A trial of 347 patients examining RT versus excision of facial BCCs of <40 mm in diameter showed fewer recurrences in the surgical cohort at 4 years (RR 0.09), and that cosmetic outcome was enhanced post-surgery (87 % rated as 'good') at 4 years compared with RT (69 %) [9]. Conversely, in a separate trial of 374 patients, no significant difference was seen in recurrence rate between patients receiving RT or Mohs surgery, and overall cosmetic outcome did not differ between treatment groups [10]. Of note, primary tumours with aggressive histology were likely to be excised more incompletely than non-aggressive ones. The evidence suggests that RT offers patients an effective option if surgery is declined or the outcome (form and/or function) is likely to be better non-surgically (Fig. 4.5a, b).

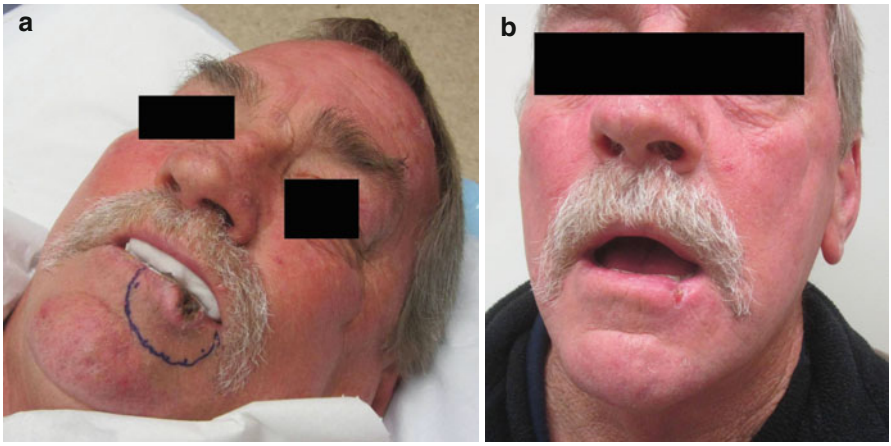

Fig. 4.5 (**a**, **b**) A 62-year-old man with a moderately advanced left side lower lip SCC. Although technically operable, the patient elected to proceed with definitive radiotherapy, thereby avoiding the potential risk of microstomia, as he would have required wedge excision. The patient received 55 Gy in 25 daily fractions using orthovoltage energy photons and following insertion of an oral cavity lead shield. At 3 months post-treatment he has experienced complete clinical regression of his cancer with no impact on function

Adjuvant RT is an option in the setting of close/positive excision margins, especially if a flap has been used for reconstruction, as detecting deep recurrence, especially in the mid-face, can be difficult. Up to 30 % of incompletely excised BCCs will recur locally [11], making RT a useful modality, especially if re-excision is not considered. In a trial of adjuvant RT versus surgery alone, RT improved the 5-year local control rate from 61 to 91 % [12]. Ten-year local control rates were similar between the two groups (92 % vs. 90 %), indicating that most local recurrences can be salvaged surgically, although some patients require reconstruction after wide local excision.

Cryotherapy

Cryotherapy (aka cryosurgery) is selective freezing of tissue (using liquid nitrogen at −50–60 °C). It results in local necrosis and is utilized in a broad spectrum of benign, pre-malignant (actinic keratosis [AK]) and malignant conditions (including NMSC). Studies consistently report cure rates of >95 % with excellent cosmesis [13]. A study of 96 patients with BCCs of <2 cm in diameter in the head and neck compared cryosurgery administered with a cone spray technique and double freeze/thaw cycle, with excision, and reported no significant difference in the rate of recurrence at 1 year and a slightly improved cosmetic outcome with surgery [14]. Cryotherapy is a relatively cheap, versatile and convenient (rooms-based) modality but does require appropriate selection and application to be effective. Relative contraindications to its application include recurrent NMSC, lesions that are deeply invasive, and those with indistinct borders.

Photodynamic Therapy (PDT)

PDT uses topically applied non-toxic photosensitive compounds, such as 5-aminolevulinic acid and methyl aminolevulinate, which are exposed selectively to light and which activate these photosensitizers that localize in malignant cutaneous lesions. In one study of 103 patients, PDT was compared to surgery for facial BCCs [15]. Despite more recurrences in the PDT group at 12 months (RR 4.42), the cosmetic outcome was significantly better ($p<0.001$). Local adverse effects of PDT were found to include burning sensation, pain and erythema in 52 % of PDT patients compared with 29 % in the surgical group ($p=0.03$) [15].

PDT is an option with an excellent cosmetic outcome that can be repeated on multiple occasions. Unlike cryotherapy it is less likely to complicate the need for future surgery in a treated area secondary to scarring. It is highly effective in treating *in situ* SCC and AK, as well as superficial BCC, especially when extensive lesions are present. Nodular BCC of <2 mm in depth is also treatable. Currently, its use is not recommended for invasive SCC and alternative modalities should be considered for these patients (e.g. RT) [16]. Unlike many other treatments, PDT requires treatment within a hospital setting.

Intralesional Interferon

Interferon, an immunomodulator, activates cells of the immune system and increases recognition of tumour cells by upregulating antigen presentation to T-lymphocytes. Trials of interferon-β versus placebo have shown a reduction in recurrence of BCCs in the interferon group [17]. The combination of interferon-α-2a and 2b does not seem to improve efficacy. Pain at the injection site and 'flu-like' symptoms are typical side-effects of interferon treatment.

Curettage and Cautery (or Electrodissection)

Curettage and cautery, similar to cryotherapy, is a destructive modality best utilized in selected, non-recurrent low-risk lesions, such as well-defined superficial and nodular BCC. The practical application of this technique varies, but when used by experienced clinicians, it achieves cure rates of >95 % [18].

Fluorouracil

5-FU is a pyrimidine analogue, which is transformed inside cancer cells into cytotoxic metabolites resulting in apoptosis by inhibition of thymidylate synthase and the cell's ability to synthesize DNA. It is applied topically (twice daily for ≥3–6 weeks), and a vehicle, such as phosphatidyl choline, can be used to enable penetration of 5-FU into lesions. It is often applied widely to the face and scalp, but because patients can experience symptomatic erythema/desquamation, they may modify or even discontinue

treatment. The evidence for its application in nodular/invasive BCC or invasive SCC is lacking and, therefore, its use is recommended predominantly for relatively small, superficial BCC, especially if other better established modalities are not considered options. Clearance rates of >90 % have been documented when applied appropriately [19].

Imiquimod

Imiquimod is a topical immunomodulator that activates immune cells through the toll-like receptor 7 (TLR7). Natural killer cells, macrophages and B-lymphocytes are activated by imiquimod via TLR7, with resultant production of cytokines, including interferon-α, interleukin-6 and tumour necrosis factor-α. It is applied once or twice per weekday for 6–12 weeks, and as with 5-FU, results in an intense local cutaneous reaction. Cost can also be an issue relative to most other treatment options. Although used in many settings, including nodular BCC, its application is best limited to superficial BCC where clearance rates of >80 % have been documented consistently [20].

Hedgehog-Pathway Inhibitors

A recent finding in patients with BCC has been genetic alterations resulting in upregulation in the hedgehog signalling pathway. A new oral drug, vismodegib, inhibits this pathway and may offer a potentially new treatment for patients with advanced (inoperable and/or previously treated) and metastatic BCC, and for those with Gorlin syndrome (basal cell nevus syndrome). A recent study reported a complete response of 21 % in eligible patients, although the median duration of response was short (7.6 months) and serious adverse effects and even death were reported [21]. With further research it is likely that the outcome for these patients will improve with molecular inhibition of the hedgehog signalling and other pathways.

Conclusion

Many studies (often small) document the treatment of patients with low-risk BCC (superficial, nodular), and it is therefore difficult to extrapolate these results to more aggressive (high-risk) subtypes, such as infiltrative/sclerosing BCC and recurrent lesions. Not all trials have adequate follow up. Also, variations in the size, location and histological subtypes of BCC limit any valid comparisons between treatments. However, numerous non-surgical options remain, which, in appropriate circumstances, offer an efficacious non-surgical option for the patient diagnosed with a BCC.

Squamous Cell Carcinoma (SCC)

SCCs are the second commonest NMSC and, in contrast to BCC, have a greater potential to recur and to metastasize to regional lymph nodes, especially in the recurrent setting [22]. Most SCCs are considered low-risk for recurrence and

developing metastases. However, a subset are referred to as high-risk SCCs on the basis of the following patient and tumour factors: (1) tumour of >4–5 mm thickness and >2 cm in diameter, (2) recurrent, high-grade histologically, (3) occurrence of perineural invasion, (4) location near the parotid gland, and (5) immunosuppressed patients [23]. The optimal approach to a high-risk patient is surgery, preferably Mohs micrographic surgery; [24] however, this option is not always available and alternatives include wide excision +/− adjuvant RT, or definitive RT.

The aim of surgery for a patient with SCC (low- or high-risk) is to obtain negative excision margins, which typically range from 3 to 10 mm, depending on the patient and tumour variables. It is unacceptable to observe patients with inadequately excised SCC because of the risk associated with recurrence. Re-excision or adjuvant RT should be offered.

Definitive RT is an efficacious option for both low- and high-risk SCCs [25] and, as with BCC, needs to be given to the cosmetic and functional outcomes of surgery versus RT. One benefit of RT is the ability to treat widely (and deeply) to encompass microscopic subclinical spread that, if surgically approached, would leave a large defect necessitating reconstruction.

Lip SCC

The sun-exposed lower lip is a site ideally suited to treatment with definitive RT where extensive surgery could result in significant morbidity from microstomia (reduction in oral cavity opening). RT can achieve excellent preservation of oral function and achieve a comparable outcome to surgery [26]. This is particularly useful for lesions involving 30–50 % of the lower lip where surgery with wide oncological margins (>5 mm) could impair oral function. Adjuvant local RT has a role in the treatment of an inadequately excised lower lip SCC. In an Australian study, patients with close (<2 mm) or positive margins after surgery, experienced a 37 % recurrence rate compared with 6 % of those receiving adjuvant RT [27]. While wedge resection and primary closure for an early lower lip SCC is usually uncomplicated and recommended in patients with larger lesions and those who may not be surgical candidates should be considered for definitive RT (50–55 Gy in 20–25 daily fractions using orthovoltage photons and a 3 mm oral cavity lead shield).

Evidence

High-level evidence assessing the efficacy of different interventions for primary cutaneous SCCs is scanty. A Cochrane review on interventions for primary non-metastatic SCC identified only one small RCT and concluded the need for future, well-designed studies [28]. However, similar to BCC, non-surgical options for superficial SCC include a variety of approaches [29]. Invasive low-risk SCCs can be treated by similar modalities, provided that the tumour is limited to the papillary dermis, is not recurrent, and does not have high-risk features.

The only published study assessing RCT treatment in SCC is of 66 patients with high-risk SCC undergoing excision with or without RT [30]. The treatment arm

received a chemotherapeutic regimen of 13-cis-retinoic acid plus interferon-a over a consecutive 6-month period [30]. No significant difference in time to recurrence was noted at 21.5 months median follow-up. In addition, the treatment did not prevent secondary SCCs from occurring. Therefore, the results did not support the role of 13-cis-retinoic acid plus interferon-a as adjuvant therapy for aggressive cutaneous SCC.

Metastatic Nodal SCC

A minority (<5 %) of patients with head and neck SCCs develop metastatic nodal SCC to the parotid gland nodes including or excluding cervical nodes. Metastatic SCC to cervical nodes, without parotid involvement, is also well documented. Patients invariably have a past history of treated NMSC of the head and neck and most will have an identifiable index lesion from which the metastatic SCC has arisen. However, in 25–30 % of cases an index lesion is not present. Many patients will have been treated for a recurrent primary SCC, emphasizing the importance of effective initial treatment. Best practice for patients with metastatic cutaneous nodal SCC is appropriate surgery and adjuvant RT [31]. Very few patients will not benefit from combined treatment, excluding perhaps those with a single involved node and no extracapsular spread [32]. The addition of adjuvant RT is well documented to improve locoregional control and survival.

Prevention of NMSC

Introduction

Up to 40–50 % of patients with a NMSC will develop another skin cancer within 5 years of treatment [33]. Important risk factors for developing further NMSC are exposure to sunlight (ultraviolet [UV] radiation), age and skin type. Less common risk factors include immunosuppression, history of previous skin cancers, inherited genetic skin disorders (e.g. XP), skin trauma, arsenic exposure, albinism, and previous treatment with psoralen and UVA (PUVA). Human papillomavirus is also postulated to be a risk factor [34]. Limited evidence exists to assess interventions to prevent the ongoing development of NMSC in these high-risk groups as evidenced by a Cochrane review [35].

Precursor Lesions

Patients with a precursor lesion are at risk of developing NMSC. Bowen disease (*in situ* SCC) transforms to an invasive SCC in 4–6 % of patients, while 0.025–20 % of AK can progress to SCC [36]. Numerous therapies have been used to treat precursor lesions, with a Cochrane review indicating PDT as an efficacious approach, among many, in the setting of AK [37]. A recent topical field treatment for AK (ingenol

mebutate) was tested in a randomized controlled trial and was shown to be highly effective in obtaining complete clearance when compared to a placebo (34.1 % vs. 4.7 %, $p<0.001$) [38].

Reduced Immunity

Organ transplant recipients are 3–4 times more likely to develop cancer compared to the immunocompetent population and are at an even greater risk of developing skin cancer [39]. Patients immunosuppressed secondary to haematological malignancy or HIV infection are similarly at increased risk of developing skin cancers. All patients ideally should have a regular dermatological review and treatment as indicated. In select circumstances transplant recipients may be candidates for a reduction in their level of immunosuppression.

Xeroderma Pigmentosum (XP)

Patients with this autosomal recessive disorder have an inability to repair UV skin damage. Skin cancers can develop from the age of 2 years, with a median age of developing NMSC of 8 years compared with 60 years in the general population. Such patients have a 100-fold increase in the incidence of SCC or BCC [40]. RT should not be given to these patients as it can predispose to further cutaneous malignancies.

Albinism

Patients with this condition lack skin pigment and the ability to tan, and are thus predisposed to developing skin cancers, particularly SCCs. A study of 164 albinos in Tanzania reported that 91 % of those in their 20s had AC, rising to 100 % in Albinos over 30 years of age [41].

Basal Cell Nevus Syndrome

This autosomal dominant condition, also known as Gorlin syndrome, is typified by skin and skeletal abnormalities, with an increased incidence of two or more BCCs by the age of 30 years [42]. These patients should be reviewed regularly.

Previous Psoralen and Ultraviolet A (PUVA) Treatment

PUVA is often used to treat psoriasis and other chronic skin conditions. Exposure to PUVA increases the risk of developing SCCs in a dose-dependent manner; this is not so for BCC. PUVA has an immunosuppressive effect on the skin, in addition to being

mutagenic and carcinogenic, and has been shown to result in a >100-fold increase in the risk of developing SCC within 10 years of completing treatment [43].

Prevention

Primary prevention of NMSCs involves decreasing excessive unprotected UV exposure. Educating people about the dangers of UV exposure is important [44]. Secondary prevention educates people about the signs of skin damage so that they can seek earlier diagnosis and treatment. Tertiary prevention entails interventions after treatment to reduce the risk of further NMSC, but supportive evidence for this is minimal.

Sunscreens and Sun Avoidance

Sunscreens contain titanium dioxide or zinc oxide, which scatter or absorb UV radiation. Damage by UV exposure is irreversible, but further damage can be avoided by use of sunscreens and, ideally, minimizing outdoor summer sunlight exposure from 10 am to 3 pm, and wearing hats and protective clothing [45]. Periodic cutaneous screening is particularly important for high-risk patients, viz. those with a family history of skin cancer, fair skin type, multiple naevi, or a past history of skin cancers.

Retinoids

Retinoids are vitamin A derivatives which control growth, differentiation and death of cells, and inhibit growth and induce normal differentiation in experimental malignant cell lines. Retinoids have the potential to prevent NMSC in high-risk patients. A number of studies have compared vitamin A compounds with a placebo. One study compared 30 mg/day of oral acitretin with placebo in 115 renal transplant patients over a 6-month period [46]. No significant differences were evident in the time to developing a new NMSC between groups during this period (HR 0.51); however, a 78 % reduction occurred in the risk of NMSC in the acitretin groups compared to placebo (RR 0.22) [46].

Evidence on the role of acitretin in high-risk NMSC is currently limited and conflicting, although renal transplant recipients may benefit. Despite this, toxicity is not inconsequential and needs to be considered.

Antioxidants

Selenium is an essential trace element found in fish and garlic, and is required for the detoxifying enzyme glutathione peroxidase to function. This enzyme reduces free radicals, which are known to be mutagenic. Murine studies have suggested that

increased dietary selenium may offer protection against UV-induced skin cancers. Comparison of oral administration of 200 μg/day of selenium with placebo given to 1312 patients for 4.5 years showed that patients in the selenium group were 17 % significantly more likely to develop NMSC (typically SCC) (HR 1.25) [47]. There was no significant difference between numbers of patients with a developing new SCC or BCC between the two groups (RR 1.09). Not surprisingly, a Cochrane review on the available evidence concluded that there was no convincing evidence that selenium prevented the development of cancer—NMSC or otherwise [48].

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Mohs Surgery and Facial Flaps

5

Dan Robinson and Jason Roth

From the early 1930s, Frederic E. Mohs developed the idea of cancer excision with microscopic assistance, a concept which has become known as Mohs micrographic surgery [1]. Initially, a fixed tissue technique was employed using zinc chloride solution; however, today most practitioners employ a fresh-tissue approach [2]. Mohs surgery is a microscopically controlled procedure that allows maximal excision of involved tumour in cutaneous neoplasms while minimizing the excision of uninvolved tissue. It achieves this through mapping the surgical site and successive resection of tumour and subsequent histological analysis of resected borders until clear margins are achieved [3]. Mohs surgery is suited to cutaneous neoplasms in areas with high risk of local recurrence or where for functional or cosmetic reasons tissue is required to be preserved, or in recurrent neoplasms, in particular, large and aggressive tumours with irregular or incomplete resection borders [1].

Reconstruction of defects after Mohs excision requires assessment of the size of the subunits that are involved, with the goal of surgery being to maintain function and appropriate cosmesis. Each area of the face has its unique reconstructive technique aimed to achieve optimal results. This chapter covers only some of the more common defects; for others the reader is referred to specialist textbooks.

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Nose Reconstruction

Modern techniques in nasal reconstruction emphasize replacing surgically removed tissue with like tissue. The nose consists of three layers—mucosa, a structural support layer, and skin. Removal of any of these layers ideally should be replaced with similar tissue.

Incisions for local flaps on the nose are best placed along the borders of aesthetic units and, wherever possible, local flaps are designed so that they do not cross the borders of these aesthetic units [4, 5]. The nose is reconstructed separately from any extension of a lesion onto the cheek or lip, which in turn is repaired by tissue with the respective aesthetic region [6]. Ensuring that this principle is adhered to facilitates preservation of the alar-facial sulcus, which in turn results in better overall cosmetic results [7].

The nose has nine aesthetic subunits [8]. These are the lobule, dorsum, two sidewalls, two alae, two soft tissue facets, and the columella. Reconstructive nasal surgery should focus on reconstructing entire subunits. If the majority of a subunit is lost, replacing the entire subunit gives optimal results. This may require discarding normal skin to optimize scar placement along the junction of the subunits.

Covering flaps should be designed using a template based on the contralateral normal unit, if possible. It is important to reconstruct skeletal elements by attaching them to the remaining stable structures, such as nasal cartilage of the maxillary bone. These skeletal elements should span the entire defect.

Not all defects require reconstruction. Small defects in concave locations on the nose may be best left to heal by secondary intention [9]. The most favourable areas for secondary intention healing are the medial canthus and alar crease. The least favourable areas are the convex sites of the nasal dorsum and tip which tend to flatten when healing. Alar and columellar margins tend to retract during healing.

Lining Flaps

Full thickness defects of the nose may require replacement of the internal nasal lining. Options include skin grafts, folding the distal aspect of the cutaneous flap on itself, or septal mucosal flaps. Techniques that create an inevitable septal perforation may cause significant secondary donor site morbidity.

Skin grafts can be used to replace small areas of nasal lining but they do tend to contract and do not survive well when placed directly on cartilage. A composite auricular cartilage-skin graft can be used for reconstruction of both the internal lining and the cartilage.

Mucosal flaps based on the septal branch of the superior labial artery can be mobilized either unilaterally or bilaterally with excellent survival [4]. Flaps can be used both ipsilaterally or contralaterally [10]. Anteriorly based inferior turbinate-based flaps are also possible [11]. The donor sites are left to heal by secondary intention.

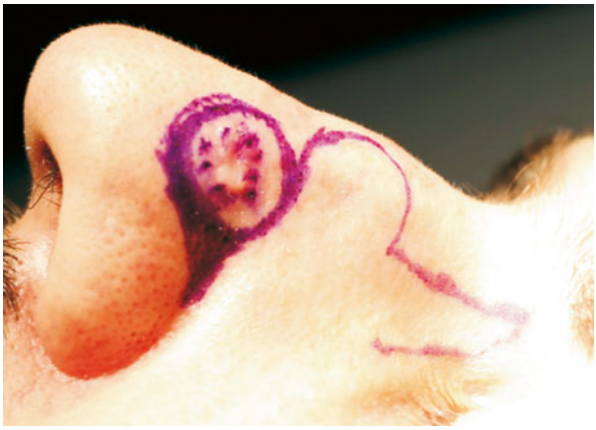

Fig. 5.1 Bilobed flap on the nose

Bipedicled bucket-handle flaps are useful to create lining for through-and-through defects of the alar rim of <1 cm in vertical dimension [12].

Epithelial turn-in flaps are also useful. Here external tissue is folded in to provide a lining and hinged along aesthetic nasal units. Folding the distal end of a forehead flap around the alar rim is the commonest application of this technique.

Local Flaps: Bilobe Flaps

The nasal dorsum and lateral nasal wall represent a relative tissue reservoir that can be used for transposition flaps. These are useful for defects of ≤2 cm. Options include the 30° transposition flap [13], note flaps [14], rhomboid flaps [15] and bilobe flaps [16–18] Bilobe flaps are the most notable and utilize two adjacent flaps of skin in series that are transposed over intervening skin. The flaps have a common base and each flap is slightly smaller than the defect it fills. Each flap should rotate no more than 45° to reduce the amount of redundant tissue and excess tension along the flap margins [19]. Disadvantages of the bilobe flap are how the incisions often do not fall in subunit junctions and the 'pin cushioning' can occur at incision edges [20]. The bilobe flap is best used to repair skin defects in the lower-third of the nose (Fig. 5.1).

Melolabial Interpolated Flap

The melolabial flap recruits tissue lateral to the melolabial fold and transfers them via interpolation so as not to violate the aesthetic boundaries between the nose and other regions of the face. It is based on random terminal branches of the facial artery. Cheek advancement is used to hide the scar in the lip – cheek junction [21].

It is most useful for defects of <2.5 cm of the ala, lateral side wall, tip and columellar [22]. Melolabial flaps tend to contract as they heal and become more rounded. This resembles the normal contour of the ala.

The flap is designed by taking a template of the contralateral ala, if possible. The flap is based superiorly and generally contains skin and fat. The centre of the template is used to position the flap on a horizontal plane in line with the lateral commissure of the lip, with the medial border in the melolabial sulcus. The flap is designed as an island flap on a subcutaneous pedicle with the base tapered superiorly to facilitate transposition and reduce skin loss from the upper part of the melolabial fold [10].

The interpolated flap is revised at 3 weeks. It can be designed as a non-interpolated rotation flap and performed as a single-stage procedure. However, this tends to cause blunting of the alar-facial sulcus and supra-alar concavity [7]. At revision, it is defatted aggressively, sculpted, and the skin is inset into the cuff of preserved alar skin.

Paramedian Interpolated Forehead Flap

Defects of the nose that are larger than 2.5 cm in horizontal length and those not amenable to the previous reconstructive methods are usually best closed with a paramedian forehead flap [5, 23, 24]. This flap is also useful when periosteum or perichondrium is missing or where tissue has been irradiated. The paramedian forehead flap is an axial interpolated flap and has an excellent blood supply. It is based on the supratrochlear artery but has many collateral vessels in the medial canthal area, including the angular artery and supraorbital arteries [11]. The supratrochlear artery crosses the superior orbital rim 1.7 – 2.2 cm lateral to the midline. After perforating the orbital septum, followed by the orbicularis and frontalis muscles, it then travels vertically 2 cm lateral to the midline in a subcutaneous plane [23].

The flap can be designed on either the same side or the contralateral side of the nasal defect and is raised in a supraperiosteal plane. An advantage of using the flap from the contralateral side is that the pedicle of the flap does not obstruct the patient's vision. A template is made of the defect to be closed and this is marked on the forehead skin. It is important to measure the length of the flap. Sometimes it is necessary to curve the flap obliquely along the non-hair-bearing skin to obtain additional length [6]. The pedicle can be narrowed to as much as 1.2 cm [25]. The tissue between the brow and hairline can be thinned aggressively of frontalis muscle and fat in order to match the much thinner nasal skin at the point of inset. The excellent blood supply allows positioning over cartilage grafts and permits the skin to be thinned to all but 1 mm of fat beneath the dermis.

Donor-site closure is achieved through extensive soft tissue undermining with possible vertical fasciotomies through the galea aponeurosis to facilitate skin mobilization. Any donor site defect that cannot be closed can either be left to heal by secondary intention or can be covered with a split skin graft.

The pedicle is detached at 3 weeks. The flap may need to be further thinned to match the thinner skin of the middle-third of the nose [4]. The base of the pedicle is rotated back into the donor site, but never higher than the eyebrows. An attempt is made to return symmetry to the eyebrows and glabella region.

Lip Reconstruction

The anatomical subunits of the lip are lateral and central upper lip subunits and a single lower lip subunit. The upper lip is bounded by the melolabial creases and base of the nose. The lower lip is bounded inferiorly by the mental crease. The philtral columns divide the central from the lateral upper lip unit. Other important landmarks are the white roll and vermilion border. The boundaries of the aesthetic units afford an excellent location to hide incisions. When a large portion of a subunit has been excised, aesthetic results are often better if the entire subunit is removed before reconstruction.

Lateral Upper Lip

Small defects can often be removed with simple advancement and primary closure. Medium-sized defects can be closed with local rotation, advancement and island flaps. As a general rule, if the defect is greater than one-third of the lip length then it should be reconstructed with a flap and not closed primarily.

The melolabial advancement flap recruits cheek skin and subcutaneous tissue and advances it medially. The main disadvantage of this flap is obliteration of the mesolabial fold; however, this can be corrected secondarily by placing an incision to simulate where the fold would normally lie [26].

Vermilionectomy

Diffuse involvement of the lip mucosa may require extensive removal of the vermilion. Vermilion can be removed to the level of orbicular oris, and the mucosa advanced from the buccal surface to close the defect. Intraoral releasing or a V-to-Y advancement flap of lip mucosa can help to relieve closure tension.

Full Thickness Upper Lip

Full thickness upper lip defects that are less than one-third the size of the lip can usually be closed with a wedge excision or W-plasty. Lesions up to two-thirds the lip size are best closed with an abbe cross-lip flap or, if more laterally located, a melolabial advancement flap. Lesions of more than two-thirds the lip size can be addressed with bilateral advancement flaps with or without an additional abbe flap.

Abbe Flap

The abbe flap [27] is a cross-lip flap from the central lower lip. When used to reconstruct lower lip defects the abbe flap is designed to be one-half the width of the defect, thereby both lips end up shortened by equal amounts. However, better aesthetic results are obtained in the upper lip if the flap is designed using a foil template from the contralateral normal lip and a size-matched flap is created.

Estlander Flap

The estlander flap [28] is a cross-lip flap used for lesions that involve the commissure.

Lateral Advancement Flaps

Lateral advancement flaps from the medial cheek can be used to repair more lateral defects or used in patients without a prominent philtrum. Incisions are made immediately below the nose and immediately above the vermilion. Excision of perialar crescents [29] can facilitate flap advancement and reduce closure tension.

Lower Lip

Lesions of up to one-third the size of the lip are best closed with a wedge excision or W-plasty (Fig. 5.2). Lesions that are one-third to two-thirds the lip size are best closed with cross-lip flaps or a Karapandzic flap. Lesions larger than two-thirds the lip size can be addressed with a free flap or bilateral abbe, bilateral Karapandzic or a Bernard-Burrow-Webster flap.

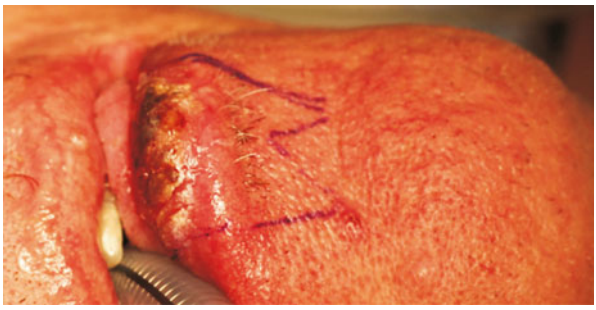

Fig. 5.2 Primary excision of the lower lip with W-plasty

Karapandzic Flap

The Karapandzic flap [30] is a musculocutaneous flap and is a modification of the Gilles fan flap that preserves the neurovascular pedicle to the lip [31]. A unilateral or bilateral circumoral advancement-rotation flap is created with releasing incisions placed around the periphery of the lip subunits. Neurovascular structures are identified and preserved in order to maintain oral competence and sensation. Microstomia may occur; however, the ability of the mouth to widen increases with time.

Bernard-Burrow-Webster Flap

This flap is useful for reconstructing defects that are more than two-thirds the size of the lower lip using tissue recruited from the cheeks. Over the years it has been modified by several workers to reach its modern form. [32, 33] A full thickness incision is extended laterally from each commissure, a triangular standing cutaneous deformity along the melolabial fold is excised and the flaps are advanced medially. Vermilion is created with a buccal mucosal flap or a tongue flap.

Forehead Reconstruction

Mohs defects of the forehead are approached with a similar algorithm for cutaneous reconstruction elsewhere on the head and neck. Options for closure include primary closure, secondary intention healing, skin grafts, local flaps and, rarely, distant flaps.

Healing of the forehead via secondary intention does not achieve excellent results, aside from the areas of the lateral forehead and temple. As a general rule, healing by secondary intention should be reserved for lesions that cannot be closed via other means [34].

Skin grafts for reconstruction of the forehead are an option but should be considered only when local flap or primary closure options are not available, as they do not provide good colour matching with the rest of the forehead [34].

Primary closure of forehead defects can allow for closure of defects and hiding the scar within an existing forehead furrow. Axially orientated closure, especially in males, can facilitate closure of small defects with the resultant scar hidden in a skin crease, provided the closure will not raise the eyebrows adversely.

Advancement flaps provide excellent options for closure of defects on the forehead, allowing for adequate skin coverage, and can be incorporated into bilateral advancement flaps to achieve greater flap surface area. Rotation flaps can be used on the forehead; however, given the curving incision of a rotation flap it is difficult to camouflage the incision adequately within the natural crease of the forehead.

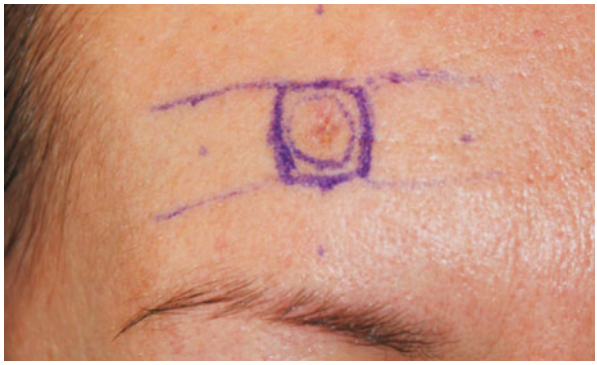

Fig. 5.3 H-plasty with advancement flaps hidden in the existing furrows

H-plasty Advancement Flap

An H-plasty advancement with axially orientated skin incisions shows excellent healing in most cases and allows for the resultant scar to be hidden in the skin creases (Fig. 5.3). In order to hide the scar properly, it might be appropriate to make the flap wider than would be planned normally. The advancement flap is designed with a length-to-width ratio of ≤4:1 so that the blood supply is not compromised [34]. The dissection of the flap should be in the subcutaneous plane. The flap can then be repeated on the contralateral side to close the defect. Standing cutaneous deformities at the lateral aspect of the incision might need to be excised after advancing the flaps.

A-T or O-T Flap

An A-T flap or O-T flap (Fig. 5.4) is useful when closing defects at the lateral aspect of the forehead or along the tricheon where a wedge excision is not appropriate. The incision of the base of the flap should be hidden, where practical, in the hairline.

Cheek Reconstruction

Defects of the cheek need to be assessed on the basis of the size of the defect and the adjacent structures that the defect might affect. Structures that are relevant in cheek reconstruction are the nose, lip and orbit, which may be distorted with excessive tension or scar contracture. Consequently, each reconstruction option must be evaluated to achieve the best cosmetic outcome by recruiting tissue from an area of appropriate laxity that can be borrowed. Scars on the cheek can be disfiguring and it is important that these scars are hidden within the relaxed skin tension lines of the face to ensure they do not become overly disfiguring (Fig. 5.5).

While there are many options for closure of cheek defects, this section will focus on some of the more commonly used methods of closure. For more in-depth technical descriptions refer to specialist textbooks.

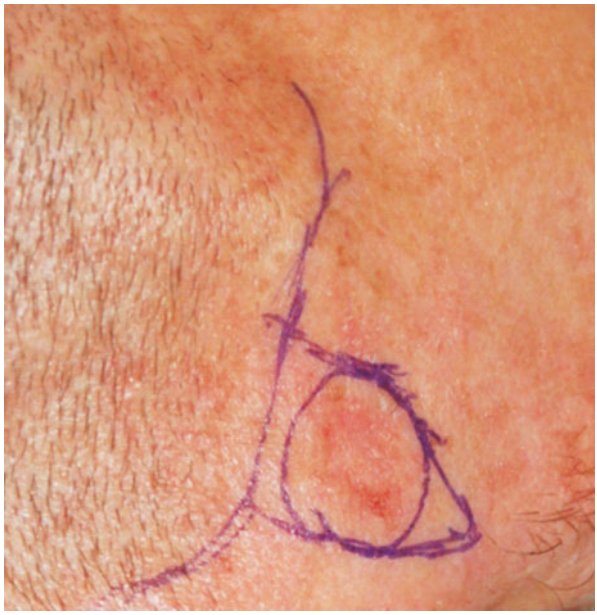

Fig. 5.4 An A-T flap on the lateral aspect of the forehead with the advancement incisions hidden in the hairline

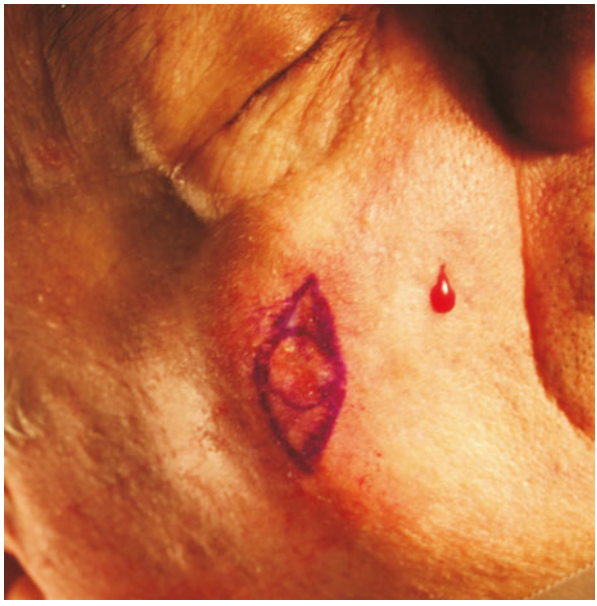

Fig. 5.5 Wedge planned for the right cheek with scar hidden in relaxed skin tension lines

Primary Closure

Primary closure in patients with significant skin laxity allows for excellent aesthetic outcomes. As a general rule, skin should be recruited medially to allow for adequate closure. The planned incision line should aim to rest in the relaxed skin tension lines

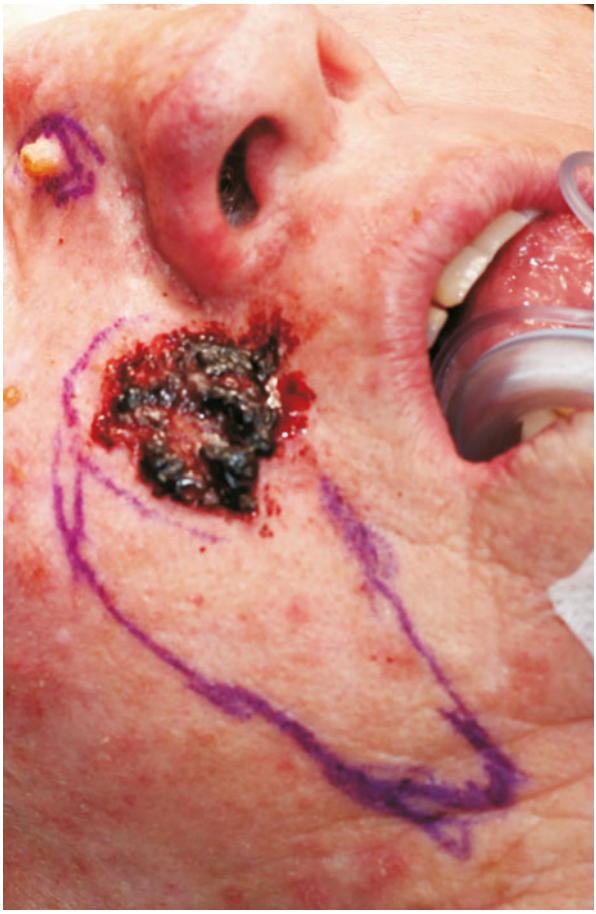

Fig. 5.6 V-Y flap planned for the medial cheek

[35]. When performing primary closure it is essential that the wound be closed with a deep layer of suturing to ensure that the skin closure is completely tension-free. Failure to do this may result in an unsightly scar.

V-Y

A V-Y island pedicle advancement flap is appropriate for use in the medial cheek region (Fig. 5.6). This flap is moved into the defect it is designed to fill with tension-free closure, achieved with appropriate deep-layered sutures [36]. The integrity of the flap is dependent on the preservation of the subcutaneous tissue beneath the advancing flap, which carries the perforating vessels supplying the overlying skin [35].

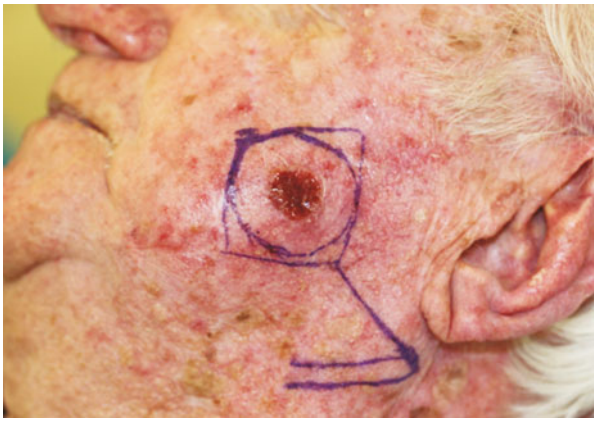

Fig. 5.7 Rhomboid flap planned for the cheek

Rhomboid

Rhomboid flaps on the cheek usually are reserved for the lateral and inferior aspects of the cheek (Fig. 5.7). Regardless of their design, one of the closure lines will be perpendicular to the relaxed skin tension lines, making them slightly more visible than other closure options. The skin that is borrowed for a rhomboid closure should have appropriate laxity.

Planning for a rhomboid flap involves creating a rhomboid around the defect with two angles of 120°, that are opposite each other and two angles of 60° [36]. The defect is excised and the first limb of the flap is taken perpendicular to the 120° angle of the defect with the second limb for the flap parallel to one of the adjacent defects. This tissue is then transposed into the defect. Modifications of this flap include the Dufourmental flap and Webster flap, which do not rely on a rhomboid-shaped excision [37].

Rotation Flap

Large cheek defects of >4 cm can be repaired with good cosmetic results with a rotation flap. The upper cervical skin usually provides enough laxity to close significant cheek defects (Fig. 5.8) [36]. Excision of the lesion and rotation of the flap often requires excision of a standing cutaneous deformity adjacent the lesion to provide adequate rotation. The incision for the flap can either extend upwards posterior to the ear or alternatively along a skin crease in the neck [35].

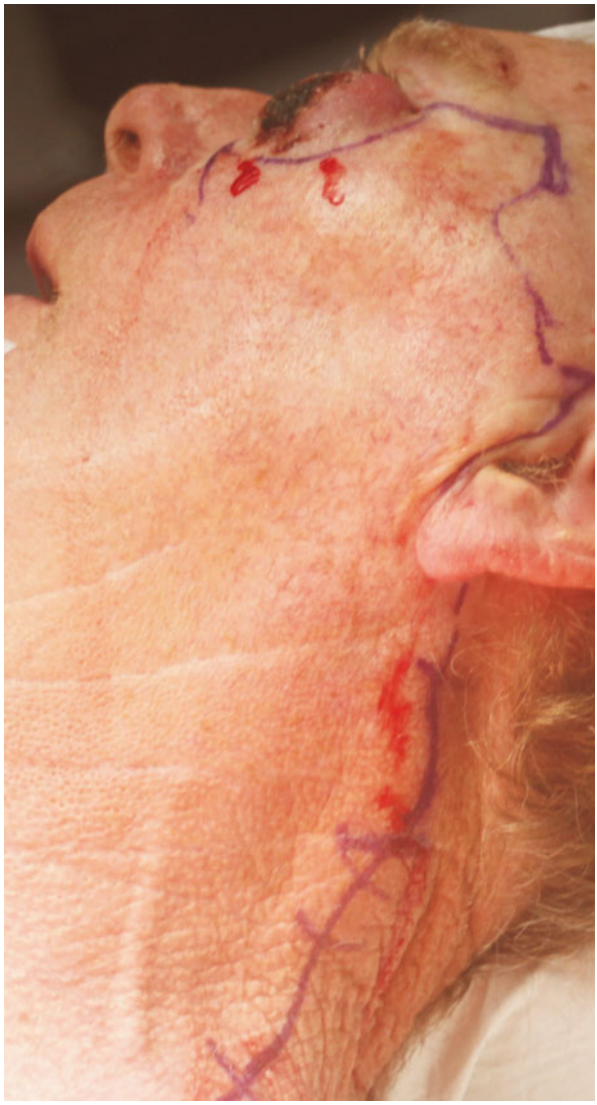

Fig. 5.8 Cervicofacial rotation flap planned for a lesion inferior to the left eye

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Merkel Cell Carcinoma, Adnexal Carcinoma and Basal Cell Carcinoma

6

Michael Veness and Julie Howle

Merkel Cell Carcinoma

Background

Merkel cell carcinomas (MCCs) are derived from the mechanoreceptor cells located in the basal layer of the epidermis and are considered a primary cutaneous neuroendocrine malignancy with characteristically small, round blue cells seen on microscopy [1]. MCC is uncommon, but the incidence is rising and markedly increased in immunosuppressed patients. Chronic sun exposure is presumed to be the chief aetiological factor but, more recently, emerging evidence suggests that merkel cell polyomavirus may also contribute to its development [2]. MCC is considered an aggressive skin malignancy in most patients, with a propensity to locoregional and distant relapse.

Patients are usually caucasian, >65 years old; men slightly outnumber women. It is rarely diagnosed clinically and requires biopsy confirmation. Lesions may appear as a purplish nodule and grow rapidly, with 50 % arising in the head and neck. Most patients will require investigations to exclude regional and distant metastases, usually via computed tomography (CT) and/or positron emission tomography (PET).

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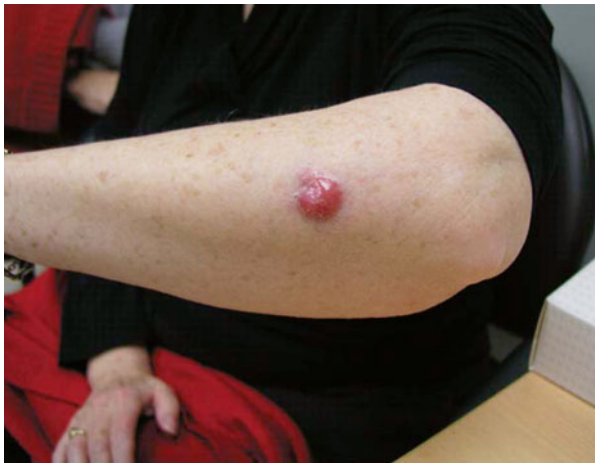

Fig. 6.1 A 65-year-old woman with a rapidly growing non-ulcerative epidermal-based lesion located on her left forearm. Biopsy confirmed this as a CK 20-positive small cell malignancy consistent with a diagnosis of Merkel cell carcinoma

Patients with a primary lesion, but without clinically present nodes, should in most cases have draining lymph nodes either electively treated or pathologically investigated with sentinel lymph node biopsies (SLNB) [3].

MCC is difficult to diagnose clinically and often mistaken for BCC or amelanotic melanoma. Growth is often rapid and lesions are usually <2 cm at diagnosis. Lesions can be painless, asymptomatic and appear blue or violaceous in colour (Fig. 6.1). Clinically, the epidermis is usually intact and lesions rarely arise in non-sun exposed skin, e.g. mucosal surface.

At presentation, 50–60 % of patients have primary disease, with only a minority of these already harbouring microscopic (occult) nodal metastases in draining nodes. Approximately l5–20 % of MCCs arise in lymph nodes without an obvious index lesion present. In these cases the aetiology is unclear but presumed regression of the primary lesion, although a nodal origin, has also been postulated. Groin nodes are the most frequent site for an unknown primary to metastasize to nodes [4].

Only 5 % of patients actually present with distant metastases (e.g. to liver, lung, etc.); however, 30–40 % of patients will subsequently develop distant relapse despite treatment and become incurable. Effective systemic adjuvant treatment is currently lacking.

Similar to other non-cutaneous small cell malignancies, MCC is highly responsive to moderate doses (50–55 Gy in 2 Gy fractions) of radiotherapy (RT). Presently, routine chemotherapy has no defined role in the curative setting, although suitable patients may be enrolled into clinical trials (Box 6.1). Similar to other small cell malignancies, the combination of carboplatinum and etoposide are used most often. Management of patients should ideally be undertaken by a multidisciplinary team with experience in treating patients with MCC.

Box 6.1 Key Aspects of Merkel Cell Carcinoma (MCC)

- MCC has a high propensity initially to spread to regional lymph nodes.
- The risk of occult nodal metastases is 30–50 %. All patients should have draining nodes either investigated or electively treated.
- MCC is a highly radioresponsive malignancy; hence radiotherapy has an important role in reducing the risk of locoregional recurrence.
- Any surgery need only be limited to achieving a negative microscopic excision margin prior to adjuvant RT.
- The routine addition of adjuvant chemotherapy has no current role.

Investigations

A biopsy is essential to confirm a diagnosis. It is important to document a history of immunosuppression. Most patients (60–80 %) present with a primary lesion and 20–30 % will have clinical lymph nodes. Distant metastases are uncommon (5 %) at presentation. Investigations using CT scans of the draining nodal basin might improve detection of small nodes otherwise undetected clinically. SLNB should be utilized in select patients; it is especially useful in midline and extremity lesions. FDG CT/PET may also detect sites of subclinical metastases; it is considered the investigation of choice if available, although equivocal sites of uptake may require biopsy confirmation [5]. Various studies suggest that the management of many patients is altered as patients are upstaged after finding undetected sites of disease. An Australian study (TROG 09.03 MP3 study) currently is under way with a secondary aim to investigate the role of FDG CT/PET scans by obtaining pathological confirmation of sites of uptake, thereby establishing the sensitivity and specificity of this modality.

Pathology

The histological features are those of a small blue cell with hyperchromatic nuclei, abundant mitoses and minimal cytoplasm. Three separate cellular patterns are reported—intermediate, small cell and trabecular. The intermediate cell variant is most common although histological variants are not prognostic. MCCs are positive for pancytokeratins and cytokeratin 20 (CK20) stains are positive in the majority, with a perinuclear dot-like staining. The presence (or absence) of lymphovascular invasion (LVI) is important to document as it is prognostic for metastases [6]. Of note, thyroid transcription factor 1 is positive in small cell lung cancer, but rarely in MCC, and occasionally small cell cutaneous lesions thought to be MCC are actually metastases in smokers.

Prognostic Factors

The presence of macroscopic lymph node metastases is the most important prognostic factor. Patients identified as having pathologically proven occult (or microscopic) metastases also have a worse prognosis compared with patients having MCC confined only to the primary site. Increasing size of the primary lesion is moderately predictive of outcome, although other tumour variables, such as thickness and Clark level are probably less helpful. Recently, the identification of LVI has been reported as predictive for the development of metastases. Immunosuppression secondary to organ transplantation, haematological malignancy (e.g. non-Hodgkin lymphoma, chronic lymphocytic leukaemia) or AIDS/HIV patients is predictive of a poor outcome.

The addition of RT is associated with improved locoregional control and survival, compared to patients undergoing surgery alone [7]. Patients with nodal metastases and without a primary (index) lesion have a better prognosis compared to patients presenting with a concomitant primary and nodal metastases. The reason for this more favourable outcome is unclear.

Staging System

Multiple staging systems have been used over the years; however, the updated AJCC 7th edition TNM stages used data from >5000 patients to establish a new prognostic staging system and reaffirming stage at diagnosis as prognostic [8]. Patients with stages I and II MCC (node-negative patients) with pathologically evaluated negative lymph nodes have the best survival, compared with those determined to be clinically node-negative. Of the stages documenting non-distant spread, stages I and II are classified by tumour size of >2 cm, and within each stage further categorized (A, B), depending on whether draining nodes have been evaluated pathologically or clinically. Because of the high false-negative rate (30–40 %) for clinically detecting occult metastatic nodal metastases, patients within the same stage but with clinically staged nodes, have a documented worse prognosis compared with patients that undergo pathological staging of nodes (e.g. SLNB). Patients with stage III disease have pathologically confirmed nodal metastases and are further divided into those with micrometastases (i.e. occult) or macrometastases (clinically detectable).

Treatment

It is debatable whether all patients should be recommended RT. Patients presenting with local disease should undergo excision to achieve, at least, negative excision margins (if possible) followed, in many cases, by adjuvant RT. Wider (5–10 mm) margins are desirable but only within constraints of the location, which can be difficult to achieve in the head and neck. Any delay in re-excision surgery should be avoided with consideration of patients proceeding directly to RT.

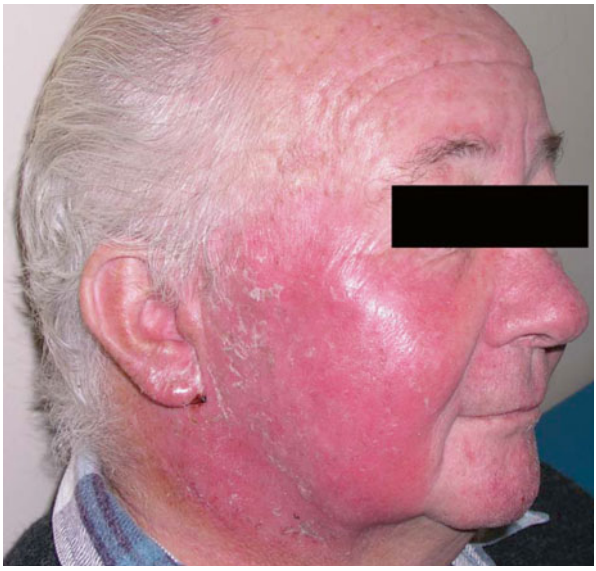

Fig. 6.2 A 70-year-old man undergoing right face and neck wide-field adjuvant RT (55 Gy in 25 fractions) using moderate energy electrons. Note the dark lines delineating the RT field and the central marked scar delineating the excision site. Superiorly the orbit and eye limit the RT field while the other field margins are generous (>3–4 cm) to adequately treat subclinical and in-transit metastases

Regional lymph nodes must be investigated or treated and a SLNB should be considered, if the expertise is available. The finding of positive SLNs dictates treatment to the nodal region, whereas a negative SLNB means nodal regions can be observed closely. With reports of false-negative SLNBs and subsequent regional relapse it remains important to monitor the patient closely (every 6–8 weeks). An alternative to SLNB is elective nodal treatment (RT or surgery), although this will needlessly treat some patients without nodal metastases. Patients presenting with clinical nodal metastases, if operable, should proceed to nodal surgery, with most patients also undergoing locoregional adjuvant RT. An option is to consider nodal RT alone if only low volume nodal metastases (single node <3 cm) are present.

Adjuvant RT should be recommended if margins are positive or close (<10 mm) and RT fields of 3–4 cm (respecting organs at risk, e.g. eye) are recommended so as to encompass in-transit lymphatics (Fig. 6.2). If the draining nodal region is also to be irradiated this should be performed *en bloc* with the primary site and in-transit tissue. However, in patients with extremity lesions this may not be possible and separate fields will be required. Doses of 50–55 Gy in 20–25 fractions are recommended, often using ipsilateral moderate energy electron fields or simple two-field megavoltage photon beams. The toxicity from this limited volume RT is usually acceptable even in this older population group.

Patients should be considered for definitive RT alone in inoperable cases and similar doses to the adjuvant setting are recommended. Studies have reported excellent (75–80 %) in-field control in inoperable patients [9].

Surgery alone may be acceptable in select patients with small lesions (<10 mm) with adequate excision margins achieved (5–10 mm) that are SLNB-negative (or negative node dissection). These patients should not be immunosuppressed and must be able to return for regular review over a 5-year period.

The role of routine chemotherapy is unclear and the toxicity, although generally tolerable, is not inconsequential in this mainly elderly population [10]. Despite this a previous single-arm study from the Trans Tasman Radiation Oncology Group (TROG 96:07) reported an excellent outcome in high-risk MCC patients receiving RT and synchronous carboplatinum/etoposide [11]. However, the addition of chemotherapy should still be considered only within the context of a clinical trial.

Recurrence

In the setting of recurrence, prognosis is poor and patients should be restaged to exclude distant recurrence. It is important to assess patient fitness for re-treatment in the elderly population. The majority of recurrences arise in the first 12 months post-treatment, and in the case of locoregional recurrence may be suitable for salvage surgery if operable. Patients should have adjuvant (postoperative) RT if outside of a previous RT field. If inoperable, low-dose re-irradiation can be undertaken if symptomatic, or a higher dose RT used if previously unirradiated. In the setting of distant metastatic recurrence, isolated symptomatic sites might benefit from palliative RT and a single fraction (6–8 Gy) is often effective. Suitable patients may be considered for palliative CT, although toxicity, especially haematological, is an issue.

Follow-up

The role of post-treatment CT/PET or CT scans is unclear. It is unlikely that surveillance investigations in an asymptomatic patient are helpful. Our group recommends close clinical examination and investigations, as warranted—with 2–3 monthly reviews for the first 12 months, 3–4 monthly reviews for the second 12-months, and 6-monthly reviews for next 3–4 years.

Malignant Skin Adnexal Tumours

Malignant skin adnexal tumours are a rare group of tumours that can be classified broadly into tumours arising from the pilo-sebaceous unit, eccrine and apocrine glands and mixed tumours (Table 6.1) [12, 13]. The site of malignant skin adnexal tumours reflects the distribution of the different types of sweat glands in the skin, with eccrine sweat glands being distributed widely throughout the skin, and apocrine sweat glands more commonly found in the skin of the axilla, groin, umbilicus, eyelid and external auditory meatus.

The head and neck region is the commonest site for microcystic adnexal carcinoma (MAC), malignant cylindroma, sebaceous carcinoma, primary cutaneous mucinous carcinoma, pilomatrix carcinoma, and adenoid cystic carcinoma [13]. Eccrine porocarcinoma is commonest on the distal extremities, but can also occur in

Table 6.1 A classification of malignant skin adnexal tumours

Skin adnexal structure	Malignant tumour
Eccrine sweat gland	Porocarcinoma Malignant cylindroma Adenoid cystic carcinoma Primary cutaneous mucinous carcinoma Syringoid carcinoma Malignant chondroidsyringoma Hidradenocarcinoma Spiradenocarcinoma Aggressive digital papillary adenocarcinoma
Apocrine sweat gland	Apocrine carcinoma Extramammary Paget disease
Pilosebaceous unit	
Hair and hair follicle	Trichilemmal carcinoma Trichoblastic carcinoma Malignant proliferating trichilemmal cyst Pilomatrix carcinoma
Sebaceous gland	Sebaceous carcinoma Basal cell carcinoma with sebaceous differentiation
Mixed	Microcystic adnexal carcinoma

the head and neck [14]. In general, most malignant skin adnexal tumours are slow-growing tumours with a low rate of metastasis.

Microcystic Adnexal Carcinoma (MAC)

MAC is a rare tumour that is derived from sweat ducts and hair follicle cells. Previous irradiation and immunosuppression are risk factors for developing MAC [15]. MAC presents as a slow-growing, solitary, flesh-coloured nodule or plaque and is an infiltrative tumour with a high rate of perineural invasion [16]. It can be locally aggressive with involvement of underlying soft tissue and bone. Lymph node metastases are rare and survival rates are excellent (10-year survival 97 %).

Sebaceous Carcinoma

Sebaceous carcinomas often arise from orbital sebaceous glands with 25 % arising from extraorbital sites. Over 70 % occur in the head and neck region, with the eyelid (meibomian glands of the tarsal plate) being the commonest site [17]. Aetiological risk factors for sebaceous carcinoma include increasing age, previous radiation exposure and Muir Torre syndrome, an autosomal dominant syndrome characterized by visceral malignancies (colorectal, upper gastrointestinal, endometrial and urological malignant neoplasms), tumours of the sebaceous glands, or keratoacanthomas. Clinically, lesions present as slowly enlarging firm nodules. At least one

study has documented a 60 % incidence of occult nodal metastases, and patients with lower eyelid lesions as having the worst prognosis [18].

Apocrine Carcinoma

Apocrine carcinomas occur predominantly in middle-aged women. Given its low incidence, information is scant on its clinical or pathological characteristics. It most commonly occurs in the axilla, but it can also arise on the eyelid, ear and scalp. Histologically, lesions may resemble metastatic adenocarcinoma of the breast and, therefore, it is important to exclude this diagnosis with relevant investigations. Apocrine carcinoma generally presents as a solitary slow-growing cutaneous nodule. The development of metastatic disease has been recorded in one small series [19]. In a series of 24 patients, only one developed nodal metastases [20].

Primary Cutaneous Mucinous Carcinoma

Primary cutaneous mucinous carcinoma is a low-grade tumour that occurs most commonly in the elderly. It is most frequently found on the eyelid, cheek and scalp, and generally presents as a slow-growing asymptomatic nodule. Histologically, it often resembles a metastatic deposit of mucinous carcinoma. Thus, it is important to exclude primary mucinous carcinomas arising in sites, such as the breast, gastrointestinal tract and lung, with appropriate investigations. Primary cutaneous mucinous carcinomas have a propensity for local recurrence, but metastases are rare [21].

Adenoid Cystic Carcinoma

Primary cutaneous adenoid cystic carcinoma occurs most frequently in the scalp, and is more common in the elderly [22, 23]. Adenoid cystic carcinoma may also occur as a primary tumour of other sites, such as the salivary glands and lung. Thus, appropriate clinical examination and imaging must be performed to exclude a primary tumour in these sites. Metastases are infrequent and the 5-year survival rate is excellent.

Eccrine Porocarcinoma

Eccrine porocarcinomas develop *de novo* or within a pre-existing eccrineporoma and commonly occur on the lower limb, but may occur in the head and neck region. Lesions develop as red or purple cutaneous nodules or plaques. Nodal metastasis occurs in ~20 % and distant metastases in ~10 % of patients [24].

Investigations

Before starting definitive treatment, we recommend that a biopsy be performed to establish a tissue diagnosis. Patients with lymphadenopathy should undergo a fine-needle aspiration biopsy to assess for metastatic disease. If nodal metastases are present, CT scans of the chest, abdomen and pelvis, or a PET/CT should be done. In patients with mucinous carcinoma, apocrine carcinoma and adenoid cystic carcinoma, investigations should be done to exclude a primary tumour arising from another organ.

Management

Achieving local control is the greatest challenge facing clinicians in the treatment of malignant skin adnexal tumours, most of which have significant rates of local recurrence.

Surgery

Wide local excision is the mainstay of treatment for malignant adnexal skin tumours. Evidence is lacking on the optimal margin of excision. However, our group recommends a margin of at least 1 cm, where possible, respecting form and function in order to minimize the risk of local recurrence.

If expertise is available, and in select patients, Mohs micrographic surgery might be beneficial in reducing the rate of local recurrence and has been shown to be an effective treatment for MAC; it is associated with a lower rate of recurrence than a simple wide excision [25].

Sentinel Lymph Node Biopsy

Most malignant skin adnexal neoplasms have a low rate of nodal metastasis, and there is little evidence in the literature regarding the use of SLNB. However, in select patients with high-risk eccrine porocarcinoma (tumour thickness >7 mm, LVI present), sentinel node biopsy might be beneficial.

Radiotherapy

Limited evidence exists for using RT, in either the definitive or adjuvant setting, for the treatment of malignant adnexal skin tumours. An Australian study on the use of adjuvant RT for MAC, however, did report an excellent local control rate with the addition of RT. [16] RT should be considered in patients in whom surgery is contraindicated, or in the adjuvant setting where there are positive margins, or if perineural invasion is present.

Basal Cell Carcinoma

Introduction

BCC is the commonest malignancy worldwide and in many countries, such as Australia, is a major public health issue. Most occur on sun-exposed regions of the body, with the head and neck being the commonest sites. BCCs arise from basal keratinocytes, and unlike most other malignancies of the skin, rarely metastasize.

Apart from sun exposure, which is the main risk factor for the development of BCCs, others include arsenic exposure, immunosuppression, exposure to ionizing radiation, and scars. Gorlin syndrome is an autosomal dominant condition caused by a mutation in the *PTCH1* gene. It is characterized by the following features: multiple BCCs, odontogenic cysts of the mandible, palmar or plantar pits, skeletal abnormalities, and medulloblastoma. BCCs are also more common in patients with xeroderma pigmentosa, a rare, autosomal recessive condition in which UV-induced DNA repair is deficient.

Types of BCC

BCC consists broadly of three main types: nodular, morphoeic and superficial. Nodular and morphoeic are the most common subtypes in the head and neck region; superficial BCCs commonly occur on the trunk [25].

Nodular BCC is the commonest subtype of BCC and presents as a pearly nodule with telangiectasia, and often ulcerates and bleeds. Morphoeic BCC appears as an ill-defined indurated macule, often resembling a scar. It is often a long-standing asymptomatic lesion and may be deeply invasive by the time of diagnosis. Perineural invasion is frequently present. Superficial BCC generally develops as an erythematous scaly macule. Most are asymptomatic, with ulceration, itching and bleeding being uncommon.

Investigations

It is usual to biopsy lesions of the head and neck region before recommending definitive treatment. In general, a punch or incisional biopsy of the lesion is adequate. CT scans of the head and/or neck are performed for patients with locally advanced disease in order to assess the depth of invasion. As BCCs rarely metastasize, staging investigations are unnecessary.

Treatment

Treatment choice is dictated by a number of factors, including tumour size and site, patient age and co-morbidities, cosmesis and function.

Surgery

Where possible, surgical excision is the preferred treatment approach, aiming for a 3–4 mm clinical margin. A positive margin(s) has been reported to be associated with a 30–40 % local recurrence rate [26], and in many cases patients should be considered for further surgery or adjuvant RT. Positive margins underlying local flaps should rarely be left untreated because of the risk of undetected deep recurrence.

The majority of lesions can be excised and closed primarily. In patients in whom primary closure is not feasible, local flaps and skin grafts are used. Patients with lesions requiring complex local flaps should be referred to a plastic surgeon.

Selected patients, such as those with morphoeic or recurrent BCC, can be referred for Mohs micrographic surgery, a technique in which serial sections of skin are excised and the peripheral and deep margins are examined, so that 100 % of the surgical margins are evaluated. A randomized controlled trial comparing surgical excision with Mohs surgery for the treatment of BCC of the face found no significant difference in recurrence rate for primary BCCs, but in the treatment of recurrent BCC, the use of Mohs surgery resulted in a significantly lower recurrence rate [27]. The higher cost and relative inaccessibility of Mohs surgery has limited its widespread application in many countries.

Radiotherapy

Definitive Setting

Randomized data comparing different modalities is scarce, with a Cochrane review [28] reporting surgery or RT as the most efficacious treatment with surgery probably showing the lowest recurrence rates (Box 6.2). However, local control rates (90–95 %) and cosmesis (>90 % rated as excellent or good) after RT are excellent and management decisions are often based on multiple factors.

RT remains an option when tumour and patient factors favour this modality; typically patients are older, with a mid-face or nasal (alanasi or nasal tip) BCC for which small skin grafts or flaps may be required (Fig. 6.3) [29]. Locations, such as the inner canthus or lower eyelid, may also be better approached with RT. Larger lesions can still be treated with definitive RT, although with increasing size and deeper invasion local control decreases and excision (+/− adjuvant RT) may result in better local control.

Box 6.2 Radiotherapy and Basal Cell Carcinoma (BCC)

- BCC can be treated adequately with either surgery or RT.
- Patients with non-mid-face operable lesions that can be closed primarily should undergo surgery, unless contraindicated.
- Lesions located on the mid-face, especially in older patients, may benefit from definitive RT, especially if graft or flap reconstruction is required.
- Patients with inadequately excised BCC with positive margins are at risk of developing local recurrence and should be considered for re-excision or adjuvant local RT.

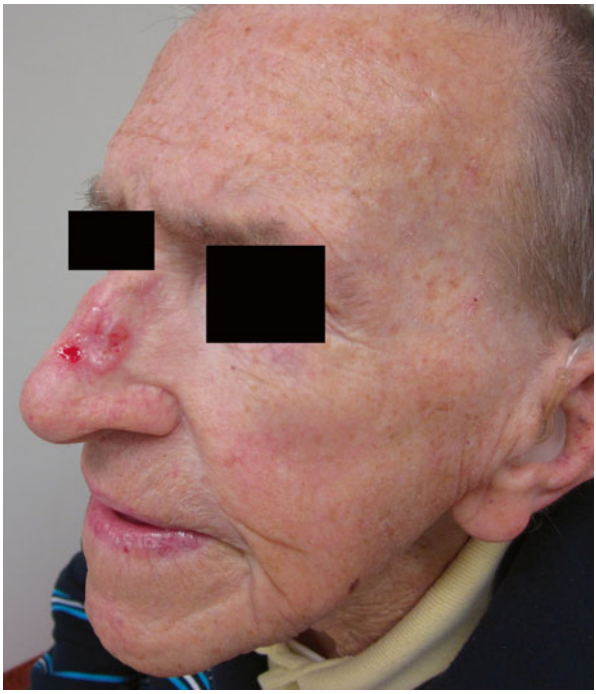

Fig. 6.3 An elderly man with a large nodular BCC occupying his mid dorsum nose. The patient was recommended wide-field definitive RT to the clinical basal cell carcinoma with 10 mm field margins to a dose of 45 Gy in 15 daily fractions

Adjuvant (postoperative) Setting

At least 30 % of incompletely excised BCCs recur and further treatment is often recommended rather than observation and expectant treatment [30]. A positive deep margin resulting in deep recurrence, particularly deep to a local flap, can be difficult to detect. When located around the mid-face and periorbit, undetected deep recurrence of can result in significant local morbidity. Re-excision is often an option although in certain circumstances the involved margin precludes simple re-excision and, therefore, adjuvant RT is also an option. Although recurrences are rarely

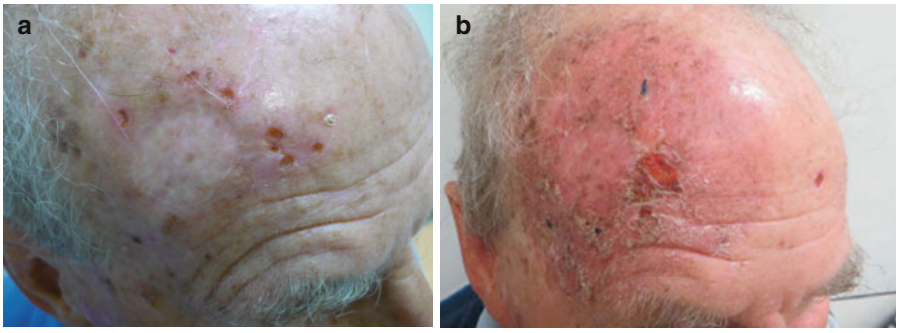

Fig. 6.4 (**a**, **b**) A 73-year-old man with wide local recurrence of a previously excised right forehead morphoeic BCC with positive margins and no further treatment. Note the multiple punch biopsy sites are all positive for recurrence. The patient underwent wide-field definitive RT (50 Gy in 20 fractions) to his right hemi-forehead with excellent results

associated with serious consequences, extensive salvage surgery might be required. Patients with the more aggressive subtype of sclerosing (morpheaform) BCC are at a higher risk of local recurrence and are best not left untreated in the setting of an inadequate excision (Fig. 6.4).

Dose Fractionation Schedules

An appropriate schedule, in the absence of a defined optimal dose fractionation schedule, encompasses both patient and tumour factors. Smaller lesions (20–30 mm) in older patients (>70 years) are treated adequately using 40–45 Gy in 10–15 daily fractions with acceptable local control and cosmesis. The data suggest that the dose-response is not marked, and local control is similar—whether 40 Gy in 10 fractions or 50 Gy in 20 fractions is prescribed.

Elderly or infirm patients can be prescribed single large fractions (10–20 Gy) or even 3–5 fractions of 6–7 Gy. Larger invasive lesions (>3–4 cm) and/or younger patients should be approached using a lower fraction size (2–2.5 Gy) and a 'hotter' total dose of 50–60 Gy to achieve the best chance of durable local control and acceptable late effects.

Data from a large centre in the United Kingdom suggest that small BCC/SCC of the head and neck, encompassed in a RT field size of <3 cm, can be treated with a single fraction of 20 Gy [31]. Although the authors documented a low recurrence rate (<5 %) and acceptable necrosis rate (6 %), late cosmetic outcome was not reported. In general, single large fractions should not be recommended although it may be an option in select older patients who decline fractionated treatment.

A field margin of 5–10 mm beyond macroscopic disease, or surgical site, is usually adequate for a well-defined nodular BCC, but for an infiltrative BCC a wider margin of 10–15 mm is required to encompass surrounding subclinical spread.

Other Treatment Modalities

Whereas surgery is the mainstay of treatment for BCC, a variety of topical treatments is available that may be suitable for patients with small and superficial tumours, who are not able to undergo surgery.

Imiquimod

Imiquimod is a topical immunomodulator that is approved in some countries for treatment of superficial BCCs; its clearance rates are reported as ~80 % [32].

Photodynamic Therapy

Photodynamic therapy involves the application of a photosensitizing agent to the tumour and a 5 mm margin of surrounding skin, followed by irradiation by a light source; it is generally used to treat superficial or thin nodular BCC with an expected good cosmetic outcome.

Cryotherapy

Cryotherapy involves the application of a cryogenic agent (most commonly liquid nitrogen) to the tumour leading to destruction of tissue. BCCs can be treated with cryotherapy, but is generally not used for BCCs of the head and neck because of higher recurrence rates.

Curettage and Diathermy

Curettage and diathermy can be used to treat non-morphoeic BCCs successfully in most areas of the body. However, this method is generally not used for BCCs of the head (in particular areas such as the nose, lips, eyelids, ears) on account of unpredictable cosmetic outcome and the risk of recurrence.

Hedgehog Pathway Inhibitors

Most BCCs arise because of upregulation of the hedgehog signalling pathway, which is caused by mutations of the patched homologue 1 (PTCH1), which results in a lack of inhibition of the smoothened homologue. Vismodegib, an inhibitor of smoothened, has been studied recently in clinical trials. A phase II study in which patients with metastatic or locally advanced BCC were treated with vismodegib reported response rates of ≤43 % [26]. At this stage, vismodegib and other hedgehog pathway inhibitors are accessible to patients only in the setting of a clinical trial. However, they represent a promising treatment modality for those with locally advanced or metastatic disease and potentially those with Gorlin syndrome.

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The Role of Sentinel Lymph Node Biopsy in Non-melanoma Skin Cancer of the Head and Neck

7

James Wykes, Jonathan Clark, and Navin Niles

Non-melanoma skin cancer (NMSC) is the most common form of skin cancer and often affects the frequently sun-exposed areas of the head and neck. In 2008, an estimated 430,000 new cases were diagnosed in Australia [1]. Two-thirds of Australians over the age of 70 years will develop a NMSC, most of which are basal cell carcinomas (BCCs) that rarely metastasize to lymph nodes. The occurrence of squamous cell carcinomas (SCCs) is approximately half that of BCCs but their capacity for lymph node metastases is much greater [2]. Merkel cell carcinoma (MCC) is a rare but aggressive cutaneous neuroendocrine tumour that has a high propensity for regional and distant spread.

Cutaneous Squamous Cell Carcinoma

While the majority of cutaneous SCC (cSCC) of the head and neck can be controlled with local ablation, <5 % of tumours will metastasize [3]. Metastatic cSCC of the head and neck is potentially curable with more extensive surgery and postoperative radiotherapy; however, as many as 30 % of patients will die of their disease [3]. Morbidity associated with these treatments is also significant [4].

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Several tumour and patient factors render a subset of patients at increased risk of nodal metastases. These higher-risk patients who are node-negative have no consensus therapeutic option other than observation. As in melanoma skin cancer [5, 6] and breast cancer [7], sentinel node biopsy (SNB) offers potential to identify occult metastases, alter staging and management, and influence local control and overall survival. In contrast to melanoma of the head and neck and mucosal SCC, the identification of patients at risk of metastatic disease is more challenging, due to the lower propensity of cSCC to metastasize [8, 9] and the lack of a single risk factor that stratifies risk, such as Breslow thickness in melanoma [5].

Much work has been done to identify those head and neck cSCC patients who are at higher risk of nodal metastasis [4, 10]. A number of risk factors associated with a higher risk have been identified: (i) *macroscopic tumour features:* e.g. diameter of >2 cm, depth of >5 mm and location, particularly around the ear, lips and nose; (ii) *histopathological features:* e.g. lymphovascular invasion, perineural invasion and poorly differentiated tumours; and (iii) *patient factors:* e.g. immunosuppression and recurrence. Quantifying risk factors is difficult. While individual studies show high metastastic risk rates for given risk factors (Table 7.1), prospective studies often fail to show a metastatic rate much greater than 10 % for patients deemed to be high-risk [11].

Oddone et al. developed an ITEM score comprising Immunosuppression, Treatment, Extranodal spread and Margin status [10]. This was shown to be a good predictor of 5-year mortality. Patients were stratified into high-risk (>3.0), moderate risk (>2.6–3.0), and low-risk (<2.6) groups correlating with 5-year mortality of 56 %, 24 % and 6 %, respectively. Within the high-risk group the rate of lymph node metastases approached 20 % [10]. However, this study looked at patients who had established nodal metastases following treatment, and so cannot be employed in a prospective way to calculate the risk of lymph node metastases.

In contrast to other body sites, lymphatic drainage of cSCC of the head and neck is relatively unpredictable, due to multiple overlapping lymph node basins. One constant finding is that intraparotid lymph nodes are a frequently involved site of

Table 7.1 Risk factors associated with the development of lymph node metastasis in cSCC [11]

Risk factor	Metastatic rate
Size >2 cm	20–30 %
Invasion into subcutaneous fat (depth ≥5 mm)	16–45 %
Poorly differentiated/metatypical phenotype	12–32 %
Desmoplasia	12 %
Perineural invasion	40–47 %
Lymphovascular invasion	40 %
Site: ear or lip	10–30 %
Local recurrence	25–62 %
Squamous cell carcinoma in pre-existing scar	38 %
Immunosuppression	13–20 %

metastasis. A review of 43 patients with metastatic NMSC of the head and neck found the parotid gland was affected in 56 %, neck level II in 39 % and level V in 22 % [9]. The PN clinical staging system developed by O'Brien et al. [12] separated and graded parotid and cervical metastases [11]. Application of this system suggests that cervical disease confers a worse prognosis than parotid disease alone. In one study a majority (67 %) had parotid disease alone, with the bulk of these patients having early-stage disease (P1) [12]. Neck disease alone was found in 19 % patients, with more than half of them having advanced metastatic disease. A total of 13 % had clinical disease in both the parotid gland and the neck [13]. Also, survival was significantly worse for patients with advanced P stage—69 % 5-year survival compared with 82 % for those with early P stage [13].

In contrast to SNB in melanoma of the head and neck [14] and to a lesser degree SNB in oral cavity SCC [15], data on the accuracy of SNB and its impact on treatment, local recurrence and survival are restricted to small series with a limited number of patients and a short follow-up. Several studies using SNB in cSCC of the head and neck have been designed as feasibility studies. The results from most studies are limiting, as they are based on small patient numbers and are heterogeneous in terms of pathology—i.e. by combining SCCs with Merkel cell tumours and melanoma, and also site, with lesions on extremities often included. Because of a lack of fixed criteria to assess high-risk SCC, the tumour characteristics vary from study to study. However, most authors cite a lesion size of >2 cm, depth and site as important prognostic factors.

Existing Literature

In 2002, Altinyollar et al. published a series of 20 patients with SCC of the lower lip who underwent SNB [16]. His group identified a sentinel node in 18 patients (90 %), 3 of which were positive (16.6 %). Of these positive patients, two had no further positive disease at neck dissection and the third patient had an additional 3 positive nodes. Bilateral supraomohyoid neck dissections were performed for the remaining patients with no positive nodes in a total of 440 nodes. No recurrence or survival data were published [16].

In 2003, Reschly et al. published a series of 9 patients with high-risk cSCC who underwent SNB, of which 4 patients had primary lesions of the head and neck. Sentinel nodes were isolated in all 4 patients, all of which were negative. The patients remained disease-free at median follow-up of 13 months [17].

In 2003, Michl et al. sought to evaluate the feasibility of SNB in 37 patients with NMSC, of which 13 patients had primary lesions of the head and neck. Two of these patients had positive sentinel nodes, although their primary pathologies were lymphoma and MCC [18].

In 2004, Nouri et al. reported a series of 8 patients with cSCC of the head and neck who underwent a SNB with one positive result. That patient went on to have an ipsilateral neck dissection and adjuvant radiotherapy and was disease-free at 18 months [19].

In 2004, Wagner et al. published a series of 24 patients who underwent SNB for high-risk NMSC across multiple body sites and involving merkel cell, squamous cell and adenocarcinoma. Five patients had cSCC of the head and neck, with consistent drainage to the parotid basin, of which 2 patients had positive sentinel nodes. These patients went on to receive radiotherapy and were followed up for 7 and 44 months [20].

In 2008, Civantos et al. identified 1 micro metastasis in 10 patients with high-risk cSCC who underwent SNB as part of a larger review of 106 patients with cutaneous and mucosal malignancy of the head and neck [20]. This paper also highlighted some of the technical challenges of re-operating on a previously biopsied field in the setting of a positive SNB, as well as the challenge of removing multiple 'hot' sentinel nodes from different drainage basins [15, 21].

In 2007, Renzi et al. reported a case series of 22 patients who underwent SNB for high-risk SCC, of which 15 lesions were on the face, none of which were positive. The median follow-up for SNB-negative patients was 17 months, with one nodal recurrence [22].

In 2010, Rastrelli et al. published a retrospective review of 20 patients with high-risk non-anogenital SCC who underwent SNB, of which 11 patients had primary lesions of the head and neck. One patient had a positive SNB and went on to receive a parotidectomy and ipsilateral neck dissection; however, only 10 nodes were removed. This patient had regional disease at follow-up. Two of the 10 patients with negative SNB developed regional nodal recurrence and underwent neck dissection. One died of disease after 17 months and the other was disease-free at 30 months [23].

Box 7.1 Cutaneous Squamous Cell Carcinoma (cSCC)

- cSCC of the head and neck spreads regionally in a small but significant percentage of patients. Regional spread is associated with a substantially increased risk of morbidity and mortality.
- A combination of the following factors increases the risk of nodal metastases: Primary tumours >2 cm in diameter and/or >5 mm in thickness, recurrent tumours, tumours around the ears, lips and nose, and immunosuppressed patients. Microscopic features that increase risk include lymphovascular invasion, perineural invasion, and poorly differentiated tumours.
- Identifying occult nodal disease in these patients is challenging. SNB is a well-tolerated procedure that can identify a draining lymph node consistently; however, the rate of sentinel node positivity is low and it is not possible to make decisions regarding prognosis and treatment on the basis of the current literature.

Pooled data across these studies reveal 73 patients with high-risk cSCC of the head and neck who underwent SNB. One or more sentinel nodes were identified in 71 patients (97 %). Seven patients (10 %) had positive sentinel nodes and their therapeutic management involved neck dissection, parotidectomy or radiotherapy. Three

patients (4 %) had regional nodal recurrence after negative SNB, of which one died of disease. Follow up of patients ranged from 7 to 24 months.

These pooled data are heterogeneous and, therefore, must be interpreted with caution (Box 7.1). Compared with melanoma or oral SCC, the rate of sentinel node positivity is low (10 % vs. 20 %) [14]. Most series consistently were able to identify sentinel nodes with minimal morbidity associated with their excision. Lymphatic mapping appears to be predictable, with the parotid basin an important reservoir, as is the case in melanoma [24]. Management of positive and negative sentinel nodes varied between trials from observation to irradiation of the nodal basin to lymphadenectomy, and the range for follow-up was wide.

As such, data are insufficient to clarify the staging or prognostic implications of SNB in cSCC. However, the accuracy of sentinel node mapping and low morbidity associated with the procedure provide hope that SNB may prove an important tool in the management of patients with high-risk cSCC of the head and neck who are at increased risk of metastatic disease.

Interim data from the SNIC trial, a prospective study aimed at determining the rate of subclinical metastases from cSCC of the head and neck, are available which helps to better identify which patients with cSCC are most at risk of lymph node metastases [24]. This showed a lymph node metastasis rate of 14 % in 57 high-risk patients, and multivariate analysis revealed that the presence of multiple risk factors, perineural invasion and lymphovascular invasion were significant predictors of metastatic disease [11].

Technique

The technique employed at our institution is similar to that of sentinel node biopsy in melanoma. Sentinel node biopsy is typically performed concurrently with primary tumour excision in patients identified to have high-risk disease based on risk factors enumerated earlier; however, a number of patients are either referred with a high-risk tumour that has undergone excision already or are thought to be at increased risk based on pathological findings and thus have a delayed sentinel node biopsy procedure.

Radiolabelled sulphur colloid dye is injected peri-tumourally as per local nuclear medicine protocols. Intraoperatively, patent blue dye in injected intradermally at four points around the edge of the scar or tumour.

Sentinel node incisions are planned based on sentinel node location and potential further lymph node dissection and sentinel nodes are identified via a combination of visually identified blue nodes and hand-held gamma probe findings.

Sentinel nodes are examined using standard haematoxylin and eosin protocols and cytokeratins for immunohistochemistry. Patients with positive sentinel nodes are offered completion lymph node dissection.

The experience at our local institution is corroborated by the literature. SNB can regularly identify a sentinel node; however, the overall rate of sentinel node

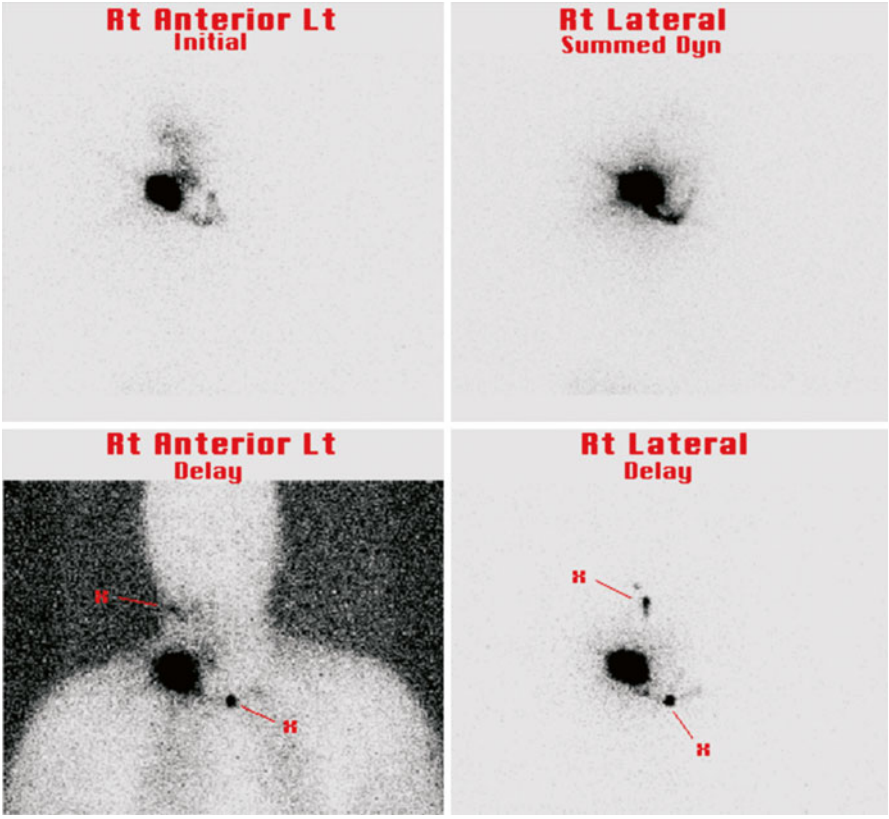

Fig. 7.1 A right cervical cutaneous SCC showing lymphatic drainage to right level II and left level IV sentinel nodes (Image provided by Professor Roger Uren, Alfred Nuclear Medicine and Ultrasound, Sydney, NSW, Australia)

positivity is low. Two frequently encountered technical issues relating to SNB are multiple sentinel node drainage sites (Fig. 7.1) and the operative approach to the sentinel node region. Our group often elects to regionally clear the area of sentinel node drainage to prevent potentially having to re-operate on a previously operated field (e.g. a selective level II neck dissection for a sentinel node localizing to level II on imaging and gamma probe). This approach is an attempt to balance the risk of over-treating against the increased risk of morbidity and difficulty of re-operating on a previously operated field.

Basal Cell Carcinoma (BCC)

BCC has an extremely low metastatic potential, with one widely quoted study indicating a metastatic risk of 0.03 % [25]. Patients with metastatic disease usually have a poor prognosis [26]. Risk factors for metastatic BCC include large-diameter

lesions of >3 cm, perineural or lymphovascular invasion, and invasion into deeper structures [27]. Aggressive surgical therapy appears to offer the best chance of cure for these patients. On account of the exceedingly low metastatic rate of BCC, the utility of SNB is minimal (Box 7.2), and only a couple of case reports on SNB for metastatic BCC are available [27], and none for BCC of the head and neck. Furthermore, BCC metastasizes through haematogenous and lymphatic routes in approximately equal proportions [28].

Box 7.2 Basal Cell Carcinoma (BCC)

- BCC of the head and neck rarely metastasizes and SNB is of little use in assessing the nodal basin.

Therefore, the extremely low yield would suggest that SNB is an inefficient way to assess for metastatic BCC, even in high-risk disease.

Merkel Cell Carcinoma (MCC)

MCC is a rare and aggressive neuroendocrine malignancy of the skin. Similar to other cutaneous malignancies, it is frequently seen in sun-exposed areas and thus has a propensity to affect the head and neck.

The hallmark of the disease is frequent metastases to draining lymph nodes, which occur in 15–66 % of patients [29]. Most patients will develop regional or distant metastatic disease over time [29], which makes SNB an ideal method for assessing a clinically negative nodal basin for a given primary tumour.

SNB consistently detects occult metastatic disease in MCC, which occurs in approximately 30 % of patients with MCC [29, 30]. Lymphatic drainage patterns are similar to those of other cutaneous malignancies, with parotid and cervical lymph nodes frequently involved in cases of head and neck MCC. Positive SNB upstages disease and leads to adjuvant treatment [31]. However, a negative sentinel node does not predict regional disease control consistently, with a number of studies showing that a significant percentage of patients with a negative sentinel node develop regional disease (Box 7.3) [30, 32].

While SNB assists in more accurate staging, it does not appear to confer a survival advantage [32–34]. One study suggested that the addition of adjuvant nodal therapy after the discovery of a positive sentinel node provided a survival advantage; however, a negative sentinel node result was not superior to observation of nodal basins [30]. The discordance between the positive predictive nature of SNB in MCC and its impact on survival is possibly explained by the overall aggressive regional and distant spread patterns of the disease.

MCC has a high rate of local and distant spread, and SNB has a role in accurately staging draining nodal basins; however, a negative SNB does not predict regional control accurately, and offers no overall survival advantage.

Box 7.3 Merkel Cell Carcinoma (MCC)

- MCC has a high rate of local and distant spread, and SNB has a role in accurately staging draining nodal basins; however, a negative SNB does not predict regional control accurately, and offers no overall survival advantage.

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Metastatic Cutaneous Squamous Cell Carcinoma of the Head and Neck

8

Carolyn Jameson, Gary Morgan, Carsten E. Palme, and Michael Veness

Epidemiology

Non-melanoma skin cancer (NMSC), comprising basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC), is the most common malignancy worldwide. The incidence of NMSC is increasing with 2–3 million new diagnoses per year globally. Australia, with chronic high ultraviolet (UV) exposure, has the highest incidence of NMSC in the world, with the majority of cSCCs (70–90 %) arising on the sun-exposed skin of the head and neck (HN) in older Caucasian males [1–4].

Epidemiology of Primary and Metastatic Head and Neck Cutaneous Squamous Cell Carcinoma (HNcSCC)

The second most common skin cancer worldwide, representing 25 % of all NMSCs, is cSCC [5]. The annual incidence of cSCC is related directly to

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Fig. 8.1 An Australian man with a very late presentation of facial cSCC. This patient presented via emergency with a large bleeding, necrotic mass, lethargy, shortness of breath and haemoglobin of 54 g/L. He required immediate blood transfusion and the mass was amputated at its base under general anaesthesia. Histopathology revealed a moderately differentiated cSCC without perineural invasion. Depth of dermal invasion was 19 mm. One month later, wide excision with a 1 cm clinical margin was performed with primary closure of the defect

equatorial proximity, and ranges from 16 cases per 100,000 people in central Europe to 300 cases per 100,000 people in Australia. In northern Australia, the annual incidence is an alarming 1300 cases per 100,000 males [6, 7]. The incidence of cSCC is increasing with increased sun exposure over decades through atmospheric ozone depletion, changes in style of clothing and increased lifespan. In addition, there is an increasingly larger cohort of patients who are immunosuppressed through solid-organ transplant schemes.

In a German study of 615 patients with primary HNcSCC, 63 % of patients were male with a median age 73 years [8]. In an Australian study of 282 patients with metastatic cSCC, treated by the Sydney Head and Neck Cancer Institute (SHNCI), 87 % were male with a median age 72 years (range 37–98 years) [4].

Currently, the majority of primary cSCC is treated by primary healthcare professionals and dermatologists. Despite the excellent prognosis with local treatment and cure rates exceeding 95 %, the median delay in diagnosis is reported to be 3 years, leading to a number of patients presenting with locally advanced disease and not infrequently, with regional metastases (Fig. 8.1) [9]. Patients who have been diagnosed with cSCC have an 18 % increased risk of developing a subsequent cSCC compared with the general population [10].

Theoretically, all patients with primary HNcSCC are at risk of developing metastases and patients with regional metastases are at the highest risk of poor outcome. Nodal metastases occur in 2–5 % of patients [8, 11]. However, patients with high-risk cSCC have a >20 % risk of developing metastatic disease [12, 13]. Most present with chronically sun-damaged skin and invariably have had numerous cSCC

previously excised from the HN region. In almost one quarter of patients the site of the primary index lesion is unidentifiable [4, 14].

It is important to be aware of the potential for development of metastatic nodal cSCC. The median time from excision of a primary HNcSCC to presentation of metastatic disease is approximately 12 months (range 8.5–13 months) [4, 8, 14–16]. Fifty to sixty percent of patients who present with nodal metastases do so after treatment of primary HNcSCC [16, 17]. Failure to detect and adequately treat both primary and regional disease is associated with a significant risk of death.

Quality of Life

Primary and metastatic cSCC can have a substantial impact on quality of life, through multimodality treatment. Morbidity associated with metastatic cSCC is considerable, with most lesions requiring major surgery and adjuvant radiotherapy. Despite appropriate treatment, a small number of patients will die as a consequence of metastatic disease to regional lymph nodes [18, 19].

Few patients develop distant metastatic disease. Lung and bone are reported to be the most common sites of distant disease [14, 19]. In a study of 122 patients treated for metastatic cSCC, 7 % developed distant metastatic disease, with lung the most common site [14].

Risk Factors

There are a number of factors which, in combination, increase the risk of developing metastases. Newer staging systems consider clinicopathological risk factors, described in the National Comprehensive Cancer Network (NCCN) guidelines and Multi-Professional Guidelines for the British Association of Dermatologists [12, 20, 21]. These newer staging systems allow better prognostication and include (1) location of the primary tumour, (2) diameter ≥2 cm, (3) thickness ≥2 mm/Clark level IV or V, (4) penetration into the subcutaneous tissue, (5) moderate or poor differentiation, (6) desmoplastic, adenoid and adenosquamous subtypes, (7) perineural invasion (PNI), (8) lymphovascular invasion (LVI), and (9) tumour recurrence. Patient factors include immunosuppression and older age.

Using the following histopathological risk factors—poor histological differentiation, PNI, LVI, diameter ≥20 mm and tumour thickness >4 mm, or Clark level V with penetration into the subcutaneous tissue—Peat et al. reported significant differences in the metastatic potential of primary cSCC [15]. High-risk cSCC had a predicted incidence of 37 % for developing nodal metastases compared with 0.3 % in low-risk cSCC [15].

Tumour Location

Generally, cSCC located on thin skin with a rich vasculature or lymphatic network, or in close proximity to the parotid, have a higher metastatic potential. The most

common primary tumour sites leading to parotid and/ or neck metastases, in descending order of frequency, are unknown primary, lip, cheek, ear, temple, forehead, scalp and nose [14, 22, 23]. The most common primary sites leading to parotid metastases are pre-auricular and cheek.

Tumour Size

Evidence shows cSCC >20 mm has a greater propensity to metastasize than a smaller lesion. In a New Zealand study of 170 patients, 46 % of patients developed metastatic cSCC. In that study, a hazard ratio (HR) of 3.10 was reported for developing metastatic disease when tumour diameter was ≥20 mm [15]. In a large review of skin and lip SCC, the rate of metastatic disease in lesions <20 mm was 9 % compared with 30 % in lesions >20 mm [24]. Interestingly, in a prospective cohort study of 612 patients, no metastatic disease was reported in cSCC <10 mm [8].

Although increasing tumour size contributes to metastatic potential, it does not explain the full extent of risk, and other factors need to be considered.

Tumour Thickness and Depth of Invasion

Tumour thickness and depth of invasion are important predictors of metastatic potential. It is well documented that tumours >4 mm have an increased risk of metastasis [25–28]. An early report by Breuninger et al. identified no metastases from lesions <2 mm thick and stated that when depth of invasion did not extend beyond the subcutis, a cSCC could be classified as low-risk [29].

In a recent study of 615 patients, who were reviewed at least once after treatment for primary cSCC and contacted by mail for up to 10 years, no patient developed metastatic disease when the primary cSCC was <2 mm thick [8]. In contrast, 4 % of patients with tumour thickness 2.1–6.0 mm and 16 % of patients with tumour thickness >6.0 mm developed metastatic disease [8].

A recent study compared 78 patients with metastatic cSCC with 92 patients who had no metastatic disease within 5 years of primary cSCC treatment [15]. A HR of 2.33 was reported for developing metastases when primary cSCC was present in subcutaneous tissue (Clark level V) [15].

Tumour Grade

Poorly differentiated cSCC is associated with a higher rate of regional metastases. Risk of metastatic disease was reported as 17 % in high-grade tumours compared with 5 % for other grades ($p<0.01$) [29]. A HR of 5.63 for poorly differentiated cSCC was reported in a study of 170 patients, which compared patients with metastatic cSCC with those who did not develop metastatic disease [15]. In a review of primary cSCC, 63 % of 95 patients with metastatic cSCC were assigned a moderate or poorly differentiated tumour grade, with tumour grade unreported in 14 % of 122 patients [14].

Desmoplasia

Desmoplastic cSCC is an aggressive variant, most frequently found on the ears, nose and forehead. It is characterized by the presence of PNI, an invasive clinical course and poor prognosis [30]. Patients with desmoplastic cSCC have 10 times the risk of local recurrence and six times the risk of metastasis compared with other cSCC subtypes [31].

Brantsch et al. reported desmoplasia to be the most important histological feature for local recurrence, with 24 % of 51 patients with desmoplasia versus 1 % of 564 patients without desmoplasia developing local recurrence [8].

Perineural Invasion (PNI)

When tumour cells gain access to the perineural space they have the potential to spread both antegrade and retrograde along the nerve. The most common nerves associated with PNI in the HN region are the facial (CN VII) and trigeminal (CN V) nerves. PNI can be diagnosed clinically, radiologically or pathologically. It is a risk factor for later metastatic disease and overall poor survival, associated with retrograde spread to the brainstem. The rate of PNI in cSCC ranges between 2.5 and 14 % [32, 33].

A New Zealand publication examined PNI in primary cSCC and identified 32 % of primary cSCC with PNI in patients who later developed metastatic disease, compared with PNI in <1 % who did not develop metastatic disease [15].

Tumour involvement of large calibre nerves appears to be a worse prognostic factor than involvement of small calibre nerves. In a study of 48 patients, tumour involvement of nerves with a diameter ≥0.1 mm was associated with significantly worse outcomes with respect to nodal metastases, distant metastases and disease-specific death. In contrast, patients with PNI associated with nerves <0.1 mm diameter had a disease-specific death of 0 % [34].

The Queensland Perineural Invasion Group at the Dermatology Research Centre, University of Queensland, Australia, has established a PNI data registry to prospectively study the association between patient outcome and PNI [35]. Factors include (1) degree of nerve involvement within the tumour, (2) number of nerves involved, (3) nerve involvement with respect to surgical and tumour margins, (4) nerve size and type, and (5) tumour size. The group aims to identify and define best practice in managing PNI and to elucidate underlying causes and mechanisms [35].

Lymphovascular Invasion (LVI)

LVI is a risk factor for metastatic disease. It denotes invasion of tumour cells into the microvasculature of the dermis and lodgement within a vessel lumen. A New Zealand study reported an HR of 4.53 for metastatic disease in the presence of LVI. Ten of 78 patients with metastatic disease had LVI identified in the primary lesion. Interestingly, no LVI was identified in any primary lesion in 92 patients without metastatic disease [15].

In a large study of 6164 patients treated for cSCC, a subset of 4740 patients was treated for HNcSCC. Multivariate analysis of this subset group identified LVI as a significant risk factor for metastatic disease in patients with a lesion in the cheek or peri-auricular region (HR 3.18 and HR 3.31, respectively), but not at other sites of the HN [36].

Recurrent cSCC

Recurrent cSCC is associated with increasing primary tumour size and invasion and a significantly higher incidence of nodal metastases compared with a non-recurrent cSCC. Patients with inadequately excised lesions are at risk of both recurrence and subsequent nodal metastases [37]. A literature review reported nodal disease in 32 % and 45 % of recurrent lip SCC and ear cSCC, respectively [24].

In one study, 18 % of 78 patients had metastatic disease following tumour recurrence [15]. In a review of 122 patients with metastatic cSCC, 11 % of patients had lesions that were recurrent [14].

Excision Margins

Excision margins that are positive with tumour are associated with recurrent cSCC in up to 50 % of patients [37]. An excision margin of 6 mm in patients with high-risk cSCC is recommended. In two studies, an excision margin of 4–5 mm for low-risk cSCC resulted in tumour clearance in 95–97 % of cases compared with 78 % clearance when a 2 mm excision margin was applied [38, 39].

The long-term prognostic benefit of negative margins is highlighted by the results of Mohs micrographic surgery. Mohs surgery involves tumour excision, horizontal sectioning and examination of the entire margin intraoperatively. Rowe et al. reported 5-year disease-free survival (DFS) for lip and ear primary cSCC treated with Mohs surgery as 97.7 % and 94.7 %, respectively [24]. In a multicentre Australian study with 1263 patients, 5-year DFS was reported as 97.4 % with >95 % of lesions located on the HN [40].

The practice of observation and expectant treatment in inadequately excised HNcSCC should be discouraged with current knowledge of the increased risk of metastases in the setting of recurrent cSCC. Re-excision or adjuvant local radiotherapy should be considered in select patients; for example, to achieve optimal excision margins, superficial parotidectomy should be considered in treatment of deeply invasive cSCC (Fig. 8.2).

Assessment of Lymph Nodes

In contrast to the improved DFS after nodal assessment and treatment of mucosal squamous cell carcinoma (mSCC) of the oral cavity and oropharynx, opinion is divided on elective nodal assessment of HNcSCC [41].

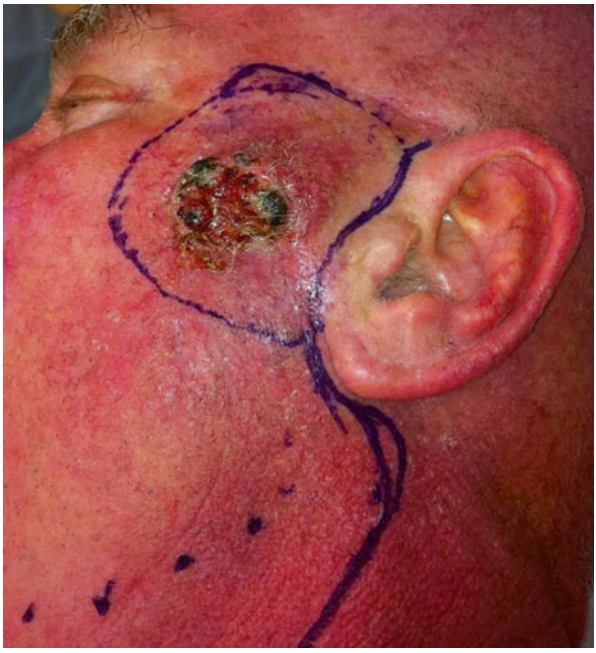

Fig. 8.2 Deeply invasive 2 cm primary cSCC overlying the left parotid. There was no clinical or radiological evidence of CN VII involvement. Surgical management involved excision with a 1 cm margin plus superficial parotidectomy with preservation of CN VII. Selective neck dissection of levels II and III lymph nodes was performed for pathological staging

Elective nodal treatment is not undertaken routinely, as compelling evidence of benefit is lacking.

Sentinel lymph nodes (SLNs) are the first echelon nodes to receive lymphatic fluid from a site of primary malignancy. Sentinel lymph node biopsy (SLNB) was first developed in the late 1970s and has been used successfully as an accurate and reproducible technique in detecting early metastatic disease in cutaneous malignancies, including melanoma and Merkel cell carcinoma [42–44]. Subsequent early intervention in melanoma in the presence of a positive SLN improves patient outcome and has cost–benefit advantages in terms of earlier detection and treatment of clinically negative but pathologically positive regional lymph nodes [45]. SLNB involves preoperative lymphoscintigraphy with a radioisotope tracer plus intraoperative peritumoural dermal infiltration with Patent Blue V dye. A SLN is identified intraoperatively with a hand-held gamma probe and the presence of blue dye staining (Fig. 8.3a, b). The recent addition of preoperative hybrid imaging with single-photon emission computed tomography with CT (SPECT/CT) provides enhanced resolution of areas of increased radiotracer activity that correspond to the SLN. SPECT/CT has provided significant improvement in the anatomical localization of SLN, particularly in the HN region [46].

Data on SLNB for HNcSCC are sparse. Most studies are limited by having a small number of patients and varying definitions for a high-risk lesion. The NCCN guidelines recommend consideration of SLNB in high-risk lesions, but acknowledge that the benefit in cSCC remains to be proven [21].

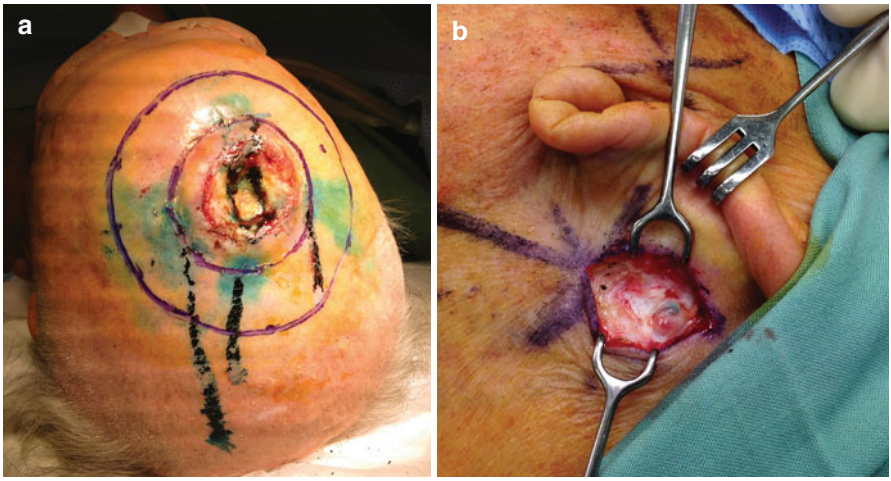

Fig. 8.3 (**a**, **b**) Technique for SLNB of cSCC of the scalp. Lymphoscintigraphy was performed: (**a**) 2 cm surgical margin marked and Patent Blue V injected intradermally for SLN identification and harvest; (**b**) post-auricular SLN. Blue dye staining is visible on the SLN. The SLN was removed for histopathological assessment

Civantos et al. reported the results of SLNB in 60 patients with HN cutaneous cancer, which included 15 patients with HNcSCC that met at least two high-risk features [47]. One patient with HNcSCC had a positive SLN and was treated with completion nodal dissection of the neck. These data, however, are confounded by 12.7 % of patients with pathologically negative SLNs having a completion neck dissection on the basis of intraoperative suspicion of metastases. Interestingly, no patient had metastases on histological examination and none of the 15 patients had recurrent disease within the median follow-up period of 21 months [47].

In a study of 20 patients with lower lip SCCs >2 cm in size, 90 % of SLNs were identified. Metastases were found in 16.6 % with no false-positive results [48]. A literature review of high-risk cSCC involving all skin sites reported 130 patients with SLNB from 11 case series and 4 case reports [49]. A SLN was identified in 98.5 % of cases. The positivity rate ranged between 10 and 18 %. In 51 patients with HNcSCC with a negative SLN, none developed regional recurrent nodal disease [49]. These data suggest that SLNB may play a future role in a high-risk subset of HNcSCC.

Currently, a 30-patient, non-randomized, 5-year follow-up study is under way at SHNCI [50]. This pilot study will assess the feasibility of SLNB for patients with high-risk clinicopathological features of cSCC. The aim of the study is to compare survival in patients who undergo SLNB followed by completion lymph node dissection when SLNB is positive for metastatic cSCC, with patients who have ultrasound (US) observation of the regional lymphatic basin without SLNB [50].

Immunosuppression

Solid-organ transplant recipients and other immunosuppressed patients tend to develop aggressive malignancies at a younger age and with poorer prognosis than their immunocompetent counterparts. The incidence of cancer is increasing in the transplant recipient population, with skin cancer the most prevalent malignancy in renal transplant recipients. With recent advances in transplant surgery and medicine, cancer has now become a leading cause of late mortality in renal transplant patients [51].

Immunosuppressed patients have 18–250 times higher risk of developing skin cancer than age-matched controls [52–54]. They are more likely to develop recurrent lesions and metastatic disease can occur with smaller, thinner primary lesions [55, 56]. The cumulative incidence of developing skin cancers increases from 7 % after the first year of immunosuppressive therapy to 70 % after 20 years [57]. Furthermore, in contrast to immunocompetent patients, in whom BCCs are four times more common than cSCC, this trend is reversed in immunocompromised patients, with cSCC five times more prevalent than BCC [58].

Solid-organ transplant recipients constitute the majority of immuno-suppressed patients with metastatic HNcSCC. However, patients with leukaemia, lymphoma or human immunodefiency virus are also at increased risk. In a review of 122 patients, 7 % of patients with metastatic HNcSCC were immunosuppressed as a consequence of transplantation or haematological disease [14]. In another study, 22 % of 51 patients with metastatic HNcSCC were immunosuppressed; 5 patients with a solid-organ transplant and 6 patients with leukaemia or lymphoma [17].

Adjuvant Radiotherapy for Primary cSCC

Adjuvant radiotherapy reduces the risk of local and regional recurrence and may be considered in high-risk patients treated for primary cSCC with close or positive surgical excision margins (Box 8.1) [59]. A lack of high quality prospective data has led to varied approaches by clinicians in utilizing adjuvant radiotherapy. The majority of outcome data are based on retrospective institutional case series or systematic reviews, which include BCC with PNI and cSCC, and are subject to treatment bias [60, 61].

Extensive PNI of multiple small nerves is an indication in the NCCN guidelines for recommending adjuvant radiotherapy, particularly if the primary is recurrent, has a mid-face location, or is in proximity to CN V or CN VII [21, 62]. Interestingly, despite guidelines, variability exists in use of adjuvant radiotherapy in the presence of PNI. A lack of consensus was identified in scenarios when an unnamed nerve was involved with tumour, with Mohs surgeons less likely to refer for consideration of adjuvant radiotherapy [63].

In an Australian study, in which 21 patients with clinical PNI were treated surgically, all but one patient received adjuvant radiotherapy either as a component of prior treatment and/or as part of definitive treatment. Five-year disease-specific survival (DSS) in that study was 64 % [64].

Box 8.1 Risk Factors for Developing Metastatic Nodal cSCC

- Location of primary tumour
- Tumour diameter ≥2 cm
- Tumour thickness ≥6 mm or penetration into subcutaneous tissue
- Moderate or poor tumour differentiation
- Desmoplastic, adenoid and adenosquamous tumour subtype
- Perineural invasion
- Lymphovascular invasion
- Tumour recurrence
- Positive/close excision margin
- Immunosuppression
- Older age

Follow-Up of Primary cSCC with High-Risk Features

As nodal metastasis is the most important prognosticator in HN cancer, accurate staging and surveillance is important. High-risk patients should be reviewed every 3–4 months for 4–5 years following treatment, particularly patients who are immunosuppressed and those with features of high-risk tumours. In the absence of clinically metastatic disease, imaging is not warranted as a routine investigation. In contrast, patients with clinically evident metastatic cSCC should undergo relevant imaging, the choice of which is dependent on clinician preference, availability of imaging modality, and patient-specific factors. Imaging options include US, CT, MRI and PET/CT.

The highly sensitive and specific nature of US, combined with low cost, low morbidity, availability and ability to guide biopsies, warrants considering its routine use in screening for regional nodal metastases in HNcSCC during follow-up. In a study of 42 patients, sensitivity and specificity of US in predicting malignancy in the HN region was 96.8 % and 93.3 %, respectively [65]. The low incidence and incurable nature of distant disease does not justify screening asymptomatic patients for distant metastases.

Lymph Node Site

Regional nodes can be separated broadly into two groups, viz. parotid (pre-auricular and parotid tail) and cervical nodes (levels I–V). The location of a primary index cSCC is an important determinant of the site of nodal metastasis. The most frequent location for an index lesion is the lateral aspect of the head and metastatic disease is most commonly identified in parotid, level II cervical and external jugular nodes. Parotid nodes represent the first echelon of lymphatic drainage from the face, forehead, anterior scalp, temple and ear, and in Australia and New Zealand, metastatic

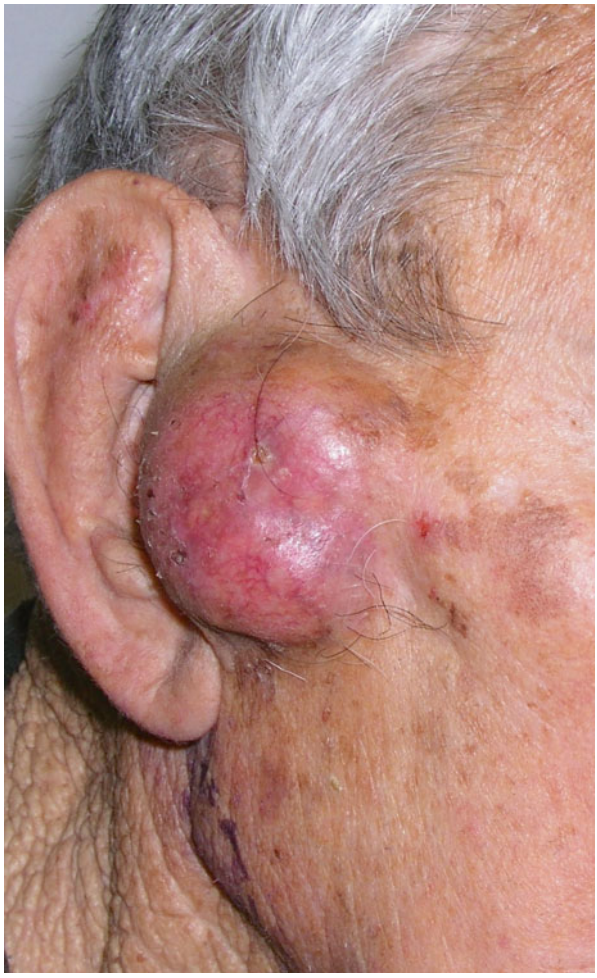

Fig. 8.4 An elderly man with metastatic cSCC to the parotid. Treatment included wide excision, parotidectomy, free-flap reconstruction and adjuvant radiotherapy

cSCC is the most common malignant neoplasm of the parotid (Fig. 8.4) [66]. Facial lesions tend to metastasize to level I and II cervical nodes, whereas anterior lesions of the scalp, ear, temple and forehead usually metastasize to parotid ± level II cervical lymph nodes [4]. Drainage to multiple SLNs is common. Drainage to contralateral nodes occurs in 10 % of patients, predominantly in those with midline lesions [67].

Lymph Node Size and Number

The size and number of metastatic lymph nodes in HNcSCC varies considerably. In a study of 603 patients in Sydney, the median size of the largest metastatic node was 25 mm (range 3–100 mm) [68]. In the same study, the median number of metastatic nodes was 1 (range 1–67 nodes) [68].

Extranodal Spread and Soft Tissue Metastases

High rates of extranodal spread (ENS) and soft tissue metastases (STM) are features of metastatic cSCC. The presence of ENS and STM have a negative impact on prognosis because of their association with regional failure and distant metastases.

ENS predicts a poor outcome [19, 68]. Oddone et al. documented that ENS is associated with reduced overall survival (OS) with an HR 9.92 [16]. A review of clinicopathological data from SHNCI and Westmead Hospital patients with HNcSCC lymph node metastases revealed that 58 % of 215 patients and 82 % of 250 patients, respectively, had ENS [69].

STMs are defined as free soft tissue tumour deposits lacking continuity with the primary tumour and without discernible lymph node tissue [69]. STMs possibly represent nodes that are completely replaced by tumour, with no remaining evidence of the pre-existing node. On reviewing pathology slides of 164 patients, 44.5 % were shown to have STMs, accounting for worse DFS and OS (HR 2.35 and 2.91, respectively) [69]. Since the adverse effect on survival from STM is comparable to that of multiple nodal metastases, adjuvant radiotherapy should be considered for all patients, even when only a single, small STM deposit is identified.

Staging Systems

In 2002, a revised clinical staging system was proposed to define the extent of metastatic HNcSCC to the parotid and/or neck [70]. At the time, the prognostic capacity of the TNM classification was limited in that it described only N0 and N1 to identify the absence or presence of neck disease, respectively. Involvement of parotid gland lymph nodes and CN VII with metastatic tumour was excluded. The proposed O'Brien staging system stratified size and number of involved lymph nodes within the parotid and neck, and incorporated metastatic cSCC of the parotid, facial nerve, skull base and contralateral neck [70].

A retrospective, multicentre trial of the new staging system reviewed data from 322 patients with metastatic HNcSCC across six centres in Australia and the USA [71]. Overall, DSS was 74 %. Patients with metastatic cSCC in both the parotid and neck had a significantly worse DSS of 61 % compared with 79 % for patients with only parotid metastases ($p = 0.027$). In addition, patients with advanced parotid disease had a DSS of 69 % compared with 82 % for patients with P1 disease ($p = 0.02$) [71]. The O'Brien staging system proved to be a superior staging system in terms of stratification and prognostication of patients with metastatic HNcSCC.

In 2010, Forest et al. proposed a relatively simple staging system entitled N1S3 [68]. N1S3 stratified patients into three stages according to the number and size of involved nodes and incorporated parotid nodes as one of the regional nodal levels. The N1S3 staging system is as follows: stage I represents a single lymph node <3 cm; stage II represents a single lymph node >3 cm or multiple nodes <3 cm; and stage III represents multiple nodes >3 cm. Patients with ENS are excluded. In a

review of 215 patients, the N1S3 staging system was predictive of locoregional control ($p<0.001$), DSS ($p<0.0001$) and OS ($p<0.0001$) [68].

The 7th edition of the *American Joint Commission of Cancer* (*AJCC*) *Staging Manual* incorporates results from previous publications and has introduced further changes to the staging of HNcSCC [72]. To improve patient stratification, classification of lymph node metastases was adjusted from the two-tiered N0/N1 system in the 6th edition to the well established N0, N1, N2, N3 system that is used for mucosal HN cancer. In the current edition, N1 represents a single involved lymph node ≤3 cm; N2 represents ≥1 involved lymph node 3–6 cm; N3 represents ≥1 involved lymph node ≥6 cm [72].

The 7th AJCC staging system has not yet been evaluated extensively. In 2012, Brunner et al. published a retrospective multicentre analysis of 603 patients with metastatic HNcSCC that compared survival data for AJCC stage IV disease—regional N2 or N3 disease versus distant metastases [73]. Survival was significantly better in N2 and N3 disease, with 5-year survival 75 % (312 patients) and 65 % (37 patients) respectively, compared with 11 % (35 patients) of patients with distant metastatic disease. Brunner concluded that stage IV disease, based on the 7th edition of the AJCC TNM staging system, was heterogeneous, with significant variation in DSS and OS and would hence benefit from further revision [73].

Treatment

To improve locoregional control and OS, optimal treatment for metastatic HNcSCC involves a multimodality approach with surgery followed by adjuvant radiotherapy [4, 74]. As patients are often older and treatment for metastatic cSCC is associated with morbidity, opinions vary regarding the extent of each treatment modality. The most common concerns of patients after treatment for metastatic HNcSCC include the following: alteration to physical appearance, xerostomia, and change in voice quality and strength [14]. In addition, a subset of patients have co-morbidities, which may limit optimal treatment.

Surgery

For patients with metastatic cSCC to cervical lymph nodes, surgery has traditionally involved a modified radical neck dissection. A trend has been initiated towards selective neck dissection in patients with a low burden of metastatic disease (N1 and N2) with HNmSCC, with the aim of reducing surgical morbidity [75–79]. A recent Australian study of patients with HNcSCC reported no statistically significant difference in 5-year OS (61 % vs. 57 %) or 5-year DFS (74 % vs. 60 %) for selective neck dissection or radical neck dissection, respectively [80].

Recent data have simplified the relationship between the site of the primary cSCC and nodal disease, allowing more selective treatment of the neck, both surgically and with adjuvant radiotherapy [4]. However, almost one quarter of patients

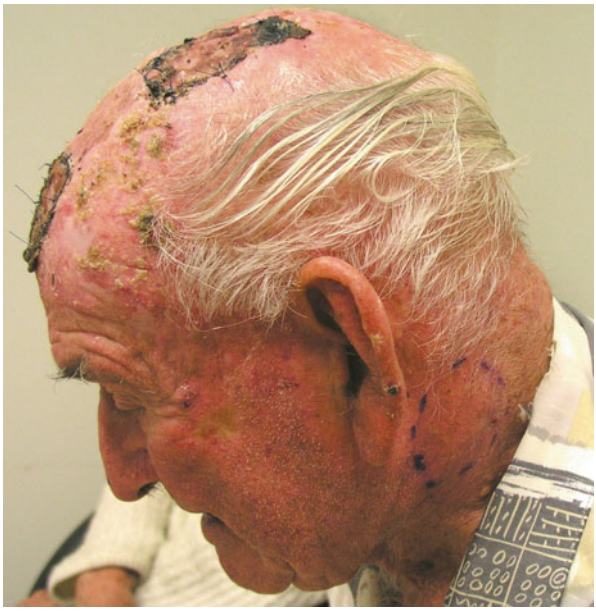

Fig. 8.5 A typical elderly Australian man with chronically sun-damaged skin who presented with left level II cervical lymphadenopathy. He had previously received treatment for multiple HNcSCC. This case highlights the difficulty in identifying the primary lesion responsible for metastatic nodal cSCC

have metastatic HNcSCC with an unknown site of the primary index lesion (Fig. 8.5) [4, 14]. One study of patients with an anterior facial cSCC, identified metastases to level I nodes in 17.9 %, whereas only 5.4 % of patients were identified with metastatic cSCC in level V lymph nodes [4]. When no metastases were identified in level II lymph nodes, only 6 % of patients with an anterior facial primary cSCC had metastatic cSCC in level I [4]. Involvement of level II lymph nodes is, therefore, a predictor of metastatic disease in level I cervical nodes.

Furthermore, patients with metastases in levels II/III were significantly more likely to have metastatic disease in levels IV/V than patients without levels II/III lymph node involvement (33.3 % vs. 6.7 %, respectively; $p < 0.001$) [4]. Examination of primary site subgroups of patients reported 15.8 % of posterior facial primary, 2.7 % of anterior facial and 0 % of external ear cSCC, without level II/III metastases had levels IV/V lymph node involvement [4].

Parotid Metastases

Parotid nodes are the most frequent site for metastatic disease from a primary HNcSCC. Metastases travel via a rich lymphatic network from the primary site to 15–20 superficial periparotid lymph nodes and 4–5 lymph nodes within the deep parotid lobe. Involvement of parotid lymph nodes has implications with respect to prognosis and management. All patients with metastatic cSCC to the parotid region and a clinically node-negative neck should undergo parotidectomy and ipsilateral selective neck dissection [3, 4, 81].

Parotidectomy usually involves superficial lobectomy with preservation of CN VII. Less commonly, an extended parotidectomy is required, with sacrifice of either the main trunk or at least one of the main branches of CN VII. If CN VII is sacrificed, facial reanimation is recommended either immediately or as a delayed procedure. As resection rarely achieves margins >5 mm, CN VII should be sacrificed only in the presence of preoperative facial nerve palsy. Consideration should be given preoperatively to both the extent of resection of involved skin overlying the parotid and reconstructive options, including local and free-flap reconstruction. Adjuvant radiotherapy should be recommended routinely to treat residual microscopic disease.

Iyer et al. examined outcomes for patients with involved margins, in whom metastatic tumour had been dissected from CN VII [82]. Data for 15 patients treated with nerve-sparing surgery plus adjuvant radiotherapy from a database of 176 patients were analysed. Two patients had residual CN VII palsy despite nerve-sparing surgery. Three patients developed recurrent disease in the parotid bed, which was salvaged successfully with radical surgery and nerve sacrifice [82]. Iyer concluded that 10 of 15 patients had normal CN VII function post-treatment with no difference in DSS when compared with patients who had clear or close margins [82]. Therefore, patients without macroscopic involvement of CN VII, but with close margins, can still undergo nerve-sparing surgery provided adjuvant radiotherapy is delivered.

Ebrahimi et al. reported 21 % of patients who underwent parotidectomy and elective neck dissection for a clinically N0 neck had pathologically proven metastatic disease in cervical lymph nodes [4]. Importantly, in the same study, patients with metastatic cSCC to the parotid region and a clinically N0 neck, had no metastases in levels IV/V in the absence of pathological metastatic disease in levels II/III. Therefore, selective neck dissection of cervical lymph node levels II and III is recommended for patients undergoing parotidectomy for metastatic cSCC.

Complications of Surgery

Complications of surgery include permanent nerve injury, most commonly caused by intentional nerve sacrifice as a consequence of proximity of a nerve to tumour, temporary neuropraxia, wound infection, haematoma, chyle leak, pneumonia and myocardial infarction.

Clinical signs and symptoms of accessory nerve dysfunction are subtle and generally missed in the immediate postoperative period, and are thus underreported. Previous studies describe shoulder dysfunction in 30 % of patients treated with level V lymph node dissection with consequent deleterious effects on activities of daily living and quality of life [83, 84].

Adjuvant Radiotherapy

Current best practice for most patients with operable metastatic nodal cSCC is surgery plus adjuvant radiotherapy. In a study of 74 Australian patients with metastatic cSCC

to cervical nodes, those treated with surgery and adjuvant radiotherapy had a lower recurrence rate (15 % vs. 77 %) and better 3-year DFS (70 % vs. 45 %) compared with patients treated with surgery alone [85]. More recently, a review of 122 Australian patients reported a 5-year OS 66 % with adjuvant radiotherapy compared with 27 % with surgery alone [14]. Patients should receive 60 Gy in 2 Gy fractions to an operative bed and 50 Gy in 2 Gy fractions to undissected regions including the lower neck.

Extent of Radiotherapy

Patients with metastatic cSCC to the parotid region, with a clinically N0 neck, who undergo parotidectomy and selective neck dissection, who are found to have pathologically evident disease in the neck, require adjuvant radiotherapy to both the parotid bed and ipsilateral neck. Selective radiotherapy only to the parotid bed may be considered in patients with a pathological N0 neck [4, 86]. Furthermore, it may be reasonable to manage with surgery, as a single treatment modality, a small group of select patients with low-risk disease, those who are immunocompetent with a single, small, low-grade metastatic node with no ECS or STM, and no PNI or LVI who have clear surgical margins [87].

Complications of Radiotherapy

Most patients do not require hospitalization or treatment interruption. Potential benefits of treatment should be considered against side-effects. Acute toxicity is most commonly cutaneous: dermatitis, skin erythema and ulceration, which may require dressings or treatment interruption. Early radiotherapy toxicity includes mucositis, xerostomia, lethargy, anorexia and taste alteration.

Late effects of concern, although relatively uncommon, affect the central nervous system and include hearing loss, retinopathy and blindness. Other late effects include xerostomia, dental caries, neck fibrosis, hypothyroidism, accelerated atherosclerosis and osteoradionecrosis.

Adjuvant Chemotherapy

Addition of concurrent platinum-based chemotherapy as a radiosensitizer is well documented in HNmSCC. Analogous data are limited in metastatic cSCC. The Trans-Tasman Radiation Oncology Group Trial (Post Operative Skin Trial 05.01) is investigating postoperative concurrent chemoradiotherapy versus postoperative radiotherapy alone for high-risk HNcSCC, and is under way at multicentre sites in Australia and New Zealand. The primary objective of the trial is to determine whether there is a difference in time to locoregional relapse between patients treated with adjuvant concurrent chemoradiotherapy with carboplatin or adjuvant radiotherapy alone.

Modification of Immunosuppression

In renal transplant recipients, it may be possible to reduce immunosuppressive medication. Unfortunately, worsening renal function with requirement for renal dialysis may complicate reduction in immunotherapy. The option of reducing

immunotherapy for heart, lung and liver transplant patients also has the potentially deleterious consequence of graft loss.

Sirolimus is an inhibitor of the mammalian target of rapamycin (mTOR) with antineoplastic properties. It might reduce the rate of cSCC in renal transplant recipients. In a large cohort study (TUMORAPA) of 110 renal transplant patients who were receiving calcineurin inhibitors (CNI) and who had had at least one cSCC, 64 patients were randomized to switch from CNI to sirolimus, and 56 patients were randomized to continue with CNI [88]. Patients who switched to sirolimus experienced significantly longer cSCC-free survival. A new cSCC occurred in 22 % of patients in the sirolimus group and in 39 % of patients in the CNI group, within a median time of 15 months versus 7 months (RR 0.56; 95 % CI 0.32–0.98). Serious adverse events were more common in the sirolimus group, with 60 events versus 14 events in the CNI group. Graft function remained stable in the two study groups [88]. This study shows early evidence that rates of cSCC can be reduced with modification of immunosuppressive medication. Further studies are warranted to minimize associated side-effects of treatment.

Outcome and Survival

Clinical stage is the most important prognostic factor and is assigned through delineation of the extent of disease, specifically, tumour (T) and regional nodes (N). Distant disease (M) is rare in HNcSCC and is investigated in cases of high suspicion.

With respect to survival, published studies are based primarily on retrospective patient selection and heterogeneous groups of patients with inherent uncontrolled patient, tumour and treatment factors. Consequently, prognostic factors and patient outcome vary significantly among studies reported in the literature. High-risk features are summarized in Box 8.2. In general, patients with metastatic HNcSCC have an OS of 30–75 % at 5 years, with markedly improved survival seen in patients treated with multimodality therapy.

Box 8.2 Poor Prognostic Factors of Metatstatic Nodal cSCC

- Immunosuppression
- Size of involved lymph node >3 cm
- Involvement of multiple lymph nodes
- Involvement of multiple lymph node levels
- Extranodal spread Soft tissue metastases

Survival

Regional recurrent cSCC occurs both as dermal metastases (Fig. 8.6) and isolated nodal disease, and may occur in the contralateral neck [89]. Five-year DFS rates vary between studies and are dependent on a variety of factors, including treatment modality (surgery only versus surgery plus adjuvant radiotherapy), patient

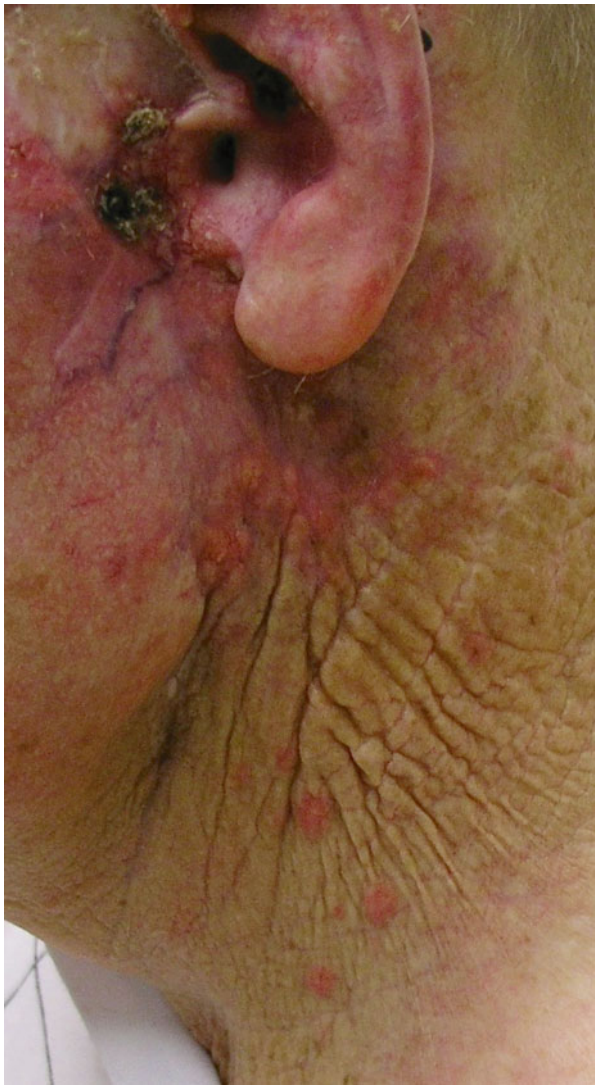

Fig. 8.6 A man with regional metastatic dermal deposits of cSCC. Dermal metastatic cSCC is not amenable to surgical management. This patient was treated with radiotherapy

immunosuppression, ENS and STM, and number and size of involved lymph nodes [14, 23, 69].

In a study of 75 patients treated with multimodality therapy for metastatic cSCC to parotid lymph nodes, the median time to regional recurrence was 9.7 months (range 2–80 months) [89]. Select patients with regional recurrent metastatic HNcSCC are treated with salvage surgery, radiotherapy, chemotherapy or a combination of these modalities. However, 60–70 % of patients, who have been treated previously with surgery plus adjuvant radiotherapy, are not amenable to further treatment and are deemed incurable (Fig. 8.7a, b).

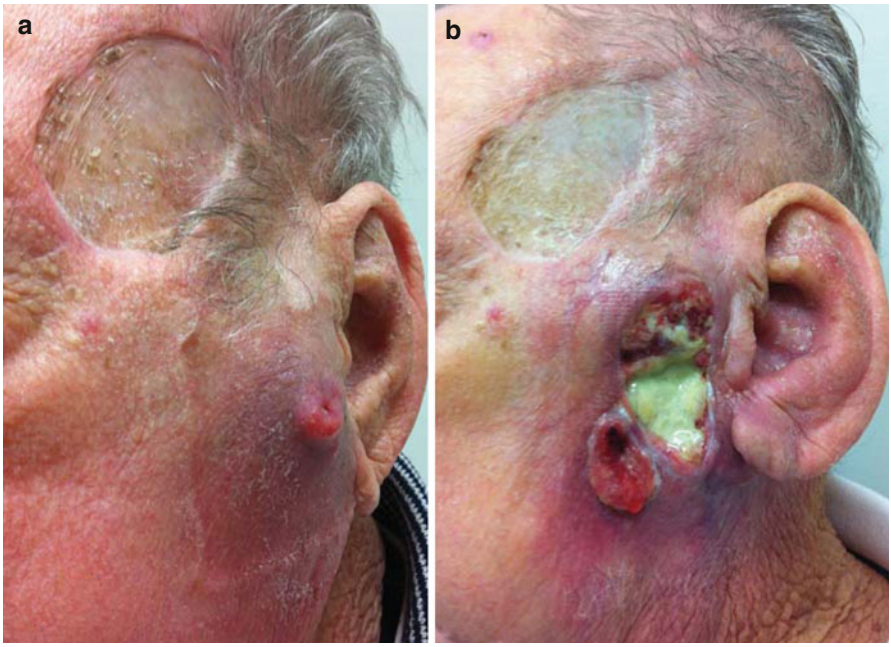

Fig. 8.7 (**a**, **b**) A 76-year-old man previously treated with surgery for a primary cSCC and with multimodality therapy for metastatic nodal cSCC to the parotid region; (**a**) incurable recurrent metastatic cSCC to the parotid; (**b**) progression of incurable metastatic cSCC 3 months later

When patients are stratified according to the N1S3 staging system, improved rates of survival in early-stage disease are highlighted. In a cohort of 168 stage I patients, DSS was 92 % at 5 years [81]. A small subset of 33 of those patients with low-risk nodal disease, who were treated with unimodality surgical resection only, had a 5-year survival of 97 %. In contrast N1S3 stage III patients had a 42 % DSS at 5 years [81]. In a larger review of 603 patients with metastatic HNcSCC treated at two large cancer centres in Sydney, 5-year DSS was reported as follows for N1S3 staging; stage I 83 % (95 % CI 75.1–88), stage II 78 % (95 % CI 70.7–83.5), and stage III 63 % (95 % CI 48.6–74.3) [68].

Conclusion

Our understanding of the pathological behaviour of HNcSCC has improved significantly. Adequate staging requires meticulous surgical technique and detailed synoptic, pathological evaluation. Strict adherence to accurate pathological reporting guidelines is imperative with respect to implications for future decision-making, patient prognosis and treatment pathways. Examination of all tumour deposits and lymph nodes should be undertaken, along with documentation of all aspects of the primary tumour, site, size, depth, PNI, LVI, number, size and location of involved lymph nodes, and description of every metastatic deposit, including ENS and STM.

Multimodality treatment is now accepted as standard of care for metastatic HNcSCC. Surgery and radiotherapy techniques are being refined, with subsequent improvements in patient care and outcome. Treatment modalities will continue to improve and become more tumour- and patient-specific as we gain a better understanding of the molecular and genetic features of this disease.

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Managing Perineural and Skull Base Involvement

9

Timothy A. Warren and Benedict Panizza

Introduction

Australia is recognized as the non-melanoma skin cancer (NMSC) capital of the world with approximately 300,000 cases diagnosed annually [1]. NMSC with perineural invasion (PNI) is an aggressive feature, which carries a worse prognosis through higher rates of locoregional recurrence and reduced survival [2–5]. NMSC with PNI has been shown to be associated with a disease-specific survival at 3 years of 64 %, compared to NMSC without PNI of 91 % [6].

PNI is the presence of tumour cells in the perineural space of a peripheral nerve. Despite being first described almost 180 years ago with several subsequent attempts at clarification, there remains no consensus on the definition [7, 8]. In 1835, Cruveilhier used the term 'neurotropism' to describe a tumour's propensity to invade neural tissue [7]. This histopathological feature, now known as perineural invasion, is a poor prognostic indicator in several malignancies, including those of the prostate [9], pancreas [10], cervix [11], stomach [12], colorectum [13], and head and neck mucosa [14].

PNI is estimated to occur in less than 5 % of NMSCs and is more common in squamous cell carcinoma (SCC) than in basal cell carcinoma (BCC) [15–17]. Perineural spread (PNS) represents extension of a tumour along the perineural

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Table 9.1 Features of high-risk cutaneous squamous cell carcinoma [21]

Large size >2 cm
Deeply invasive >4 mm
Incomplete excision
Recurrent disease
Poorly differentiated
Perineural invasion
Location on or around ear or lower lip
Immunosuppressed

space, and this occurs over a variable timeframe (months to years) [18]. The majority of cases involve small-calibre peritumoural cutaneous nerves, which are diagnosed only after biopsy or excision with careful histological sectioning and microscopy. This subtype is known as 'incidental PNI' and is asymptomatic in the patient. Typically, it is managed with definitive surgical excision, yet postoperative radiotherapy should be considered, particularly when other high-risk features of the patient and/ or primary tumour are present (Table 9.1) [3, 5, 19–21].

The aggressive reputation of PNI stems from the ability of tumour cells to invade the perineural space and spread continuously via this conduit to the central nervous system (CNS). A form of tumour metastasis, PNS is otherwise known as 'clinical PNI', a term that reflects clinically evident deficits in the distribution of the involved nerve at presentation. Clinical PNI has a well-recognized, worse prognosis than incidental PNI [4, 5, 19, 22]. Patients present with progressive symptoms and/or signs of nerve dysfunction. Depending on the nerve and branch involved, these can include facial paralysis and/or sensory nerve dysfunction. The trigeminal (V) and facial (VII) cranial nerves are the most common nerves involved. PNS is detected on magnetic resonance (MR) imaging in the majority of cases using a targeted neurography study [23]. Imaging-defined disease extent guides treatment, which is typically a combination of surgery and postoperative radiotherapy.

This disease is often under-recognized clinically and pathologically, leading to critical delays in diagnosis [18, 24]. The terminology utilized varies throughout the literature, limiting efforts to produce clinical practice guidelines [7, 8]. This chapter reviews the natural history of NMSC with PNI and outlines the approach to diagnosis and treatment, with particular focus on the surgical management of skull base disease. The limitations within the current staging system for perineural disease are also discussed.

Natural History

The perineural space is a potential space between or beneath the layers of the perineurium, the middle-layer of the peripheral nerve sheath. The perineurium is formed from tightly packed perineural cells arranged as a tubular structure that protects nerve fascicles from the surrounding environment as part of the blood–nerve barrier

[25]. It also appears to provide an anatomical barrier to tumour spread, especially in the proximal aspect of cranial nerves at the skull base where it is multilayered. Animal models have shown anatomical continuity of the perineural space proximally with the subarachnoid space and distally with the dermis, thus providing a conduit for disease in the periphery to spread into the CNS [26, 27].

The ability of tumour cells to invade the perineural space and then spread contiguously into the CNS has long been understood [28, 29]. The tumour likely invades the perineurium at the periphery where it is thin and unilayered, and then spreads axially along the perineural space with relatively low resistance [30]. However, the precise mechanism remains unclear. Nerves are maintained and stimulated to proliferate by neurotrophins, growth factors and axon-guidance molecules [31, 32]. The potential importance of these factors in PNI was shown in an *in vitro* model of PNI using prostate cancer cells cultured alongside mouse dorsal root ganglia tissue [33]. This process demonstrated reciprocal signalling within the tumour microenvironment, consistently resulting in simultaneous tumour growth and neurite axonogenesis to culminate in nerve invasion [33–36]. This seemingly symbiotic process may result from the presence of tumour cells within an especially favourable environment for growth and proliferation, and probably involves complex tumour, nerve and stromal signalling [37].

PNI appears to occur in regions with a high incidence of cutaneous malignancies [4, 38, 39]. Middle-aged men are the most commonly affected; however, patients with clinical PNI aged 34–91 years have required treatment at our institution. The typical patient is a middle-aged man, and the intrinsic primary tumour factors that are associated with PNI include large size (>2 cm diameter), location on the midface or cheek, recurrent disease and poor differentiation [40]. The head and neck is the most frequent site of disease for NMSC. That this region is richly innervated by the trigeminal and facial cranial nerves is consistent with the fact that these nerves are the most frequently affected by PNS [41].

PNS occurs over a variable timeframe, from months to years [18]. Without timely treatment, the natural history of NMSC with PNS is a slow central spread of disease to the brainstem, with poor prognosis (i.e. 'central failure') [42–44]. PNS is contiguous along the nerve and occurs in the absence of 'skip lesions'. Skip lesions describe non-contiguous spread, akin to embolic spread, and have been reported in the literature without clear histological evidence [2]. However, this phenomena is probably the product of technical processing artifact [45]. Our group has recently assessed 50 cranial nerve specimens affected by PNS and found no evidence of a skip in tumour growth [46].

The direction of PNS is either centripetal (toward the brainstem) or centrifugal (toward the skin). Centripetal spread is the more common pattern, and it occurs after PNI in the periphery with subsequent primary PNS along a cranial nerve. Centrifugal spread is seen less frequently and typically represents secondary PNS that commences at nerve branching points or after ganglion invasion [39]. These features of tumour spread are unique to PNS in the head and neck.

Most central failure is by direct spread into the brainstem; however, leptomeningeal carcinomatosis (also known as drop metastases), a form of central failure, can

occur less commonly as advanced end-stage disease [44]. It refers to the spread of perineural disease into the subarachnoid space and extensive disease dissemination throughout the meninges via the cerebrospinal fluid. This reflects the anatomical continuity of the perineural space with the subarachnoid space. Palliative radiotherapy for symptom control might be required.

PNI has been shown to portend a higher risk of nodal metastasis in patients with cutaneous SCC (cSCC) and PNI [47]. One study in patients with cSCC showed that those with incidental PNI in the primary had a rate of nodal metastasis of 40 % compared to those with no PNI in the primary who had a rate of nodal metastasis of 18.2 %, and this was independent of tumour size (p = 005; OR 2.0) [47]. Yet interestingly, several recent, focused studies have shown that regional nodal disease at presentation in clinical PNI patients is uncommon, with recorded rates of between 0 and 16 % [38, 39, 48, 49]. This suggests that PNS is a form of tumour spread that is often distinct from metastasis via a lymphatic or haematogenous route, and can often exist independent of nodal or distant disease [40, 50]. Primary tumour biology is clearly a significant factor, and is presently little understood.

Diagnosis

Clinicopathological Features

The diagnosis of PNI requires a high index of suspicion by the treating surgeon, radiologist and histopathologist. Incidental PNI can be diagnosed only on histology with careful sectioning and staining. Common stains include haemotoxylin and eosin, broad-spectrum keratin (AE1/AE3), cytokeratin (MNF116) and S100 (Fig. 9.1). The microscopic detection of PNI and clarification of margin status can be challenging on account of the inherent ramification pattern of small nerves throughout the dermis and soft tissues. This is particularly relevant in Mohs micrographic surgery (MMS) because of the use of horizontal sectioning, which can generate artifact and the false impression of margin clearance, or even a ‘skip’ in tumour growth [24, 45]. The use of longitudinal and/or perpendicular sectioning can improve accuracy [24, 45]. Currently, standardized histopathological reporting schemes for PNI are unavailable. The assessment of incidental PNI typically includes the maximum nerve diameter involved. A diameter >0.1 mm is an aggressive feature and this has been shown recently to be associated with worse outcomes [51, 52].

In a recent series of 50 patients with clinical PNI from cSCC treated with surgery and postoperative radiotherapy, approximately one-third of patients had either unassessable or unknown primary tumours (i.e. TX or T0) [49]. Also, over a third of patients with a known primary tumour did not have PNI reported. This could reflect either of the following facts: (i) PNI did not exist in the primary; (ii) PNI did exist in the primary but remained undetected; or (iii) another NMSC may be the ‘culprit’ primary, as many of these patients have had chronic sun exposure and multiple NMSCs.

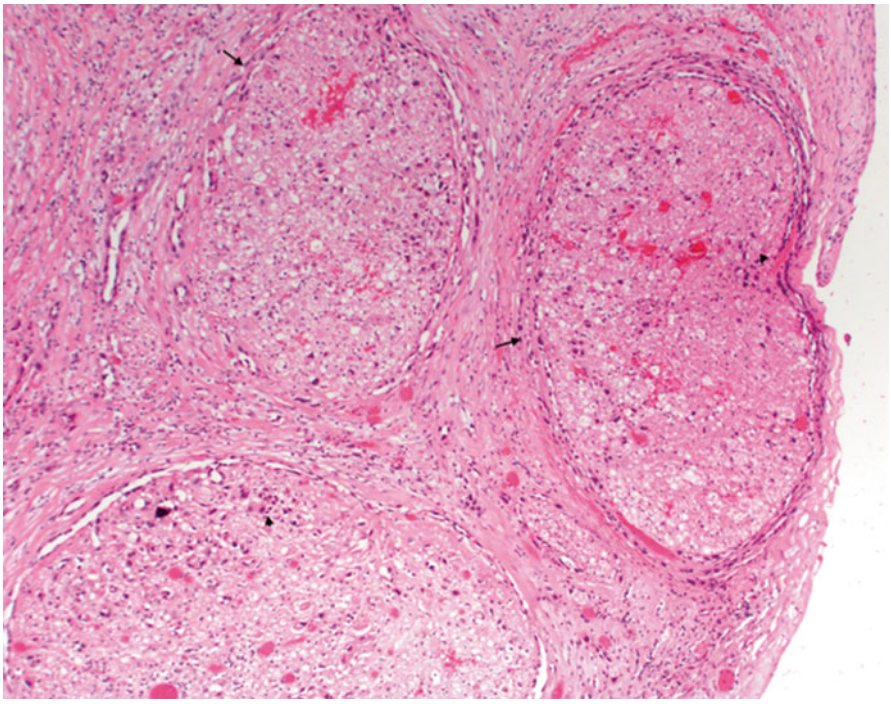

Fig. 9.1 Histopathological section showing perineural spread along the perineural space of cranial nerve (*arrows*) with areas of intraneural invasion (*arrowheads*: H&E staining; magnification 100×)

Symptoms and signs are likely to be the result of gradual nerve fascicle invasion and/or compression by the tumour. It is not uncommon for a patient's symptoms/signs to be present for several years and the diagnostic clues misinterpreted as benign conditions, such as Bell's palsy or trigeminal neuralgia. The typical patient with trigeminal nerve disease presents with a slowly progressive dysaesthesia in the distribution of one of the three main branches (V1, V2 or V3). Symptoms can include any combination of numbness, paraesthesia, burning, neuropathic pain or formication (i.e. crawling of ants), which progressively spread over time into the dermal distribution of other V nerve branches, reflecting retrograde invasion into the gasserian ganglion. Direct questioning of the patient for these symptoms is often required. Also, a local subcutaneous mass or nodule might be present concurrently, and can be useful to facilitate initial tissue diagnosis.

While facial nerve involvement is generally a more obvious presentation, it is often misinterpreted as Bell's palsy. The typical patient presents with a partial yet progressive facial paralysis in the distribution of one of the major facial nerve branches. As disease slowly spreads antegrade to the stylomastoid foramen, unilateral complete facial paralysis develops. Bell's palsy can be distinguished by its tendency to manifest as a sudden partial or complete facial nerve palsy that affects all the branches and which shows at least some recovery over a period of weeks.

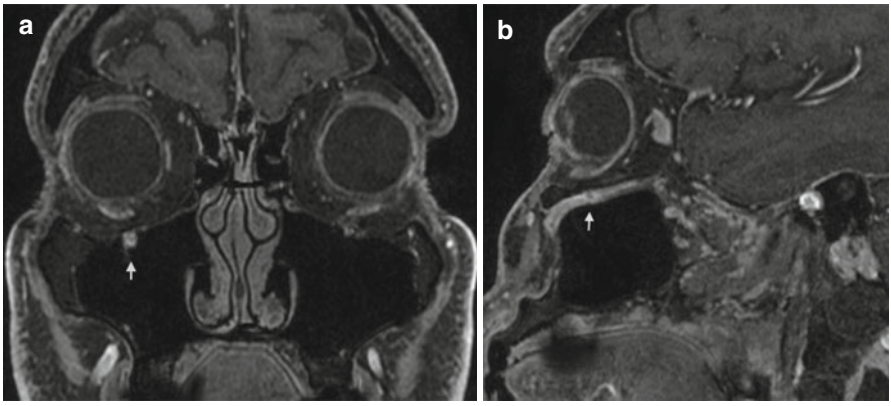

Fig. 9.2 (**a**) Coronal, (**b**) sagittal: magnetic resonance neurography showing perineural spread from cutaneous squamous cell carcinoma of the head and neck. Zone 1 disease is present in the right infraorbital nerve (*arrow*)

The trigeminal and facial nerves can be involved simultaneously in a patient, probably resulting from the known extensive communicating branches between these nerves [53, 54]. These communications can be between the temporal branch of the facial nerve and the zygomaticotemporal nerve, the facial nerve and the buccal nerve, and the facial nerve and the infraorbital nerve [55, 56]. Involvement of the great auricular nerve with PNI is rare, yet can spread via the cervical spinal nerve root to the CNS [57, 58].

Imaging Features

Targeted MR neurography reviewed by a skull base radiologist is the gold standard for imaging assessment of PNS, and is vital for diagnosis, treatment planning and surveillance [23]. MR neurography utilizes a targeted high resolution matrix, small field of view, thin slices and gadolinium enhancement to improve spatial resolution and diagnostic ability, preferably with a 3.0-T platform [23]. MR neurography can detect and assess the extent of PNS accurately in the majority of cases. Gandhi et al. detected PNS in 100 % of nerves (30/30), and correctly identified the extent of PNS in 83.3 % (25/30) using targeted 1.5 T MR neurography when matched to pathological specimens [23].

PNS is typically shown by the presence of thickening and enhancement of involved nerve(s) (Fig. 9.2), with obliteration of the fat planes that surround skull base foramina [59]. Denervation from motor nerve involvement (V3, VII) can also produce T2 hyperintensity and abnormal gadolinium enhancement of the innervated muscle, which should not be misinterpreted as primary pathology within the muscle.

The imaging zonal system described by Williams et al. is useful for grading the extent of disease spread (Table 9.2) [60]. The zonal extent influences clinical

Table 9.2 Classification of imaging-defined extent of perineural spread of cutaneous malignancy in the head and neck

Zone	Imaging-defined extent
1	V1 (ophthalmic nerve) to the superior orbital fissure; V2 (infraorbital nerve) to the external aperture of the foramen rotundum; V3 (mandibular nerve) to the external aperture of the foramen ovale; VII (facial nerve) to the external aperture of the stylomastoid foramen
2	V1, V2, V3: From Zone 1 to the gasserian ganglion cistern; VII: From Zone 1 up to the lateral end of the internal auditory canal, including the geniculate ganglion and the labyrinthine segment
3	All nerves: proximal to the ganglion, into the cisterns, or into the brainstem

Adapted from Williams et al. [60]

decision-making and has been shown to be a predictor of overall survival at 5 years: (i) zone 1—71.4 %; (ii) zone 2—66.7 %, and (iii) zone 3—18.2 % ($p=0.025$) [61]. Computed tomography (CT) is useful to stage regional lymph nodes and assess bone involvement. It can detect only advanced perineural disease evidenced by bulky advanced disease or skull base foraminal erosion/expansion by the tumour [50, 59, 62]. In cases in which the diagnosis of PNS is uncertain after adequate imaging, a nerve biopsy should be considered. A segment of nerve of ≤2 cm in length should be resected, preferably under frozen-section control.

Imaging is generally not necessary for patients with incidental PNI. However, if postoperative symptoms or signs (i.e. those present immediately after surgery) progressively worsen during follow-up, imaging with MR neurogram is required. In the experience of our team, detecting PNS on imaging in the absence of symptoms is rare.

The use of standard, unfocused MR imaging or CT of the brain will not appreciate perineural disease as effectively as tailored protocols, such as MR neurography [23]. Some centres report imaging-negative PNS at rates of 22–52 %, yet the imaging modality and protocol used are not always defined [3, 4]. At our institution, all clinical PNI patients with trigeminal nerve symptoms had positive preoperative MR neurography, and this probably reflects both improved technology and targeted imaging [23]. Small-calibre, low-volume peripheral nerve involvement cannot always be detected. Detecting distal VII nerve branches with early PNS (i.e. those presenting with partial facial palsy) remains a challenge with current MR technology. This problem may also be compounded by an irradiated or postoperative parotid bed.

Staging

Acknowledging its aggressive nature, the American Joint Committee on Cancer (AJCC) recognize the presence of PNI for staging cutaneous malignancies. Evidence of PNI in the primary tumour (T) is regarded as T1 or T2, depending on the co-presence of other high-risk features, such as size and depth of invasion. PNS to the

skull base is classified as T4 [63]. At present, this system does not reflect clinical practice and has limited applicability for PNI patients. It classifies PNS as a feature of the primary tumour, despite being a distinct form of tumour spread. In addition, it would be useful to include the zonal system, as this has been shown to correlate with prognosis [61]. Under the current system, zone 1 PNS that does not reach the skull base can be classified as T1 or T2, despite clearly worse outcomes when compared with a NMSC without PNI [6, 61].

In addition, the involved nerve diameter for incidental PNI has been shown to correlate with prognosis [51]. Ross et al. recorded the maximal diameter of involved nerves in 48 patients with incidental PNI of cSCC, and found that a nerve diameter of >0.1 mm was associated with significantly worse outcomes (local recurrence, disease-specific death, metastasis and overall survival; $p<0.05$) [51]. Similarly, Carter et al. showed a higher risk of death from disease and nodal metastasis in patients with nerve diameter of >0.1 mm [52]. Currently, it is unclear whether a greater nerve diameter is associated with higher risk of PNS.

At our institution, patients with NMSC and PNS are staged using the primary tumour characteristics (to predict regional nodal risk) and the zonal extent of PNS on imaging (Table 9.2). It is important to note that many patients present with PNS as recurrence, and this, therefore, requires appropriate notation (i.e. 'rTNM' stage).

Management

Incidental PNI

Incidental PNI is most often diagnosed at treatment after surgical excision of a NMSC. This may be via routine wide-local excision or MMS. The aim should always be to obtain a clear margin, if possible. Consideration should be given to postoperative radiotherapy, particularly in cases with a positive margin, large nerve diameter (>0.1 mm), or the co-presence of features associated with increased aggressiveness (Table 9.1) [2, 52]. Radiotherapy should encompass the primary tumour with a surrounding margin for PNI [2]. The decision to offer postoperative radiotherapy is often the most challenging aspect in management, with 'under-treatment' being a common feature in many patients seen later with recurrent disease and PNS. However, clear treatment guidelines remain unavailable.

Clinical PNI

The more aggressive nature of clinical PNI ultimately necessitates more complex multidisciplinary management involving surgical resection and/or radiotherapy (definitive or postoperative). Surgical resection is a significant undertaking, typically requiring input from many teams, including an otolaryngologist/head and neck surgeon, neurosurgeon and plastic/reconstructive surgeon.

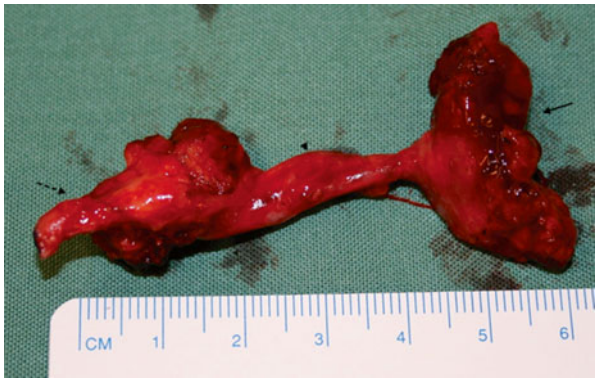

Fig. 9.3 Surgical specimen from *en-bloc* resection of infraorbital nerve (*arrowhead*) with subcutaneous soft tissues (*arrow*), along with ptyergopalatine fossa contents and initial part of V2 (*broken arrow*) via a trans-facial approach

Effective management requires an understanding of the natural history of the disease. Each operation is designed to resect the involved nerve *en-bloc*, with the extent of surgery determined by the zonal extent on MR neurography (Figs. 9.2 and 9.3). The aim of surgery is to prevent the central progression of disease (with a clear margin if safe and technically feasible), while maintaining form and function [38]. Patients need to be aware of the sometimes disfiguring nature of surgery, and the need for reconstruction. The surgical approach of our group, based on nerve and zonal extent, is detailed in Table 9.3 [64].

Surgery does not play a role in removing the entire peripheral spread of the disease, from which skin involvement can be diffuse. As nerves travel proximally toward the brainstem, branches should be assessed for involvement with biopsy and frozen section or removed *en-bloc*. One must be cognizant of not disturbing anatomical barriers that can result in iatrogenic tumour spread and decreased survival, such as subarachnoid or dural tears, which can lead to cerebrospinal fluid dissemination. Therefore, bulky disease into zone 3 is generally managed with definitive radiotherapy, yet subtotal resection may be offered on a case-by-case basis, being mindful of precise imaging extent and patient factors (age, general health and patient wishes).

Trigeminal nerve disease into zone 2 typically requires a craniotomy for disease clearance. Tumour invading the supraorbital nerve extending approximately 1 cm beyond the supraorbital notch usually warrants orbital exenteration, and this can provide access to the ganglion via a transorbital approach for zone 2 disease. Alternatively, a pterional craniotomy can be used to access the ganglion. A functioning orbit is difficult to preserve after postoperative radiotherapy and associated morbidity. A neck dissection is undertaken only for the following reasons: (i) if AJCC≥N1 nodal disease is present on imaging/clinical assessment; or (ii) if access to the neck vessels is required to enable reconstruction.

Radiotherapy plays a key role in the management of PNS; yet there are no standardized treatment recommendations and the approach is largely case-dependent. Using intensity-modulated radiation therapy (IMRT) to minimize morbidity, radiation fields generally cover the following: (i) primary tumour (if present) and the

Table 9.3 Surgical approach based on the nerve involved and zonal extent of PNS on imaging [63]

Nerve involved	Zone 1	Zone 2	Zone 3
V1	To supraorbital ridge: resect nerve Approximately 1 cm beyond ridge: orbital exenteration ± superior orbital fissure	Include gasserian ganglion via a lateral craniotomy or transorbital approach	XRT alone Consider subtotal resection
V2	Infraorbital nerve resection + PPF contents + maxillary division via trans-facial (endoscopic or sublabial)	Include gasserian ganglion via trans-facial or lateral craniotomy approach	XRT alone Consider subtotal resection
V3	Ascending mandibulectomy + ITF contents preserving parotid, VII and masseter muscle	Include gasserian ganglion via a lateral craniotomy	XRT alone Consider subtotal resection
VII	Radical parotidectomy + mastoid segment of VII	Include geniculate ganglion via lateral temporal bone resection	XRT alone Consider surgery: geniculate ganglion + surrounding dura + contents of IAM
VII + V3	Radical parotidectomy + ascending mandibulectomy + ITF contents	Include gasserian and geniculate ganglia via lateral craniotomy and lateral temporal bone resection	XRT alone Consider subtotal resection

PPF pterygopalatine fossa, *XRT* definitive radiotherapy, *ITF* infratemporal fossa, *IAM* internal auditory meatus

peripheral branches of the involved nerve(s); and (ii) the proximal course of the involved nerve(s) back to the ganglion for zone 1, to the prepontine aspect of the nerve for zone 2, and up to the brainstem for zone 3. Delayed contralateral spread of perineural disease has been reported ($n=6$), and consideration should be given to limited field coverage across the facial midline to the contralateral mid-face, particularly given the relative safety profile of IMRT [65, 66]. A standardized approach to the radiotherapy management of the regional lymph nodes in PNI patients is lacking, yet many centres still advocate elective nodal irradiation because of the risk of subclinical nodal disease with PNI and documented regional failure rates of 6–11 % [3, 4, 39]. However, quality controlled trials are lacking.

Treatment outcome data should be interpreted with caution because of inherent limitations in earlier studies, which include the following: (i) varying definitions as to what constitutes PNI; [7, 8, 67] (ii) varying definitions of clinical and incidental PNI, and therefore potential pooling of subgroups; [3, 50] (iii) pooling of BCC and SCC patients; [19, 57, 60] and (iv) varying treatment approaches. Large-scale controlled trials that assess clearly defined patient subgroups are inherently lacking. However, studies in patients treated with surgery and/or radiotherapy consistently show worse 5-year local control rates for clinical PNI (25–48 %) compared to

incidental PNI (78–92 %) [3, 4, 19, 22, 39]. Local control is a significant issue, and the common mode of recurrence [5, 39, 48]. In addition, 5-year disease-specific survival (DSS) is reduced in clinical PNI (54–61 %), compared to incidental PNI (73–90 %) [3, 22, 39].

Our institution reported on the outcomes of 21 consecutive patients with clinical PNI from cSCC after treatment with surgery and postoperative radiotherapy, and showed a 5-year DSS rate of 64.3 % and local control rate of 64 % [38]. An updated series of 50 consecutive patients shows an improved DSS rate of 74 % at 5 years [49].

Follow-Up

It is recommended that patients be closely monitored for 2 years, reducing visits in frequency until 5 years post-treatment. This is based on the observation that the majority of recurrences occur within the first 2 years post-treatment [3, 4, 38, 49]. At our institution, patients also undergo MR neurography at regular intervals for surveillance of early recurrence.

Summary

NMSC with PNI is an aggressive disease that significantly reduces patient outcomes, particularly once disease has spread along cranial nerves and elicited clinical features. The disease is frequently misinterpreted, with significant delays in potentially curable patients. Diagnosis is aided by MR neurography, and the zonal extent guides surgical resection and planning for radiotherapy. Universally accepted management guidelines for NMSC with PNI or PNS are lacking. Surgical resection requires a clear understanding of the natural history of the disease. With increased awareness and management within specialized centres, patient outcomes can be improved significantly.

Key Points

- Perineural invasion and perineural spread should be recognized as distinct prognostic features of a disease process.
- Perineural spread is often misdiagnosed and treatment delays can have poor consequences for patient outcomes.
- Patients with perineural spread may present without an obvious primary cutaneous lesion, or with no evidence of perineural invasion in the primary itself.
- In patients with perineural spread, the rate of nodal metastasis at presentation is low (~10 %).
- 3-T magnetic resonance (MR) neurography is the gold standard for the imaging assessment of perineural spread, and the zonal extent of disease is

useful for staging and treatment planning. MR neurography-negative perineural spread is rare.
- Skip lesions almost certainly do not exist and are the result of technical processing artifact.
- *En-bloc* surgical resection of disease with a clear margin and postoperative radiotherapy offers improved survival outcomes.

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Squamous Cell Carcinoma Extending to the Temporal Bone

10

Shane Anderson, Parag Patel, and Benedict Panizza

Introduction

Squamous cell carcinoma (SCC) of the temporal bone is an aggressive malignancy. It presents as a primary tumour of the temporal bone arising in the middle ear or external auditory canal (EAC). Secondary invasion of the temporal bone occurs because of direct spread from a primary lesion of the pinna and its surrounds, or from cutaneous SCC (cSCC) metastasis to the first echelon lymph node bed. In Australia, SCC of the temporal bone typically presents from direct invasion from a cutaneous primary, or from metastatic spread from a cutaneous primary to the parotid lymph nodes abutting the temporal bone [1].

The rarity of disease, variety of histological subtypes, location of the primary, lack of a universally accepted staging, and surgical nomenclature make evidence-based management problematic. Most reports include primary and secondary invasive malignancy in the same cohort [1]. Hence, treatment is driven by consensus and observational studies.

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The aggressive nature of this disease mandates aggressive surgery with a focus on achieving clear margins. Management requires a motivated patient who accepts the significant morbidity associated with achieving this result.

This chapter discusses the pathology and epidemiology of temporal bone SCC. An overview is given of the special circumstances and controversies in staging; and strategies to achieve clear surgical margins are also outlined.

Pathology and Epidemiology

Primary SCC of the temporal bone is rare (6:1,000,000) [2]. Most primary tumours occur in the EAC with only 5 % occurring in the middle ear [3]. The majority of SCCs involving the temporal bone is secondary, with direct invasion from primary lesions of adjacent structures (Fig. 10.1) or invasion from cutaneous metastatic deposits of the parotid or occipital lymph node beds. In our institution, 90 % of lateral temporal bone resections (LTBR) performed are for the treatment of metastatic cutaneous malignancy [1].

Whereas the risk factors for primary skin cancers are well documented, metastatic spread is relatively uncommon and occurs more frequently in the immunocompromised patient [4]. Primary carcinoma of the temporal bone arises in the setting of chronic inflammation [5]. Histologically, the majority of neoplasms encountered on the pinna are basal cell carcinomas (BCCs). SCC, on the other hand, is found chiefly in the EAC and middle ear. Carcinoma in the middle ear can also have an origin in the salivary gland, but this is rare [6].

Most cSCCs do not metastasize. Therefore, when they do spread to the adjacent lymph node beds of the temporal bone and become invasive, they are an aggressive phenotype [4]. SCC involving the temporal bone spreads rapidly, as the embryological fusion planes that form the temporal bone facilitate spread by the path of least resistance. Primary cutaneous malignancy of the pinna has easy access to the EAC by direct invasion. Typically, metastatic cutaneous carcinoma to the first echelon lymph nodes of the parotid bed will grow and abut the

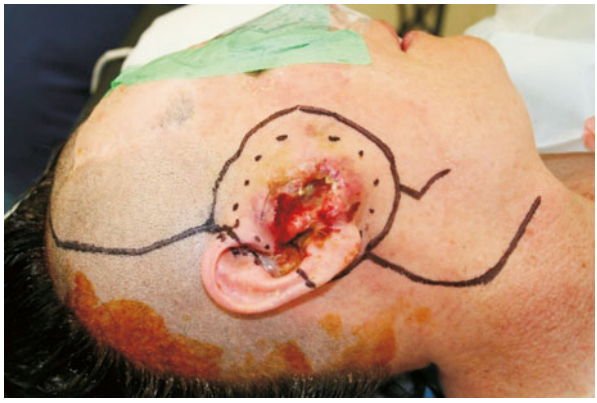

Fig. 10.1 Cutaneous SCC invading the parotid and anterior temporal bone

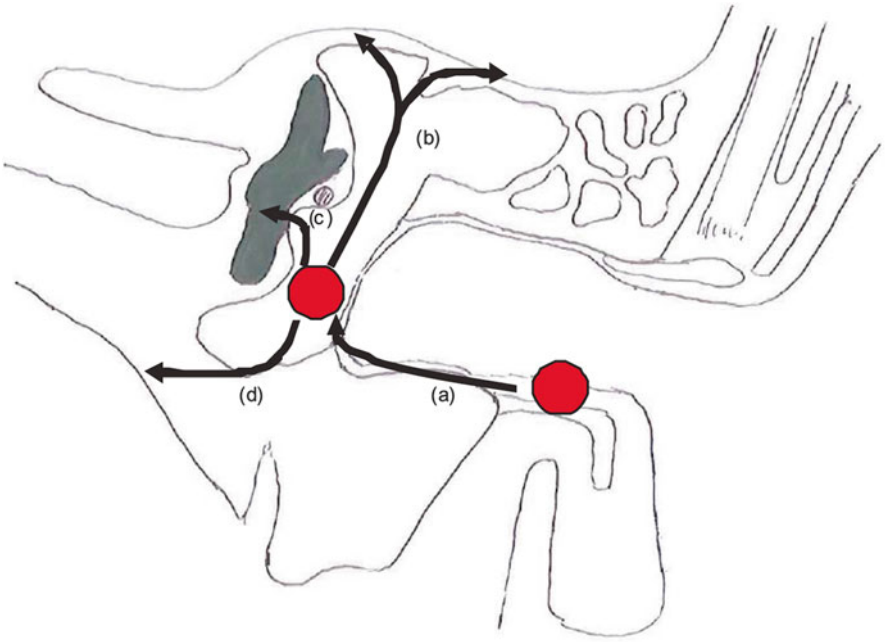

Fig. 10.2 Coronal view of the temporal bone showing tumour spread from (*a*) the cartilaginous EAC to the annulus. Once the annulus is breached, tumour in the middle ear can spread by the path of least resistance, (*b*) superiorly to the tegmen, (*c*) medially through the otic capsule, and (*d*) inferiorly into the hypotympanum

EAC. From here tumour can spread into the ear canal by the fissure of santorini in the tragal cartilage. This same pathway allows anterior spread of primary EAC malignancy to the first echelon lymph node bed in the parotid gland. Within the cartilaginous EAC a tumour can spread posteriorly through the conchae into the post-auricular sulcus. Once the bony EAC is involved, the tumour spreads rapidly under the thin skin of the EAC medially through to the tympanic membrane before entering the middle ear [7]. The skin within the EAC is thin and its proximity to underlying cartilage and bone make complete excision challenging [8]. Regardless of the origin of temporal bone malignancy, once the EAC is involved, the tumours tend to spread in a similar fashion [9].

Within the middle ear, the tumour can spread in multiple directions, depending on aeration of the middle ear and path of least resistance. Anteriorly, the tumour spreads through the mesotympanum into the carotid canal and eustachian tube. Once the carotid canal is involved, spread can proceed superiorly into Meckel's cave and the cavernous sinus. Medially, weak points in the otic capsule at the round and oval windows allow spread into the vestibule, cochlea, internal acoustic meatus and posterior cranial fossa. Inferior spread allows invasion to the jugular foramen and lower cranial nerves. Superior spread can cause tegmen erosion and dural/temporal lobe involvement (Figs. 10.2 and 10.3).

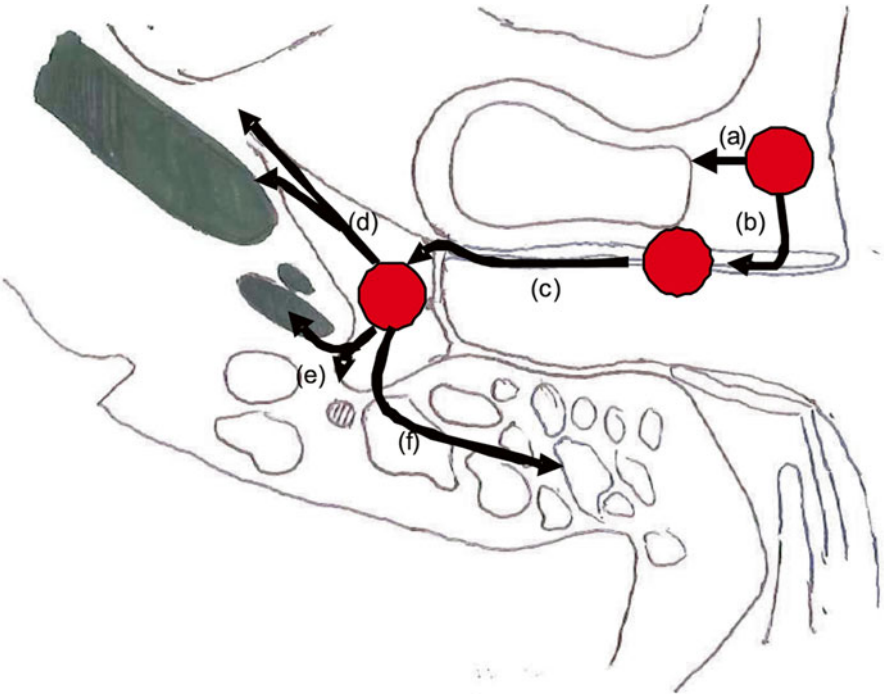

Fig. 10.3 Axial view of the temporal bone showing tumour spread (*a*) directly from the parotid bed into the temporo-mandibular joint, (*b*) from the parotid bed through the fissure of santorini into the external auditory canal (EAC), (*c*) the cartilaginous EAC to the annulus. Once the annulus is breached, tumour in the middle ear can spread by the path of least resistance, (*d*) anteriorly to the eustachian tube and internal carotid artery, (*e*) medially through the otic capsule and facial nerve, and (*f*) posteriorly to the mastoid cavity

The facial nerve can be involved by several mechanisms. Direct invasion in the mesotympanic portion of the facial nerve or, in advanced disease, direct invasion of the mastoid segment can occur. More commonly, the facial nerve is involved by metastatic deposits in the extra-tympanic portion of the facial nerve. This occurs because of large nerve perineural spread or direct invasion at the stylomastoid foramen [7].

Clinical Presentation

Primary pinna lesions often present after attempts at local excision result in a positive margin. Typically, in this scenario the degree of spread is underestimated and extends medially along tissue planes underneath the approximated skin. Metastatic cSCC spread to the temporal bone is usually obvious, with a history of progressive swelling in the adjacent lymph node beds prior to otological symptoms. The rarity of primary temporal bone carcinoma results in complacency; in the early stages it

Table 10.1 Signs and symptoms that often predict the path of invasion in temporal bone malignancy

Path of invasion	Signs and symptoms
Middle ear and eustachian tube	Conductive hearing loss, otalgia, taste disturbance
Otic capsule	Sensorineural hearing loss, facial nerve palsy, vertigo
Carotid canal	Horner syndrome, syncopal episodes
Temporomandibular joint	Trismus, malocclusion
Jugular foramen	Lower cranial nerve palsies
Intracranial	Seizure, cognitive deficits, meningitis/encephalitis
Infratemporal fossa	Mandibular nerve (V3) paresis

tends to be misdiagnosed as symptoms of otalgia and otorrhoea are non-specific [2]. Deep unrelenting pain that does not improve rapidly with standard treatment should prompt a biopsy [7]. As the tumour advances, the presentation becomes more obvious, with a facial nerve palsy or noticeable tumour extension.

A thorough clinical examination is paramount, and includes skin survey, cranial nerve examination and comprehensive head and neck examination of the nodal basins. Often, signs and symptoms can predict the path of invasion (Table 10.1). Facial nerve palsy indicates advanced disease. It is important to differentiate facial nerve weakness as a consequence of previous surgical excisions and progressive weakness indicative of perineural invasion. Often the medial EAC and tympanic membrane are not accessible because of the tumour or pain—hence imaging is vital.

Imaging

Arriaga et al. studied the correlation between computed tomography (CT) and surgical findings and concluded that CT helps to define the pathological extent of tumour and bone erosion but is limited in that mucosal inflammation cannot be distinguished from tumour without bone erosion [10]. MRI (magnetic resonance imaging) can be useful to evaluate soft tissue extension and to differentiate the contents of the middle ear [11]. The 3-Tesla (3 T) platform improves resolution and signal to noise ratio when defining cranial nerves and the skull base [12]. In our institution, we routinely perform a high-resolution CT with contrast using both bone and soft tissue windows in conjunction with a 3 T MRI neurogram. This differentiates pathological soft tissue growth from retained mucosal secretions, temporomandibular joint (TMJ) capsule invasion, and perineural spread (PNS) within the facial nerve and auriculotemporal nerve.

Staging

The complexity of anatomical relations within the temporal bone mandates accurate preoperative staging [13]. This imaging is essential for prognostication and staging when developing a surgical plan with other specialties, such as neurosurgery.

Table 10.2 Comparison of the evolution of staging of external auditory canal (EAC) squamous cell carcinoma from the standard American Joint Committee on Cancer (AJCC) cutaneous malignancy staging system with the Pittsburgh staging system

	AJCC	Arriaga et al. [13]	Moody et al. [11]
T1	Tumour <2 cm with <2 high-risk features	Tumour limited to the EAM without bony erosion or evidence of soft-tissue extension	Tumour limited to the EAM without bony erosion or evidence of soft-tissue involvement
T2	Tumour >2 cm in greatest dimension or tumour of any size, with ≥2 high-risk features	Limited EAM bone erosion (not full thickness) or radiographic finding consistent with limited (<5 mm) soft-tissue involvement	Tumour limited to the EAC with bone erosion (not full thickness) or limited soft-tissue involvement (<5 mm)
T3	Tumour with invasion of maxilla, orbit or temporal bone	Full thickness erosion of the EAM bone, tumour involving the middle ear or mastoid—facial nerve palsy	Tumour eroding the osseous EAC with limited soft-tissue involvement (<5 mm) or tumour in the middle ear or mastoid
T4	Tumour invasion of skeleton or perineural invasion of the skull base	Tumour eroding cochlea, petrous apex, medial wall of middle ear, carotid canal, jugular foramen or dura, with 5 mm soft-tissue involvement	Tumour eroding cochlea, petrous apex, medial wall of middle ear, carotid canal, jugular foramen, dura, with >5 mm soft-tissue involvement, or evidence of facial paresis

EAM external auditory meatus, *EAC* external auditory canal

Staging of invasive cSCC of the temporal bone with the American Joint Committee on Cancer (AJCC) guideline for cutaneous malignancy is problematic, as even early SCC of the EAC which has easy access to bone, is given a T4 status [8]. These tumours are allocated the same status as deep parotid tumours with facial nerve palsy that is clearly not representative of the extent of tumour spread.

Arriaga et al. developed a comprehensive system to stage tumours of the EAC on the basis of CT and pathological findings [13]. Moody et al. argue that by definition, facial nerve paralysis, when the middle ear is involved, reflects extension through the annulus and into bone of the medial wall of the middle ear [11]. If paralysis occurs on account of extra-temporal invasion, >5 mm of soft tissue is likely to be involved; thus they recommended upstaging facial paralysis to T4 (Table 10.2) [11]. The Pittsburgh tumour staging system for EAC SCC is gaining support in the literature and has been validated by other studies [8].

The N and M status of the Pittsburgh staging system is based on the original AJCC classification [14]. The staging system places considerable importance on metastasis as a T2 lesion, with any cervical metastasis considered to be stage IV disease.

Prognosis

Poor prognostic indicators are debated in the literature and reflect the variability in presentations and management. Although still debated, the following features are suggestive of a poor outcome: (i) bone invasion [15, 16], (ii) extension to middle ear [15, 17],

(iii) facial paralysis [9], (iv) dural involvement [5], (v) PNS [8], (vi) early (T1–T2) versus late (T3–T4) presentation [1], and (vii) regional lymphadenopathy [18].

Whereas these features might be debatable, the fact that recurrence after initial management offers a dismal outcome is undisputed [18], as is the fact that achieving clear margins significantly improves survival [1, 10, 19]. Often, recurrence occurs quickly and aggressively, prompting many investigators to believe that a disease-free survival of 2 years can be considered a cure [18]. Arriaga et al. quote a 75 % disease-specific survival (DSS) in patients with negative margins compared with a 25 % DSS in patients with positive margins [13]. This is corroborated by Prasad and Janecka who report that in locations where clear margins cannot be achieved, such as the petrous apex, ICA, dura and brain, survival is poor [5]. In the senior author's experience (BP), DSS was 79 % and 62 % for 2 and 5 years, respectively, with T1–2 tumours having a 100 % 5-year survival [1].

Management (History and Surgical Rationale)

Management requires close collaboration in the setting of a head and neck multidisciplinary team (HNMDT) meeting. Importantly, the meeting must have a skill mix that allows for accurate radiological staging so that an appropriate surgical plan can be established. Resection should aim to achieve clear margins, if possible. The ablative surgeon should plan to achieve this either with primary surgery to the temporal bone or in association with ancillary manoeuvres, such as parotidectomy, TMJ resection, infratemporal fossa resection, access to the middle cranial fossa, and neck dissection to gain clearance. Like others in the field, our team considers involvement of the internal carotid artery, cavernous sinus and jugular bulb incurable, and hence would offer debulking surgery or palliative radiotherapy [19]. Reconstruction is required after ablation. In our institution, this is usually achieved with a vascularized free flap. Finally, detailed specimen labelling and description is required so that a specialized head and neck pathologist can give an accurate report of the relevant margins and be aware of the air–tumour interface in the mastoid cavity for postoperative treatment by radiation and medical oncologists.

Oncologically sound surgery mandates resection with clear surgical margins [20]. Incomplete excision, in an effort to preserve cosmesis and function, places the patient at risk of local recurrence, metastasis [21], and a poor prognosis [18, 22]. The aggressive nature of this disease mandates a surgical plan that can result in morbidity. Before undertaking surgery, patient comorbidities must be taken into account by the HNMDT, who should make a decision with a motivated patient only after a frank discussion on the risks and benefits of surgery. Surgical management to address the temporal bone component of disease does not vary for primary or secondary disease [9]. Our group does not advocate the use of sleeve resection in SCC of the EAC. Less aggressive procedures, such as local canal resection, make clear margins difficult to achieve, with 54 % of tumours treated this way showing positive margins in one cohort [23] In this study, recurrence rates of 46 % for T1 and T2 tumours were reported [23].

Confusion has occurred because descriptions for temporal bone resection vary [11]. Traditionally, these malignancies were addressed with a radical mastoidectomy and ablation of the EAC. Parsons and Lewis proposed an *en-bloc* subtotal temporal bone resection (STBR) as an alternative to a radical mastoidectomy, with resection of the medial surface of the mesotympanum, leaving only the air cells of the petrous apex and internal carotid artery [24]. The total temporal bone resection (TTBR) is an extension of this with incorporation of the petrous apex and sacrifice of the internal carotid artery. To preserve facial nerve function, Conley and Novack described the lateral temporal bone resection (LTBR) [25]. In 1997, Hirsch and Chang rationalized the nomenclature for temporal bone resection with LTBR, STBR, TTBR [7].

Surgical Philosophy

To achieve a reasonable outcome, the intent of surgery must be to resect with clear margins. The temporal bone resection allows for clear medial margins in the properly selected patient. To achieve a clear peripheral margin requires the use of ancillary manoeuvres. At a minimum, Leong et al. advocate a superficial parotidectomy in conjunction with a LTBR to ensure resection of SCCs that involve the EAC [22]. The rationale for this is that often invasion through the fissure of santorini is not detected on radiology. The operation is extended to a radical parotidectomy if evidence exists of facial nerve involvement, or if there is obvious tumour medial to the facial nerve, as in this scenario facial nerve involvement is inevitable. Our group does not advocate a prophylactic comprehensive neck dissection, as only 7.5–15 % of patients will have occult cervical lymphadenopathy at the time of presentation [6, 26, 27]. Often, a limited level 1B-III neck dissection is performed to facilitate vascular access for free-flap reconstruction. Further spread medially is often limited by the tough capsule of the TMJ. This can be resected as a medial margin with a parotidectomy. If involvement of the TMJ or mandible is evident on preoperative staging, then this is sacrificed to gain clear margins (Figs. 10.4 and 10.5). In the experience of the senior author, the incorporation of the TMJ or mandible *en bloc* with the temporal bone resection was required in 30 % of the advanced cases seen in our institution [1].

A significant factor in the evolution of skull base surgery has been the use of radiology to improve surgical planning. Specifically, in lateral skull base surgery a 3 T MRI neurogram allows for proper surgical planning to address PNS and soft-tissue extension. In obvious facial nerve PNS to the stylomastoid foramen, the facial nerve is sacrificed to the second genu and frozen section assessment is carried out to determine clearance. If PNS exists, then further resection with a STBR is required and more frozen sections are taken to achieve at least a 5 mm clearance margin. Surgery for perineural spread beyond the geniculate ganglion is controversial. However, as the tumour is often confined within the perineurium [28] and the nerve is surrounded by the cerebrospinal fluid, the senior author will resect the facial nerve back to the brainstem to achieve a clear margin. Perineural spread along the

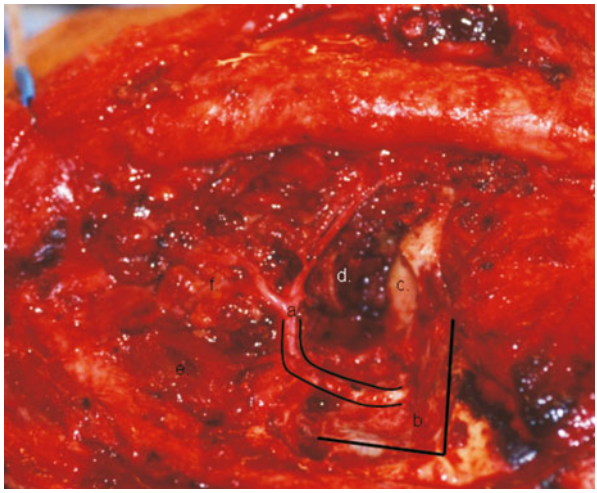

Fig. 10.4 Clinical photo after lateral temporal bone resection with extended resection to include the temporo-mandibular joint demonstrating (*a*) intact facial nerve from second genu to periphery, (*b*) sino-dural angle, (*c*) glenoid fossa, (*d*) cut end of the neck of mandible, (*e*) posterior belly of digastric with removal of mastoid tip, and (*f*) remaining deep lobe of parotid

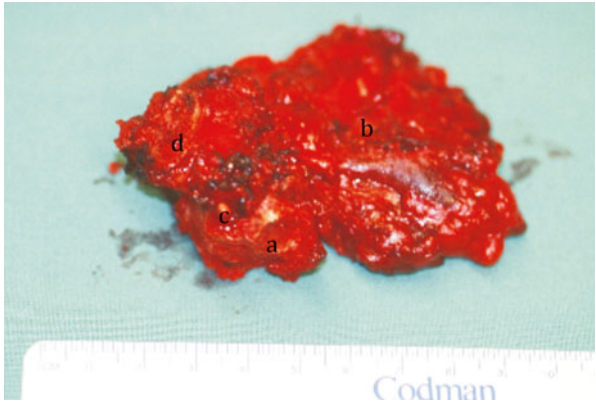

Fig. 10.5 Clinical photo of *en-bloc* specimen demonstrating (*a*) lateral temporal bone, (*b*) conservative parotid, (*c*) head of malleus, and (*d*) neck of mandible

auriculotemporal branch of the mandibular nerve requires clearance of the infratemporal fossa. This is achieved by resecting the TMJ, ascending mandible and pterygoid muscles. Again, frozen section control of the mandibular nerve at the foramen ovale is performed. The philosophy of preserving the facial nerve, if it is fully functioning, is well documented in parotid malignancy [29]. Whereas every effort is made to preserve the facial nerve if it is functioning, this is not done at the expense of involved margins, in temporal bone resection.

Using this philosophy, the senior author has achieved a 2-year overall survival rate of 79 % for all stages of disease. This compares favourably to other cohorts in which large tumours of the parotid (>6 cm or involving skull base) treated with a radical parotidectomy have achieved survival rates for 2 years of only 37 % [30]. Although these cohorts are small it shows the importance of aggressive surgery for this disease.

Lateral Temporal Bone Resection (LTBR)

The surgical goal of a LTBR is to completely excise the EAC with its bony margins. The medial boundary of resection is the tympanic membrane which is excised with the specimen, leaving the intact facial nerve.

Soft-tissue incisions are dictated by the location of the primary lesion but require enough exposure to identify the sigmoid sinus posteriorly and the tegmen superiorly. Once this is achieved a standard mastoidectomy is performed to expose the bony plate over the sigmoid sinus and the middle cranial fossa dura. A posterior tympanotomy is formed and the incudostapedial joint is disarticulated. The posterior tympanotomy is extended inferiorly into the hypotympanum, sacrificing the chorda tympani with sharp dissection; this is extended into the hypotympanum and extended anteriorly into the TMJ. The mastoidectomy is extended into the epitympanum to the root of the zygoma to reach the superior TMJ. The specimen can be rolled forward with digital pressure on the remaining EAC bone. Sometimes an osteotome passed though the posterior tympanotomy is required to liberate the tympanic plate [26]. This manoeuvre can also be used to gain access if the posterior tympanotomy is narrow (for a detailed description of this procedure, *see* Ref. [26]).

Subtotal Temporal Bone Resection (STBR) and Total Temporal Bone Resection (TTBR)

The STBR describes resection of the medial surface of the mesotympanum, leaving only the air cells of the petrous apex and internal carotid artery. Before proceeding, it is important to inspect both the middle and posterior cranial fossa dura for invasion before committing to a large resection. Invasion through the dura results in meningeal carcinomatosis and is irresectable.

Again, soft-tissue exposure is dictated by the location of the primary lesion but needs to be sufficient for access to the middle and posterior cranial fossa. A middle and posterior temporal craniotomy is performed, extending to the root of the zygoma. The middle cranial fossa is dissected from the petrous bone to ensure that the dura is not involved. Posteriorly the dissection is extended to identify the sigmoid sinus and jugular bulb before exposing the pre- and post-sigmoid dura. It is at this point a decision is made to proceed, if the dura is not breached. Once this decision is made, venous control is gained by incising the sigmoid sinus with packing proximally and opening the jugular bulb and packing the inferior petrosal sinus to gain inflow control. A preoperative MRI venogram is performed to assess the torcula for patency. If the contralateral flow is inadequate, sacrificing the jugular bulb may lead to venous infarction. To free the temporal bone, a diamond drill is used to make a cut along the superomedial aspect of the jugular bulb into the hypotympanum and up to the posterior wall of the carotid canal. Next, the middle cranial fossa is dissected free to the foramen ovale. The middle meningeal artery is coagulated at the foramen spinosum and the dissection is continued to the connective tissue of the

posterolateral margin of the foramen lacerum. The roof and lateral wall of the internal carotid canal are removed using a diamond drill all the way to the cochlea. A diamond drill is then used to create an osteotomy via the middle cranial fossa from the petrous bone just lateral to the porus acousticus anteriorly to the carotid canal and inferiorly to the jugular foramen. Finally, a cut is made from the root of the zygoma, across the floor of the middle cranial fossa immediately behind the foramen ovale to the carotid canal. The specimen is then freed by pushing anteroinferiorly and using sharp dissection to free any soft-tissue attachments, including the nerves of the internal acoustic meatus. Haemostasis is achieved and the dural defect is repaired. This can be completed with primary closure or the use of a fascial graft, such as tensor fascia lata followed by free-flap reconstruction (for a detailed description, *see* Ref. [26]).

The morbidity of a STBR is limited to facial nerve palsy, loss of hearing and balance, which most patients can compensate. However, a TTBR involves extending the dissection to include the petrous apex with resection of the internal carotid artery. The potential damage to the cavernous sinus, internal carotid artery and postoperative cranial nerve 3–6 palsy makes this procedure extremely morbid. The consensus is that TTBR is unjustified because of the increased morbidity with no proven survival benefit [20].

Postoperative Radiotherapy

In the experience of our group and that of others, the greatest chance of survival occurs with clear margins and postoperative radiotherapy [1, 8, 20, 29]. In the setting of positive margins, postoperative radiotherapy improves survival [20]. Several groups advocate surgery alone for limited T1 surgical disease [2, 20] and radiation in the event of adverse histological markers only [22].

We advocate adjuvant radiation for stage T2 – 3 cancers. In the setting of T4 temporal bone cancer, the outcomes are dismal, with 5-year DSS varying between 10 and 50 % [11, 20]. In the setting of T4 disease, our group advocates surgery with radiotherapy only if clear margins can be achieved or if debulking will aid in palliation. If clear margins cannot be achieved, several workers advocate radiotherapy alone, giving comparable results to palliative surgery [20, 31].

Conclusion

Typically in Australia, temporal bone carcinoma occurs in the setting of metastatic cSCC to the parotid bed with tumour abutting the EAC. In order to achieve satisfactory cure rates this requires an aggressive surgical resection with a focus on clear margins. The temporal bone resection allows for posterior and medial clearance of the temporal bone. In association with ancillary manoeuvres, such as parotidectomy, TMJ resection, infratemporal fossa resection and neck dissection, temporal bone resection also allows for anterior and inferior control. Our group advocates the use of postoperative radiotherapy to improve survival.

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Reconstructive Options for the Face

11

Ashlin J. Alexander, Sinclair M. Gore, and Jonathan Clark

Introduction

Non-melanoma skin cancer (NMSC) is the most common form of cancer worldwide. In 2008, approximately 430,000 cases of NMSC were diagnosed in Australia; of these, 296,000 were basal cell carcinoma (BCC) and 138,000 were squamous cell carcinoma (SCC) [1, 2]. Whereas many treatment options exist, the mainstay of management is surgical excision with adequate margins, followed by reconstruction. The functional and aesthetic consequences of surgery of the face, more than that of any other part of the body, can be dramatic. Therefore, the reconstructive surgeon must apply a thorough and thoughtful approach to the repair of facial defects. While a full analysis of the topic is outside the scope of this chapter, an overview of the general concepts and techniques used to address the various subunits of the face are discussed.

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Principles of Reconstruction

Since the time of Sushruta in 1500 BC, facial reconstruction techniques have advanced considerably. Yet, the overriding goals have remained the same, i.e. to restore form and function. As one climbs the reconstructive ladder, the choice of reconstructive options is wide. Healing by secondary intention can provide a perfectly satisfactory result for certain concave areas, such as the conchal bowl, and perialar and medial canthal regions. Primary closure, with the incision oriented along a relaxed skin tension line, is especially feasible in elderly patients with skin and soft tissue laxity. Full-thickness skin grafting can provide an aesthetically satisfactory result for superficial defects of the nasal dorsum, or as a temporizing measure while awaiting final pathological assessment of resection margins. Although regional and distant (free flap) options can be considered for larger and more complex defects, local flap reconstruction is the workhorse technique for facial defect repair. Local flaps offer the ability to replace 'like with like' tissue, while maintaining minimal donor site morbidity and ease of harvest. Local flaps are defined as tissue adjacent to the wound, which resurface the wound by means of advancement, rotation or transposition. Numerous composite terms and eponymous flaps have been described, but these three methods of tissue movement are constant.

Preoperative Assessment

Surgical planning begins with a thorough history and physical examination. A prior history of poor wound healing or keloid formation should be elicited, and any old scars should be examined. Co-morbid conditions should be considered that could affect healing, such as diabetes, immunosuppressive medications, or previous radiotherapy to the region. Radiological investigations should be employed, when warranted, to assess local extent of disease and to rule out regional or distant metastases. Finally, the patient's own goals should be reviewed, and expectations should be appropriately managed.

Intraoperative Assessment

The primary factors for consideration in facial reconstruction involve an understanding of facial subunits, and orientation of relaxed skin tension lines (RSTLs). In general, subunits should be reconstructed separately so that the junctions between the different facial subunits are not effaced. For optimal scar camouflage, incision lines ought to be placed within or parallel to RSTLs, and/or within the boundaries between subunits. For defects in the vicinity of the lower eyelid, careful consideration must be given to the risk of postoperative lower lid malposition and ectropion; local flaps should be anchored to the periosteum where feasible, and a Frost stitch or temporary lateral tarsorrhaphy may be employed to resist downward pull on the lower eyelid during the healing period. With a Frost stitch, a 5–0 nylon suture is

passed into and out of the grey line of the lower eyelid to engage the tarsal plate, at the lateral limbus; the needle is then removed and the two loose ends are fixated to the forehead with steristrips such that the eyelids are in apposition. If lower eyelid laxity is already present, additional support could be provided using a canthopexy or lateral tarsal strip technique.

Postoperative Considerations

Wound closure is accomplished in at least two layers, with interrupted deep absorbable sutures, and a non-absorbable cutaneous suture. Timing of cutaneous suture removal is dependent on the tissue characteristics of the wound (patient age, diminished wound healing capacity, tension, previous radiotherapy). In general, skin sutures would be removed 5–7 days postoperatively in non-irradiated patients, and at 10–14 days in irradiated tissue beds. Steristrips may be applied at the time of surgery to further reduce wound tension, and the liberal use of ointment applied to the incision line is recommended for the week following suture removal. Patients are advised to avoid sun exposure for 6–9 months post-surgery to prevent scar hyperpigmentation. In the appropriate patient, dermabrasion or laser resurfacing can be considered to optimize scar camouflage by smoothing and blending wound edges with surrounding skin. Finally, consultation with an experienced aesthetician can help patients apply cosmetic products to further camouflage scars, as needed.

Reconstruction by Subunit

Scalp

Scalp tissue is relatively immobile, limited by the galea aponeurotica, which makes the repair of even small scalp defects challenging. Defects <3 cm can be closed primarily, with the aid of various manoeuvres. These include wide subgaleal undermining, intraoperative tissue stretching, and performing galeotomies. Raposio et al. showed that three full-thickness galeotomies parallel to a sagittal scalp incision produced a 40 % reduction in scalp closing tension and 1.7 mm gain of tissue length, per galeotomy [3].

Intermediate-sized defects are best reconstructed using two or more rotation flaps. Rotation flaps have a curvilinear configuration, which suits the spherical shape of the scalp, and they do not rely on tissue advancement, which is difficult to achieve on account of the scalp's inherent inelasticity. If using a single rotation flap, the arc of the flap should be at least four times the diameter of the defect, and back cuts at the base of the flap may be required [4, 5]. Commonly, the secondary defect might necessitate skin grafting. Standing cutaneous deformities should not be resected at this time to maintain as much flap width as possible. If the deformity has not flattened at 6 weeks, it can be resected in a delayed fashion, as recipient site vascularity will be sufficient to maintain flap viability. Where possible, multiple

rotation flaps are preferred because this recruits tissue from different locations on the scalp, and also shares the burden of secondary defect closure between the flaps. Ideally, two or three rotation flaps are used, thereby producing an O-Z or pinwheel configuration, respectively (Fig. 11.1a–d).

Large (≥6 cm) partial thickness defects can be repaired with a fullthickness skin graft if a vascularized wound base is preserved (pericranium or muscle). The disadvantage of skin grafting is that a contour discrepancy will occur between the native tissue and the grafted region. To overcome this, provided that the patient does not need radiotherapy soon after extirpation, the wound can be left to granulate; the area can then be skin grafted secondarily in order to reduce the contour irregularity. Large fullthickness defects or near-total scalp defects are suited to resurfacing with free tissue transfer. Particularly in the setting of a previously irradiated scalp, these large scalp defects are best reconstructed with a latissimus dorsi muscle-only free flap combined with split-thickness skin graft (STSG) [6]. In this case, the flap is designed to be excessively bulky in the first instance, with the understanding that muscle atrophy will eventually lead to an ideal contour (Figs. 11.1e–h). If the scalp defect includes the full thickness of the cranium, a chimeric free flap, including latissimus dorsi and the bony scapular tip, can be employed [7].

Forehead

The forehead is that region of the face which is bounded superiorly by the frontal hairline, inferiorly by the supraorbital ridge and laterally by the temporal regions. The area can be divided into three zones: midline, paramedian and lateral. The midpupillary line separates the latter two regions. Aesthetically, rhytides are oriented horizontally, except in the glabellar region where they are vertical.

Defects of the central one-third, if closed with a vertically oriented scar (which is perpendicular to the RSTLs), may still produce a cosmetically pleasing result; this is because of the natural attenuation or dehiscence of the frontalis muscle in the midline. Tissue should be elevated in a subgaleal plane and closed primarily, leaving any areas that cannot be closed directly to heal by secondary intention.

In the paramedian and lateral regions, one or more advancement flaps provide the best aesthetic result because the incisions can be placed in a horizontal orientation, parallel to the hairline, eyebrows and forehead creases.

Because forehead tissue is relatively inelastic, bilateral advancement flaps are preferred in order to reduce wound closure tension. These flaps should be elevated in the subcutaneous plane to avoid damage to the supraorbital and supratrochlear nerves. Defects of the upper central forehead can be approached using a large scalp rotation flap, with the incision camouflaged within the frontal hairline (Fig. 11.1i–k). Laterally, care should be taken not to damage the frontal branch of the facial nerve, which lies within the temporoparietal fascia along a line from a point 5 mm below the tragus to a point 15 mm lateral to the lateral eyebrow (the so-called Pitanguy line).

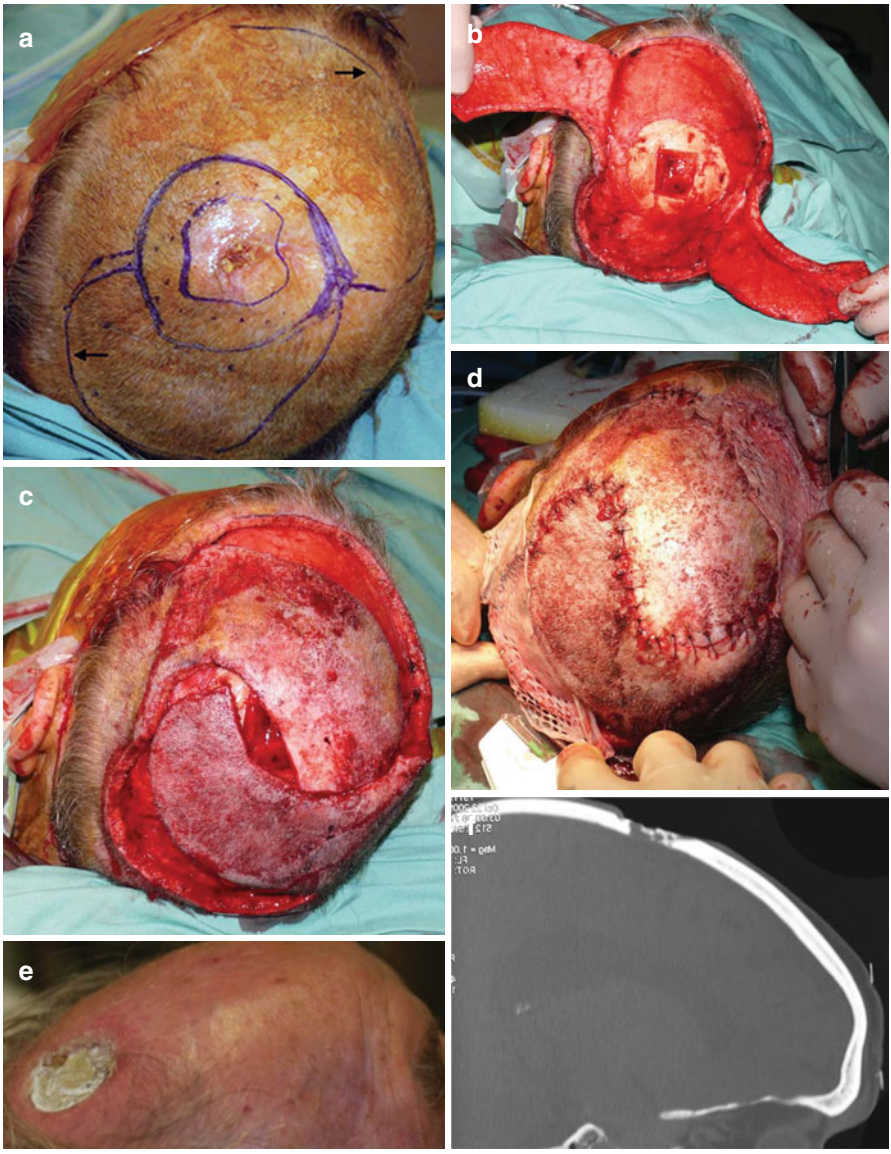

Fig. 11.1 (**a**) Scalp vertex squamous cell carcinoma. *Black arrows* indicate which markings were incised. (**b**) Full-thickness vertex scalp defect involving the outer table of calvarium. Flaps elevated in a subgaleal plane. (**c**) Large O-to-Z flap with clockwise rotation of the individual flaps into the defect. (**d**) Donor site resultant defects covered with split-thickness skin grafts. (**e**) Scalp squamous cell carcinoma involving calvarium, requiring full-thickness soft tissue and bone resection. (**f**) Sagittal computer tomography scan showing calvarial inner table involvement. (**g**) Reconstruction with latissimus dorsi and scapular tip chimeric free flap, splitthickness skin graft on muscle. (**h**) A different patient with a larger scalp defect also reconstructed with latissimus dorsi free flap; approximately 4 months postoperatively. Notice atrophy of the latissimus dorsi muscle to provide excellent scalp contour. (**i**) Upper central forehead basal cell carcinoma. Large scalp rotation flap designed, with resultant standing cutaneous deformity to be excised marked out. (**j**) Note primary limb of flap design is camouflaged in frontal hairline. (**k**) Six months postoperative result

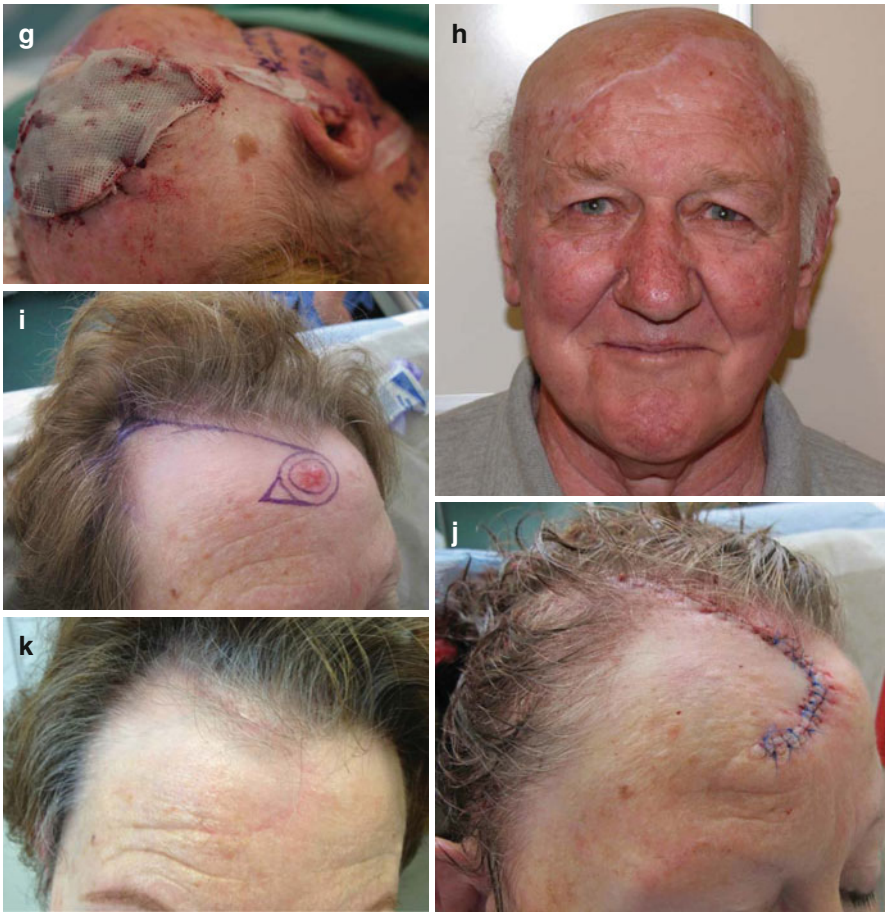

Fig. 11.1 (continued)

Defects involving 25–30 % of the forehead region may be treated using a multistage approach involving initial stabilization of the wound with a skin graft, followed by serial tissue expansion [8, 9]. Alternatively, secondary intention can provide a highly satisfactory result in this setting. Defects >50 % of the forehead surface area may be reconstructed with free tissue transfer. Although adequate contour is feasible, colour match is commonly a problem. Gilbert and colleagues recommend a scapular free flap, or latissimus dorsi free flap with STSG for this defect [6]. The best split skin graft colour match for the face comes from the scalp. Shaving the hair, tumescently infiltrating the scalp with >1000 mm of saline, and harvesting the graft with a dermatome aid this process. Subsequent hair re-growth leaves a non-visible donor site and the risk of alopecia is low.

Cheek

The cheek covers a large area of the face, and is a common site for cutaneous malignancy. The parotid gland overlies the masseter muscle, and the facial nerve emanates from the parotid gland into the cheek, deep to the superficial musculoaponeurotic system.

The medial cheek region typically has an abundance of redundant skin and subcutaneous tissue, which greatly aids in the reconstruction of medial cheek defects. Transposition or advancement flaps provide the best options. Transposition flaps are designed to recruit the redundancy of the jowl region, which can often allow primary closure of the donor site; flaps are usually superiorly based, and incisions are designed such that their closure will lie in the melolabial and labial mandibular creases. A V-Y subcutaneous tissue pedicle island advancement flap provides a good option for defects situated at or below the level of the nasal alae. A triangle-shaped flap is designed to move along an axis parallel to the melolabial crease, with the width equal to that of the defect, and the length equal to twice the height of the defect. A subcutaneous pedicle is dissected to allow flap mobility, and the flap is advanced into the defect in a V-Y fashion.

Lateral cheek tissue adheres more to the underlying fascia, and lacks the elasticity of the medial cheek. Therefore, smaller defects in this region rely on transposition flaps, typically recruited from the skin immediately above the angle of the mandible; this tissue has increased mobility compared to the skin near the temple. Larger defects (>3–4 cm) are better suited to reconstruction using rotation-advancement flaps recruiting cervical skin. These flaps are based medially and inferiorly, and can transfer large amounts of skin from the remaining cheek and upper neck tissue. These cervicofacial rotation flaps can be used to cover defects as large as 10 cm [10].

Defects >10 cm, and full-thickness defects of the cheek, can be reconstructed using free tissue transfer. Many options are available, and the type of tissue needed, colour match and donor site morbidity must be factored into the decision. Through-and-through full-thickness cheek defects require either two skin paddles or a single folded paddle with a central de-epithelialized section. Options with inherent flexibility include the anterolateral thigh, scapular/parascapular or radial forearm free flaps. Cheek contour is critical to the aesthetics of the region; to that end, free tissue transfer can also be employed solely for the purpose of providing volume, followed by coverage with a skin graft or local flap. Free flap options with relatively low donor site morbidity include the groin flap or the anterolateral thigh flap.

For cheek reconstruction, the surgeon must remain mindful of the surrounding important structures. Gravity-induced ectropion can be prevented by suspending flaps to the periosteum with permanent sutures. If the facial nerve is involved with the tumour and requires resection, interposition nerve grafts and/or static sling procedures can be incorporated. Parotid duct resection requires management via ligation or duct repositioning.

Radical Parotidectomy Defect Reconstruction

Australia has among the world's highest rates of parotidectomy for malignancy, secondary to the prevalence of cutaneous SCC with metastatic spread to the parotid. The need for radical parotidectomy, however, remains relatively infrequent. When radical extirpation is required, the resultant defect poses significant morbidity for patients. Reconstruction of the radical parotidectomy defect should aim to achieve complete rehabilitation, i.e. full eye closure, facial symmetry, oral competence, nasal valve support, normal facial contour, appropriate skin colour match, and eventual facial muscle tone. The Sydney Head and Neck Cancer Institute paradigm has been to utilize the anterolateral thigh free flap to achieve many of these goals (Fig. 11.2a–h); a fasciocutaneous flap provides bulk to restore cheek contour and replace skin defects that cannot be otherwise repaired with a cervicofacial rotation flap. Fascia lata is harvested in three strips in order to suspend the oral commissure and nasal ala, and nasolabial crease. The temporalis tendon is released from the

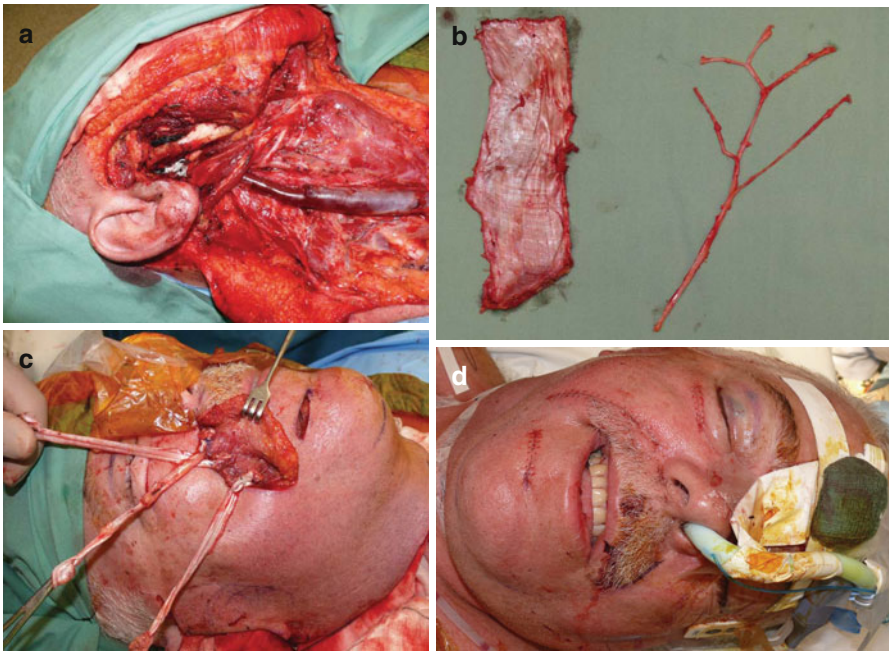

Fig. 11.2 (**a**) Radical parotidectomy defect. (**b**) Strip of fascia lata and motor nerve to vastuslateralis which has been split to provide multiple branches for anastomosis. (**c**) Individual fascia lata strips applied at 3 points of fixation along melolabial fold. Proximal ends of fascia lata strips will be attached to the detached temporalis tendon. (**d**) Immediately postoperatively, exaggeration of the smile is intentionally performed to account for eventual relaxation of the suspension. (**e**) Insertion of upper lid platinum chain. (**f**) Lateral tarsal strip (different patient). (**g**) Re-suspension of the lateral tarsal plate to provide close apposition of the lower lid to globe with minimal laxity. (**h**) Two years postoperatively. Full eye closure, and good facial symmetry at rest. Melolabial fold elevation has relaxed partially, but the patient remains mildly overcorrected

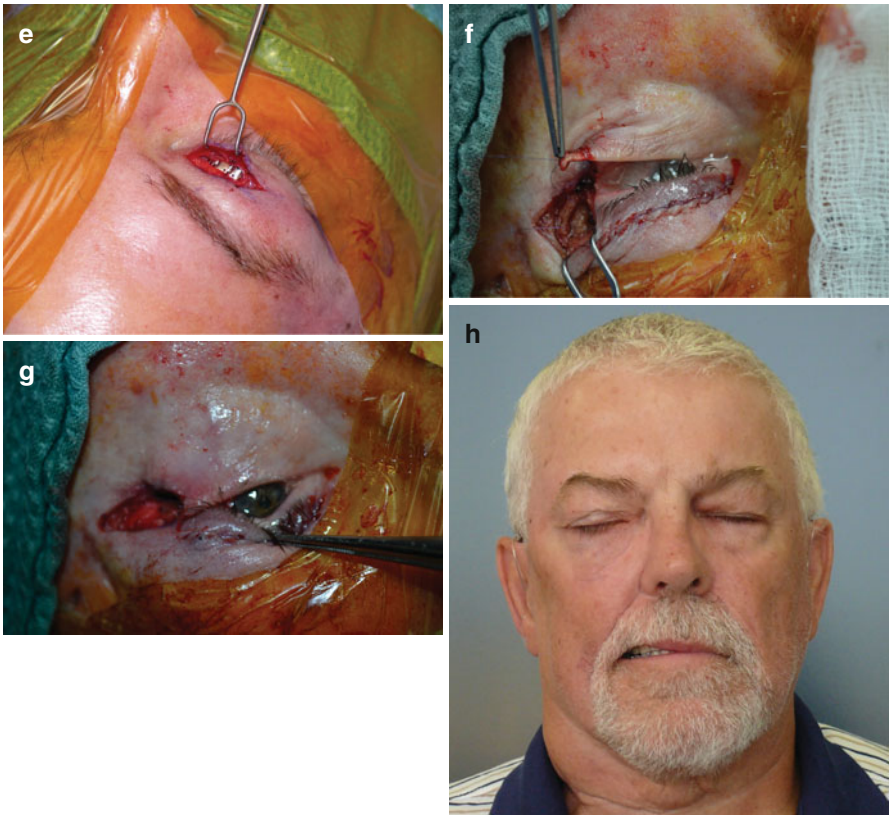

Fig. 11.2 (continued)

coronoid process and is fixated to the fascia lata slings. This provides an element of dynamic reanimation. Alternatively, standard fascia lata static slings can be suspended to the deep temporal fascia. The motor nerve to the vastus lateralis muscle is harvested and used for interposition grafting where appropriate. An anterior belly of digastric muscle transposition allows for lower lip eversion. A gold weight is fixed to the tarsal plate of the upper lid, and the lower lid is stabilized with a lateral tarsal strip technique [11].

Lip

The lips play an important role in speech, deglutition and cosmesis. Structurally, they are composed of the skin of the lip externally, the dry and wet vermilion, the intraoral mucosa internally and the lip musculature between these layers. Key aesthetic landmarks include the vermilion border, the upper lip Cupid bow and philtrum. Several muscles coordinate to produce the complex movements of the lips. As such, reconstruction can be challenging.

Vermilion-only defects can be repaired with a labial mucosal advancement procedure or by using a facial artery musculomucosal flap [12]. Defects up to one-third the length of the lower lip typically can be closed primarily as a V-shaped wedge resection. Primary closure requires closing mucosa, muscle and skin as three separate layers, with precise realignment of the vermilion border. Cutaneous defects of this size can be converted to full-thickness defects to facilitate primary closure. If the wedge resection transgresses the mental crease, a W-plasty modification can be employed. Lower lip defects that are one-third to two-thirds the length of the lip are best managed using either transoral cross-lip flaps (Abbe [13], Estlander) or circumoral advancement-rotation flaps (Karapandzic) (Fig. 11.3a–d). Advantages of the Karapandzic flap include a single-stage procedure, incisions placed in melolabial and mentolabial creases, and preservation of the neurovascular bundles within the mobilized tissue. The main disadvantage is microstomia. Another option for full-thickness lower lip defects greater than one-half the lip length is the Webster modification of the Bernard–Burow cheiloplasty (bilateral cheek advancement flap) [14]. Webster et al.'s modifications placed the Burow's triangles in more aesthetic locations while at the same time preserving more chin tissue. Their design also minimized the tendency for vertical deficiency at the midline of the reconstructed lip (Fig. 11.3e–h) [14].

Total lower lip reconstruction can be achieved with a radial forearm free flap incorporating the palmaris longus tendon to provide a sling from which to suspend the reconstructed lower lip from each modiolus (Fig. 11.3i–n) [15].

Upper lip reconstruction is challenging because of its relatively less elasticity compared with the lower lip, and because of the presence of a number of important aesthetic features. Central upper lip defects can be repaired with an Abbe flap from the midline lower lip [13], which can replicate the philtrum; to that end, Abbe flaps are harvested more commonly from the lower lip than from the upper lip. The flap remains pedicled on the contralateral labial artery; in a second stage a few weeks later, the pedicle is divided and inset is completed. Alternatively, bilateral advancement flaps with perialar-crescentric resections can be utilized. Total upper lip defects can be repaired using bilateral island nasolabial fold flaps [16] (so-called Fujimori gate flaps), or a pedicled or free temporal scalp flap, which is hair-bearing and suitable for men [17].

The Estlander flap is the classic reconstruction for oral commissure defects. Again, this is a lip switch technique involving the rotation of full-thickness lower lip tissue, pedicled on the labial artery, into the commissure/upper lip defect. The main disadvantage is rounding of the commissure, which might necessitate a subsequent commissuroplasty. Alternatively, Robotti and colleagues [18] describe using the elastic flap, first described by Goldstein [19], to reconstruct the commissure by taking advantage of the inherent elasticity of the vermilion and orbicular oris muscle. This is a single-stage reconstruction of the orbicularis ring that keeps scars within the vermilion and oral mucosa.

Eyelids

The eyelids are complex trilaminar structures whose principal function is to protect the cornea. To conceptualize the reconstructive approach, the eyelid can be divided into an anterior lamella (skin, orbicularis oculi muscle) and posterior lamella

(conjunctiva, tarsus, eyelid retractors); the orbital septum can be considered as a middle lamella. The tarsal plates are anchored posteriorly and superolaterally by the lateral canthal tendon, which attaches to Whitnall's tubercle inside the lateral orbital rim. The medial canthal tendon (MCT) supports the medial canthus by enveloping the lacrimal sac and inserting into the maxilla and posterior lacrimal crest. Tears

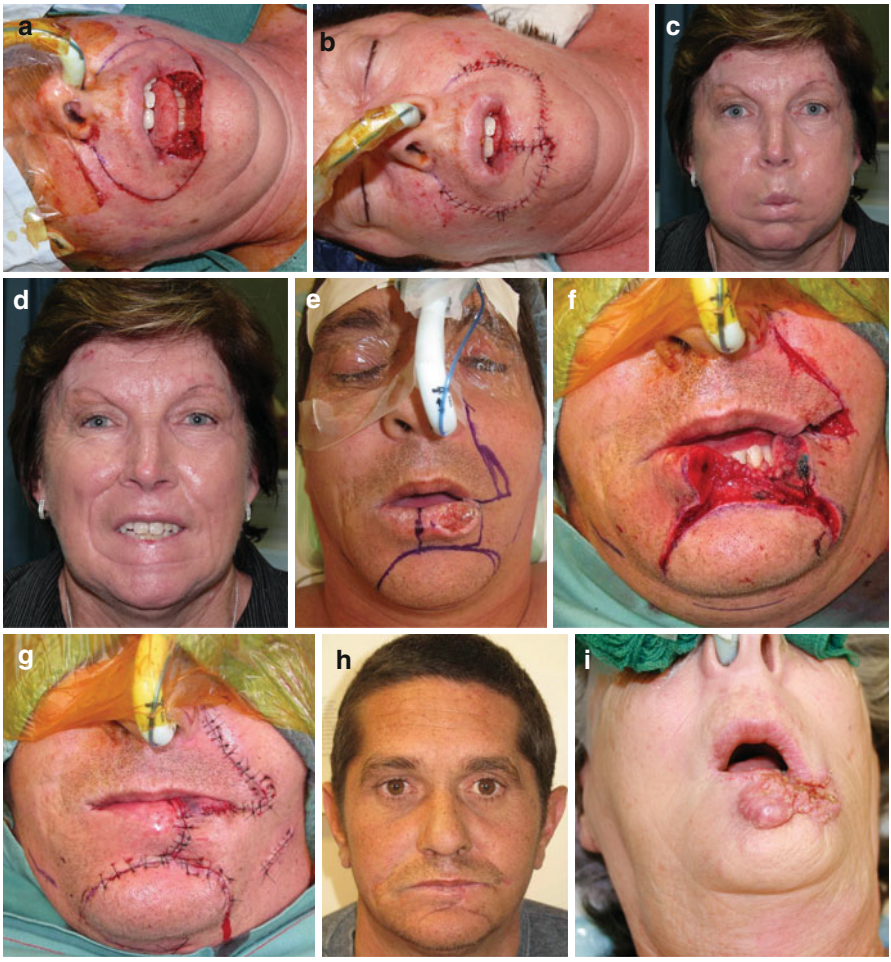

Fig. 11.3 (**a**) Subtotal lower lip defect with incisions for Karapandzic flap. (**b**) Bilateral flaps rotated and sutured into position. (**c**) Six months postoperatively, with good oral competence with whistling. (**d**) Six months postoperatively, smiling view. (**e**) Greater than 50 % lower lip defect with planned incisions for Bernard-Webster flap reconstruction. (**f**) Incisions for Bernard-Webster flap. (**g**) Flap inset. Left neck incision secondary to sentinel node biopsy as part of a clinical trial. (**h**) Six month postoperative result at rest. (**i**) Lower lip squamous cell carcinoma. (**j**) Position of radial forearm free flap with palmaris longus tendon after total lower lip resection. (**k**) Each end of the palmaris longus tendon is anchored to the modiolus using permanent suture to provide a tensioned suspension of the neo-lip. (**l**) Two-year postoperative view at rest. (**m**) Two-year postoperative view on smiling. (**n**) Two-year postoperative view with mouth opening

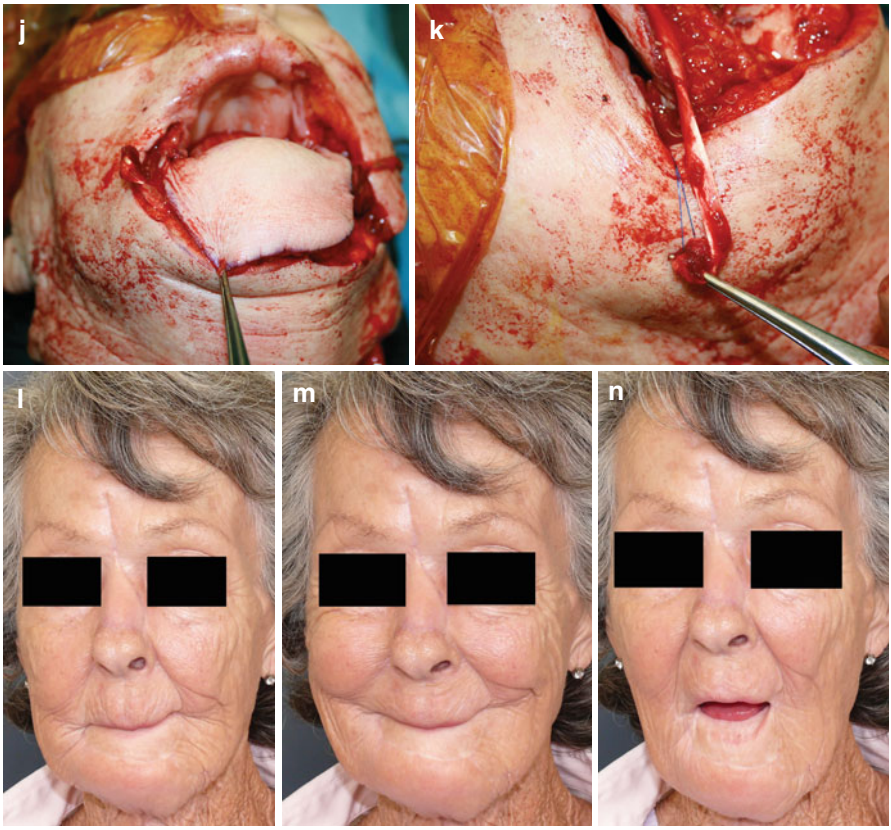

Fig. 11.3 (continued)

drain from the superolateral lacrimal gland to the medially placed puncta of the lacrimaldrainage system. Awareness of the lacrimal drainage system is important for functionally successful medial eyelid reconstruction. The anatomy of the periorbital region is complex and is reviewed comprehensively elsewhere [20].

Eyelid defects should be considered by location, size, orientation and lamellar involvement. For full-thickness defects, both lamellae must be reconstructed. Tables 11.1 and 11.2 provide an algorithm for reconstruction [21]. If direct closure can be achieved, this will usually give the best functional and aesthetic results in a single stage. Wherever possible, vertical closure tension should be converted to horizontally directed tension to avoid cicatricial ectropion. Primary closure is typically best suited for defects of ≥25 % of eyelid length, although it can be applied to ≤50 % defects if sufficient eyelid laxity is present. Conversion to a pentagonal defect, with clean tarsal edges, which are perpendicular to the lid margin, can aid in primary closure. Meticulous closure of each layer is critical, and begins with reapproximation of the tarsal edges to achieve perfect vertical alignment of the eyelid margin, followed by closure of the posterior lamella, and then vertical mattress sutures in the grey line.

Table 11.1 Full-thickness lower eyelid reconstruction [21]

Size of eyelid margin defect (% of eyelid width)	Reconstruction
<25 %	Direct closure
25–50 %	Direct closure with lateral cantholysis
33–66 %	Semicircular flap
50–75 %	Semicircular flap with periosteal flap
50–100 %	Transconjunctival flap

Table 11.2 Full-thickness upper eyelid reconstruction [21]

Size of eyelid margin defect (% of eyelid width)	Reconstruction
<25 %	Direct closure
25–50 %	Direct closure with lateral cantholysis
33–66 %	Semicircular flap with periosteal flap
50–100 %	Cutler–Beard flap

Subsequently, the orbicularis layer and skin are closed, with careful attention to suture placement in order to avoid irritation of the cornea from the stitches. If wound closure tension is excessive at the start, a lateral cantholysis can be performed.

Anterior lamella-only defects are reconstructed more favourably with local flaps than skin grafts on account of the advantages of better colour match, less contraction with healing, and an improved vascular supply that can support free grafts for posterior lamella reconstruction (in the absence of prior surgeries or irradiation). Rhombic flaps are best suited to periocular cutaneous defects, with the caveat that the vector of maximal tension should be oriented parallel to the lid margin. Another option is the uni- or bi-pedicled transposition flap from the upper eyelid used to reconstitute defects of the lower lid anterior lamella (Tripier flap). Secondary intention healing is suitable for defects of the medial canthus <1 cm in diameter and centred about the MCT; otherwise it should be avoided.

Larger full-thickness defects (approximately one-third to two-thirds) of the central or lateral eyelid can be repaired using the Tenzel semicircular advancement flap [22]. This technique is conceptually similar to a Mustarde flap, but has the added advantage of better dynamic reconstruction. When no lateral tarsus is present, reconstruction is aided with the use of a periosteal flap, or auricular cartilage, hard palate mucosa or nasal septalchondromucosal graft for posterior lamella reconstitution.

Larger full-thickness defects (greater than two-thirds) of the lower eyelid can be repaired with a Hughes tarsoconjunctival flap [23]. This two-stage procedure borrows tissue from the upper eyelid, and provides vascularized autogenous tarsus lined with conjunctiva; the anterior lamella is repaired with a skin graft or local flap. Alternatively, a single-stage operation using a composite nasal septalchondromucosal graft fixated in position, and overlayed with a temporal forehead cutaneous flap pedicled on the superficial temporal artery, can be performed [24].

Full-thickness total upper eyelid reconstruction is best achieved using a Cutler–Beard lid-sharing flap [25]. This skin-muscle-conjunctiva flap is harvested from the lower lid, and subsequently divided 4–6 weeks postoperatively.

In general, potential complications of eyelid reconstruction include infection, flap dehiscence, entropion, ectropion, lagophthalmos, upper eyelid ptosis, and lid margin notching.

Postoperatively it can be expected that significant swelling might be present for some weeks, but a well designed thin, bilaminar, mobile eyelid reconstruction should provide robust corneal protection and good cosmesis in the long term.

Nose

The nose is of central importance in the mid-face and nasal defects have particular impact on facial form and function. Nasal reconstruction is one of the oldest forms of plastic surgery, having been described in the Edwin Smith Papyrus, dating from approximately 3000 BC. As in the eyelid, the nose should be reconstructed by paying attention to individual layers—lining, structure, and cover. Without adequate provision for lining and support, wound contraction and structural collapse will mar the final contour needed for a good functional and aesthetic outcome.

Topographically, the nose is composed of subunits, both convex (tip, columella, alae nasi and dorsum) and concave (sidewalls, soft triangles). Burget and Menick elegantly described the reconstruction of the nose according to subunits, emphasizing the need to use flaps for convexities, place scars between subunits and consider sacrifice of normal tissue to achieve total subunit reconstruction [26].

Nasal lining can be replaced in a number of ways, including intranasal mucosal flaps (local bipedicled flaps, pedicled transposition flaps), skin grafts (including as part of composite grafts from the ear) and skin flaps (local hinge flaps, turnover nasolabial flaps, folded forehead flaps and free flaps) [27]. All these options, however, need to be thin to maintain an adequate nasal airway and, as such, their transfer may need to be refined over a number of surgical stages. Skeletal support may need to be provided; autologous options include the use of conchal ear cartilage (for support of convex alar subunits), nasal septal cartilage, rib cartilage and cranial bone graft. Skin replacement should be the final stage of any such reconstruction—without an adequate foundation the outer layer cannot correct underlying contour problems.

The ideal source of skin for nasal reconstruction comes from the forehead. The paramedian forehead flap based on the supratrochlear vessels is the workhorse in this setting. It may be transferred as a pedicled flap based at the medial brow; the pedicle can be divided some weeks later when the transferred tissue has gained vascularity from the recipient site. Inclusion of frontalis muscle will enhance vascularity of the flap tip; additional stages are usually required to thin the flap adequately, but this extra effort will bring rewards in terms of final contour and healing. Advantages of the forehead donor site include excellent colour match, suitable tissue thickness, reliable blood supply and, if carefully managed, an acceptable donor site scar (Fig. 11.4a–b). Alternative options for nasal skin replacement include interpolated cheek flaps, transposition flaps of nasolabial skin or nasal skin (Fig. 11.4c–e), advancement of cheek or nasal skin [28, 29] (Fig. 11.4f–i), regional flaps from postauricular skin [30], or free flaps from the ear [31]. Many of these

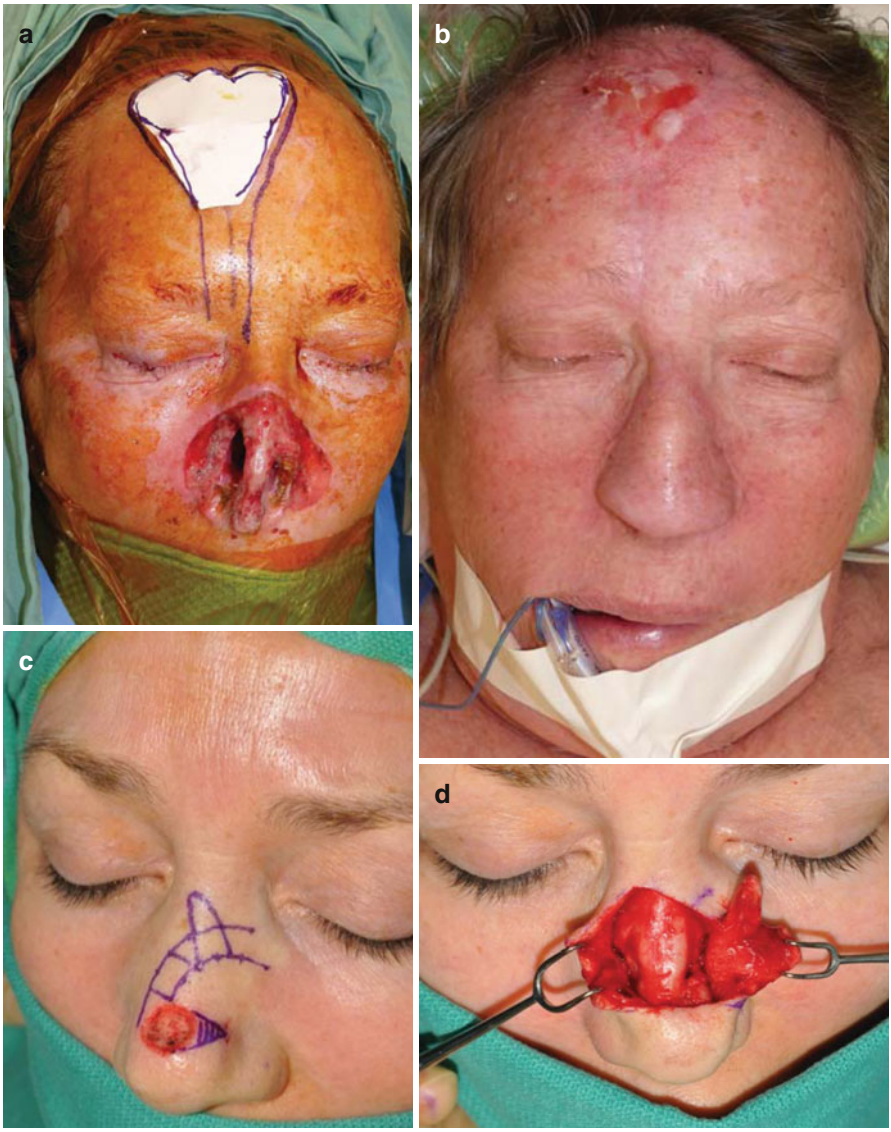

Fig. 11.4 (**a**) Full-thickness defect of lower third of the nose, with planned incisions for paramedian forehead flap. (**b**) Three months following initial reconstruction, following flap pedicle division and two separate contouring procedures. (**c**) Nasal tip defect with planned incisions for bilobe flap reconstruction. (**d**) Flap elevation with wide undermining in the sub-nasal SMAS plane. (**e**) Flap inset and closure. (**f**) Nasal dorsum defect following basal cell carcinoma resection, with planned incisions for nasal dorsum advancement flap (Rieger flap). (**g**) Flap elevation in the sub-nasal SMAS plane. (**h**) Flap inset. (**i**) Six weeks postoperative result

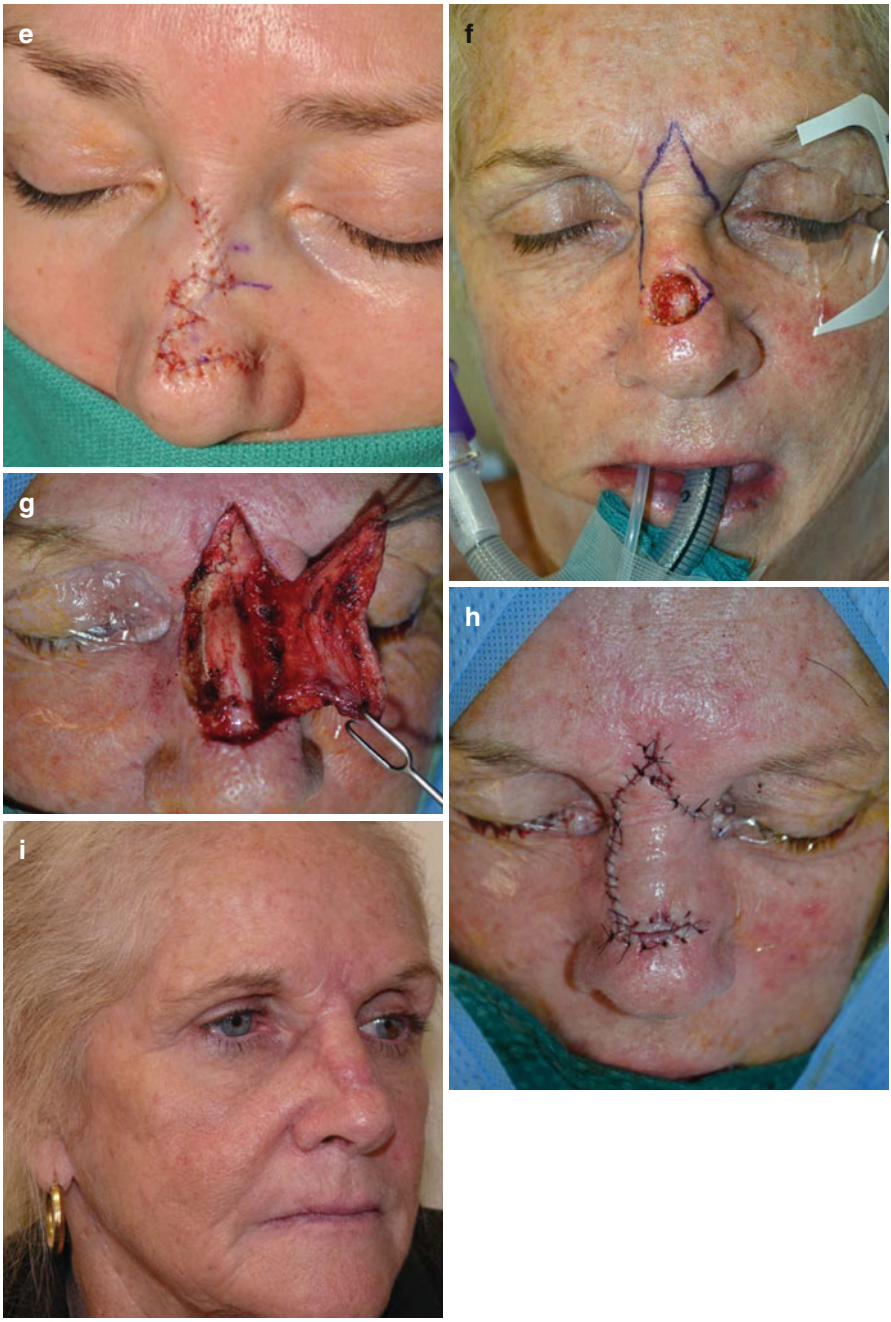

Fig. 11.4 (continued)

options are suitable for small skin defects but none have the inherent versatility of the paramedian forehead flap for larger defects.

As with many reconstructive endeavours, adequate results can be obtained with fewer steps; however, extra stages for flap thinning, contour refinement and scar revision invariably result in better aesthetic outcomes. It is useful when planning such treatment to tailor the refinement to the expectations of the patient and suitability for multiple operations. In some advanced cases, rhinectomy defects may be more appropriately managed with a nasal prosthesis, both from a cosmetic standpoint, and for minimizing the number of trips to the operating theatre.

Ear

Post-resection reconstruction of the pinna has both functional (wearing of spectacles) and aesthetic consequences. Particular zones of the pinna may be reconstructed in different ways using local skin flaps; total and subtotal defects, however, should be reconstructed either by means of prostheses (which may be anchored to osseointegrated implants) or autologous constructs using combinations of rib cartilage, temporoparietal fascia flaps, expanded local mastoid skin, and skin grafts.

Defects of the conchal bowl and helical root have a number of reconstructive options. Wounds in this area left to heal by secondary intention typically produce excellent cosmetic results. Subtotal conchal bowl defects can be repaired with a full-thickness skin graft, which is harvested from the post-auricular region or supraclavicular neck skin. If exposed cartilage is devoid of perichondrium, the cartilage can be resected and the skin graft applied to the medial auricular skin. Large defects involving lateral conchal bowl skin and cartilage can be repaired using a post-auricular subcutaneous tissue pedicle island advancement flap. The main advantage is the avoidance of a skin graft and bolster. The flap is transferred through a slit in the medial auricular skin into the defect, and the post-auricular donor site is closed primarily (Fig. 11.5a–g). If the medial skin of the pinna is also absent, this flap can be bi-valved, or simply skin grafted on its medial surface.

The superior one-third of the auricle can be closed primarily, in the form of a wedge or stellate closure, when the defect is <1.5 cm in width. Cupping of the ear should be avoided with primary closure. If the defect is limited to the helix and measures 1.5–2.5 cm in length, bilateral helical chondrocutaneous advancement flaps (Antia–Buch) can be performed. This technique often requires reduction of the outer margin of the conchal bowl to decrease the circumference required for the advancement flaps to traverse. Defects of >2.5 cm confined to the helical rim should be considered for a pre-auricular or post-auricular interpolated tubed flap. The flap is initially tubed with maintenance of intact superior and inferior attachments, then two subsequent stages to allow inset of the tubed flap into the helical defect.

Large defects of the superior third, involving helix, scapha and triangular fossa, require incorporation of a rigid framework using rib, which is covered by a temporoparietal fascia flap and STSG.

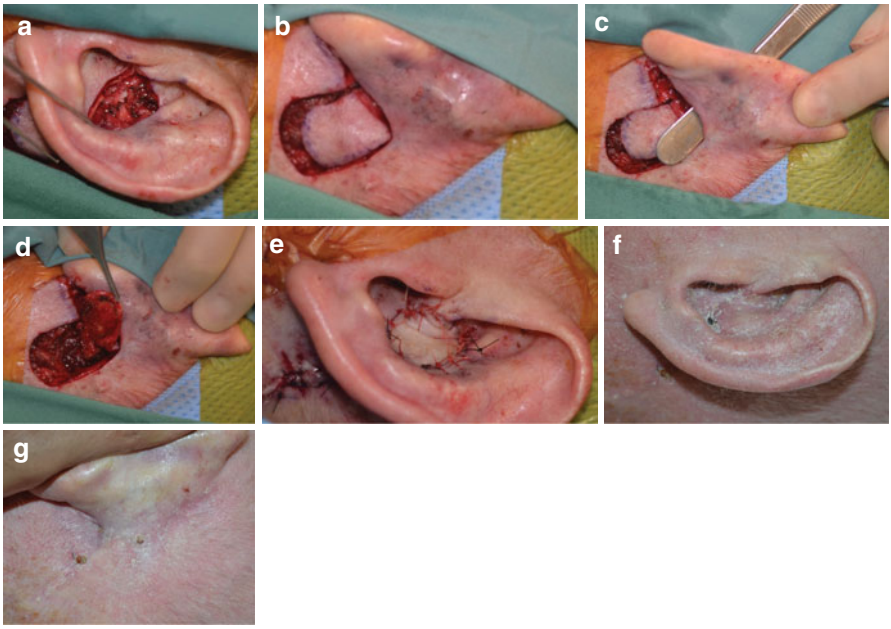

Fig. 11.5 (**a**) Subtotal conchal bowl defect involving cartilage and lateral skin (medial auricular skin preserved). (**b**) Post-auricular pedicled flap incised. (**c**) Through-and-through tunnel. (**d**) Post-auricular flap elevated just above the mastoid periosteal layer and maintained on a subcutaneous deep soft tissue pedicle. (**e**) Inset of flap into conchal bowl defect, primary closure of post-auricular donor site. (**f**) Four weeks postoperative result conchal bowl. (**g**) Post-auricular region

Defects of the middle third of the auricle can again be closed primarily as a wedge excision if <1.5 cm in width. Full-thickness helical defects that are <2.5 cm can be addressed with superior and inferior chondrocutaneous helical advancement flaps. Larger helical defects are again repaired with a tubed skin and subcutaneous tissue flap. Large defects of the helix and antihelix require a multi-staged procedure involving a posteriorly based scalp advancement flap sutured to the lateral edge of the auricular defect, with a piece of septal or conchal cartilage sutured to the defect edges and buried under the flap to provide structural support. Three weeks later, the second stage involves division of the scalp flap and folding of this tissue around the cartilage graft; the skin flap is then sutured to the medial edge of the auricular defect. If the scalp donor site cannot be closed primarily, a full-thickness skin graft is applied.

The inferior third of the auricle is relatively easier to reconstruct, owing to the laxity of skin in the region. Up to 50 % of the lobule can be resected as a wedge and closed primarily with minimal effect on cosmesis. Total earlobe reconstruction requires two stages. In the first, a piece of cartilage shaped like an earlobe is embedded in a subcutaneous pocket created in approximately the position where the new earlobe will be; the leading edge of the pocket is sutured up to the lateral edge of the lobule defect. Six weeks later, the skin and cartilage are elevated as a composite flap based superiorly off the auricle, and the back of this composite flap is skin grafted. The donor site is closed primarily.

Conclusion

Facial reconstruction presents a unique subset of functional and aesthetic challenges. However, with a stepwise analytical approach, careful planning and precise execution, form and function can be restored satisfactorily.

Step-by-Step Approach to Selected Local Flaps

Scalp Rotation Flaps: O-to-Z or Pinwheel Flap

A single rotation scalp flap is designed 4–6 times as long as the width of the defect. Multiple rotation flaps offer the advantage of distributing wound closure tension over a larger area, and recruiting tissue from multiple areas of the scalp where more laxity may be present (occiput, or overlying the temporalis muscle). Centrally located scalp defects can be repaired with two rotation flaps, whereas three rotation flaps can be used to repair central scalp defects situated anteriorly or posteriorly. In this case, all three flaps are designed to rotate in the same direction, as in a pinwheel. Each rotation flaps should be designed symmetrically to its counterpart(s), and should curve to meet the defect border at a 90° angle. Incisions should always parallel hair follicle direction, and cautery should be used judiciously to avoid alopecia. Wide undermining in the subgaleal plane, from ear to ear and from forehead to occiput, typically is required (Fig. 11.1a–d).

Scalp Rotation Flap for Upper Forehead Defects

Forehead defects are often challenging to close primarily because of limited tissue elasticity. Direct closure by advancing tissue in a vertical direction might alter the position of the brows, especially in lower and lateral defects. Direct closure by advancing tissue in a horizontal plane will result in a vertical scar that could be aesthetically unpleasing. This technique recruits tissue from the upper forehead and temple bay by designing a large forehead and scalp rotation flap to enable advancement of tissue vertically downwards into the defect with minimal distortion of the lower forehead and brow.

Steps (Fig. 11.1i–k)
A large rotation flap is designed with the lower aspect of the semicircular flap running vertically upwards from the medial edge of the tissue defect.

This flap incision should run into the interface between the anterior central hairline and the temple bay. The flap margin continues into the scalp curving down behind the ear.

The rotation flap is then raised in a subgaleal plane and horizontal galeotomies in the inferior flap may help advance the upper forehead tissue into the defect. Excess tissue lateral to the defect (a ‘dog-ear’) can be excised at this point. This will elongate the horizontal scar but will produce a better contour.

Closure of the forehead should be achieved in layers with particular attention paid to accurate apposition of forehead layers. Thus, a fine vertical scar can be achieved that can fade well over time.

Using this method some hair-bearing scalp is advanced forward but in a manner that has minimal aesthetic impact on the forehead. The orientation of the anterior hairline is variable and some patients are more suitable for this technique than others.

Karapandzic Flap

The Karapandzic flap is best suited to full-thickness defects involving one-third to two-thirds of the central lower lip; a modified approach can be used for the upper lip. Essentially, it is a circumoral composite rotation advancement lip flap with preservation of the neurovascular supply, which allows maximum functionality to the reconstructed lip.

Steps (Fig. 11.3a–d)
Incision lines are marked parallel to the free margin of the lip, thereby maintaining uniform width. The incision is made along the mental crease and then carried around the oral commissure and into the melolabial crease, typically up to the level of the nasal alae. In order to ensure equal flap width, take the incision lateral to the melolabial fold at the level of the oral commissure. The width of the flap must be at least equal to the height of the defect. For lateral defects, the flaps will be designed to be of unequal lengths.

Incisions are made through skin and subcutaneous tissue, but not through muscle. Separate incisions are made through the intraoral mucosa, but typically do not need to be as long. Scissors are used to gently spread through the muscular layer in a radial direction, thereby allowing the identification and preservation of vessels and nerves. Sufficient dissection is performed to allow the neurovascular bundles to stretch with flap mobilization.

After flap dissection, the two flap edges are first secured together, and the remaining wound closure is then adjusted accordingly. The wound is closed in layers, carefully re-approximating muscles in the correct anatomical orientation.

Bernard–Webster Cheiloplasty

The Webster cheiloplasty is a modification of the Bernard–Burow flap for lower lip reconstruction.

Steps (Fig. 11.3e–h)
Incisions are placed along the junctions of aesthetic subunits; triangles of skin and subcutaneous tissue are resected from the bilateral melolabial folds and the mentolabial folds to allow linear horizontal advancement of cheek skin into the lower lip

defect, as required. Transverse incisions are then made from the base of the melolabial fold Burow's triangle to the oral commissure and along the mental crease. It is preferred to take the flap incisions through skin and subcutaneous tissue only, and make separate oral mucosal incisions; the intraoral incisions can be offset superiorly from the skin incisions to provide extra mucosa for vermilion reconstruction. Blunt spreading through the orbicularis muscle to permit sufficient mobilization is performed.

The advancing edges of the bilateral flaps are re-approximated in layers, followed by the remainder of the incisions. The offset mucosal incisions allow for advancement of this mucosa to create a neo-vermilion. Whereas excessive wound tension is undesirable, a slightly tight flap helps to counterbalance the essentially dynamic nature of the reconstruction.

Abbe Flap from Lower Lip to Upper Lip Defects

This flap comprises a section of full-thickness lower lip that is transposed up into an upper lip defect. Because of relative lower lip laxity and upper lip aesthetics, it is a more common procedure than transferring upper lip to lower lip. As a lip sharing technique, it is performed in a minimum of two stages.

Steps

The flap is outlined with upper incisions perpendicular to the lip margin. The lip is incised through skin, fat, muscle and mucosa except for where the pedicle is preserved. This area includes the vermilion, lower lip mucosa and labial vessels deep to the orbicularis muscle layer.

The flap is hinged at this point and is transferred up into the upper lip. The secondary defect in the lower lip is closed directly, ensuring accurate muscle and skin layer apposition. The uppermost section is not closed at this stage because of the flap remaining attached.

At least 2 weeks later the flap pedicle is divided and inset is completed of both the flap into the upper lip and the lower lip donor site. Nutrition during this intervening period can be achieved by eating soft or pureed foods.

Tenzel Semicircular Flap

The Tenzel flap is well suited for reconstruction of full-thickness defects involving 33–75 % of the horizontal length of the upper eyelid, and 30–66 % of the lower eyelid. The flap is conceptually similar to a Mustarde cheek rotation flap, but offers better dynamic reconstruction with less tissue manipulation. It is best applied in the setting of adequate lateral canthal skin laxity and availability of a small segment of full-thickness eyelid on either side of the defect. If the lateral tarsal plate is absent, a periosteal flap or auricular cartilage graft can be utilized.

Steps

First, the actual defect size is estimated by pulling the edges of the defect together using fine-toothed forceps. If the edges are within 1–2 mm, primary closure with a lateral cantholysis might be adequate.

Starting at the lateral canthus, a semicircular line is drawn arching superiorly with a diameter of ~20 mm, extending to the lateral eyebrow. The mirror image is used for upper eyelid reconstruction.

Next, the defect margins are revised so that they are perpendicular to the lid margin. This is followed by undermining a musculocutaneous flap widely ~10 mm below the orbital rim. Lateral canthotomy and inferior cantholysis is performed subsequently to allow complete mobilization of the lateral lower eyelid soft tissue toward the medial defect margin.

The most critical step of the reconstruction is the re-approximation of the tarsal edges using interrupted absorbable sutures, followed by simple or vertical mattress silk sutures through the grey line to align the wound edges perfectly.

In order to provide adequate lateral eyelid support, lateral canthal fixation can be performed by suturing the deep tissue up onto the lateral orbital rim periosteum. Alternatively, a strip of periosteum, pedicled on the arcus marginalis, hinged high at least at the level of the pupil and angled at 45°, can be flipped down and attached to the deep lateral flap tissue for improved contour and support.

For large defects or those lacking tarsus at the lateral edge, posterior lamella reconstruction can be accomplished using a nasal septal chondromucosal graft, or a tarsoconjunctival flap from the upper lid. If a mucosal graft or periosteal flap is not used laterally, then the musculocutaneous flap should be lined internally with conjunctiva by advancing it from the inferolateral fornix.

Finally, skin incisions are closed in layers. The standing cutaneous deformity, which may develop at the inferior margin of the defect, is now resected. Ointment is applied to the incision lines.

Tripier Flap

Deficiencies of the anterior lamella of the lower eyelid, because of oncological resection, trauma or leading to ectropion, can be repaired with a uni- or bi-pedicle musculocutaneous flap from the upper eyelid. For fullthickness defects, the posterior lamella can be reconstituted with a septal condromucosal graft, with a Tripier flap placed on top. The bi-pedicled flap has a more robust blood supply, but is not well suited to extreme medial or lateral defects, and requires a second stage. Bi-pedicled flaps are typically used for defects greater than two-thirds of the lower lid, whereas medial or lateral defects are addressed with a uni-pedicle flap.

Steps

In the case of generalized cicatricial ectropion, a releasing subciliary incision (2 mm below the lid margin) is made along the length of the lower lid. The skin is then undermined down into the cheek to release any scar band tethering. The lower lid is

pushed up slightly and the vertical height of the anterior lamella defect is measured; this will ensure that the defect will be slightly smaller than the flap height.

The supratarsal crease is marked along the upper eyelid. With the eyelids gently closed, the maximum amount of skin that can be pinched with forceps before elevating the upper eyelid lashes is determined, and this point is marked along the upper lid, parallel to the supratarsal crease, to define the flap's upper incision. The vertical height of this flap will be the limiting factor in determining how large a defect can be repaired with this technique. In adults, the vertical height of this flap will typically be 10–15 mm.

For a bi-pedicled flap, the superior and inferior upper lid incisions are made through skin and orbicularis oculi, and the flap is undermined in a sub-orbicularis plane, while maintaining the pedicle on either end. The flap can then be transposed down to the lower lid defect.

Prior to flap inset, medial and lateral canthal support can be achieved by suturing each edge of the lower tarsal plate to the corresponding orbital rim periosteum with a 5–0 clear permanent suture. The flap is then inset with a 6–0 absorbable suture, and the upper lid defect is closed primarily with the same stitch. The pedicles can be divided 2 weeks postoperatively.

Paramedian Forehead Flap for Large Nasal Defects

Forehead tissue undoubtedly supplies the best tissue for reconstructing the skin of the nose for moderate to large defects. This is an axial flap based on the supratrochlear vessels that pass superiorly within the forehead. Details of raising this flap are described eloquently elsewhere [32]. Several methods have been employed and are valid; this description of a full-thickness three-stage approach permits accurate sculpting of the reconstructed nose compared to two-stage alternatives. The inclusion of frontalis along its whole length increases vascularity of the flap tip and thereby reduces delayed healing and adverse scarring at its inset. Additionally, the process of raising it from the nose and thinning it as an intermediate step both enables accurate contour creation and enhances blood supply by the lengthened period of surgical delay.

Steps (Fig. 11.4a–b)

Under general anaesthesia a template is used to measure the nasal defect. This template is transferred to the forehead, allowing for a pivot point of the flap at the medial brow. For a lower nasal defect (tip/alar subunit) the flap island will be high on the forehead or temple bay.

The flap is raised by incising the lateral, superior and medial borders, continuing vertically down to the brow. A flap pedicle skin width of 1.5 cm is adequate in most cases, and is based on the medial aspect of the brow.

The flap is raised, including frontalis, along its whole length. Subperiosteal dissection lower in the forehead is not required, as the supratrochlear vessels are supraperiosteal in location deep to the brow.

Following haemostasis the raised flap is transposed into the nasal defect and sutured. The deep aspect of the pedicle may be dressed or resurfaced using a small

skin graft to reduce dressing requirements. The forehead wound should be closed in layers. The upper forehead defect will usually not be closed completely—secondary intention healing will give a superior long-term result compared to skin grafting.

After approximately 4 weeks, the flap may be raised with 2–3 mm of subcutaneous fat. The underlying tissue can be sculpted to an appropriate contour. Cartilage grafts can be placed at this stage if required. The thinned flap is then re-sutured. The pedicle is not adjusted at this stage.

After a further 4 weeks, the pedicle of the flap is divided and a small inverted 'V' is replaced into the forehead and medial brow. The upper part of the nasal flap is refined and sutured into the remaining nasal defect. It can be expected that after some weeks the final contour will be seen.

At each of these additional procedures the forehead scar can be revised, progressively recruiting tissue from the lateral forehead, as stress relaxation permits. Excellent outcomes of vertical forehead scars can be achieved with good technique, multiple stages, and quality wound care.

Bilobed Flap for Small Nasal Defects

This random-pattern local skin flap is a transposition flap that aims to redistribute tissue from adjacent to the circular primary defect while closing the secondary defect with an additional transposition flap.

Steps (Fig. 11.4c–e)

Templates of many designs have been described. A reliable method is described by Zitelli [33]. The flap is designed to include a primary 'lobe' adjacent to the defect with a semicircular margin; the axis of this lobe is at 45° to a line drawn from the centre of the defect to the pivot point lateral to the primary defect. The triangular secondary flap runs at 45° to the primary flap and is longer than the primary flap. By raising this oddly-shaped flap in a plane above the nasal skeleton, the primary flap can be transposed into the primary defect, while the secondary flap moves in to resurface the secondary defect. The triangular tertiary defect (under what was the secondary flap) is closed primarily, ensuring no tension is transmitted to the eyelids to cause ectropion.

All wound margins are sutured. Longer-term problems with this flap include 'pincushioning' of the convex flap because of persistent oedema and peri- and sub-flap wound contraction. This may detract from the longer-term contour appearance.

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Management of Critically Ill Head and Neck Surgical Patients

12

Vineet Nayyar

Introduction

Head and neck surgery has made tremendous advances during the past 50 years. These advances have led to increasing specialization and offering of complex surgical therapy to high-risk individuals, such that many head and neck patients now require critical care inputs as a key component of their care. The complex anatomy, rich vasculature and proximity to structures within a narrow space predispose patients to serious complications from infectious and non-infectious processes in the perioperative period. Yet, in spite of its importance, critical care literature on the topic has remained agonizingly sparse. The last substantial review was undertaken in 2003 [1].

Issues of clinical importance identified in the 2003 review form the backbone of this chapter. Only two prototype disease processes (cancer and infection) have been highlighted in this chapter, as much of the published literature centres around these two themes. In a significant departure from the norm, this chapter avoids too narrow a focus on individual disease entities, but summarizes information relevant to the critically ill adult; it is, therefore, written from the perspective of an intensivist, and although comprehensive, it is not exhaustive. For an overview of the impact of comorbid conditions and disease entities, the reader is referred to two good reviews on the topic [1, 2].

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Head and Neck Surgery: Overview

In different parts of the world, many surgical specialists undertake surgery of the head and neck region either alone or as part of a multidisciplinary team [3]. The latter includes general surgeons, oral and maxillofacial surgeons, plastic and reconstructive surgeons, and otorhinolaryngology and head and neck surgeons, each bringing their own perspective to the patient's care and management.

Irrespective of the surgical specialty involved, patients with a head and neck problem usually undergo an extensive and often prolonged surgery that involves large fluid shifts, blood loss, and results in significant postoperative pain and inflammation. All these factors are considered important contributors to postoperative morbidity. These, coupled with pre-existing co-morbid medical conditions, such as advanced age and lifestyle choices, make postoperative complications not only more likely, but also considerably more serious.

Need for Intensive Care

Options for postoperative management depend on the country of practice, available healthcare resources, volume of cases, and expertise of nursing and medical staff [3]. The three main categories of head and neck patients that require admission to an intensive care unit (ICU) are; (i) the head and neck cancer (HNC) patient; (ii) the head and neck trauma patient; and (iii) the head and neck patient with medical complications [1].

HNC patients require intensive care for the following reasons:

- Routine close observation and nursing care postoperatively
- Treatment of complications after surgery, such as wound dehiscence, flap necrosis, airway compromise, bleeding or infection
- Management of underlying medical conditions, such as chronic obstructive airways disease, ischaemic heart disease, renal failure or uncontrolled diabetes
- Management of new medical conditions, e.g. myocardial infarction (MI), pulmonary embolism, respiratory failure, persistent hypotension, delirium or sepsis
- Complications related to progression of disease, including airway obstruction, aspiration, respiratory distress caused by pleural effusions, or malnutrition
- Complications related to chemotherapy or radiotherapy, such as mucositis, neutropenic sepsis, immune-compromised status or metabolic.

The risk of developing complications in HNC patients does not necessarily equate with the need for a critical-care bed. Not surprisingly, reports from Hong Kong [4], UK [5] and USA [6] have questioned the rationale for routinely admitting postoperative major HNC patients to the ICU, citing no advantage of this approach compared to postoperative observation in a specialist ward. While it is hard to ignore the evidence that the rate of complications remains unaffected, whether or not patients are admitted electively to the ICU, it is also difficult to extrapolate the

findings of singlecentre studies [2]. Morton recommended caution, believing that decision making about postoperative care may not be as simple as an argument over observed complication rates reported from highly specialized centres [7]. It is conceivable that prompt recognition of adverse events in an ICU environment may guide proactive interventions early and might improve survival. Clearly, each healthcare facility must be able to establish whether such benefits outweigh the costs of a day's observation in the ICU. To ensure that these benefits accrue to patients, favourable policies related to staffing and skill-mix in the ICU are essential, as they are important determinants of outcome among patients undergoing free flap reconstruction [9].

A stratification of postoperative cases on the basis of pre-existing conditions, the nature and extent of surgical procedures, and intraoperative complications has been proposed [8] but has not been adopted widely. Clearly, the type and site of surgery and duration of anaesthesia are some of the important determinants of the need for a critical-care bed. Although traditionally not thought to be risk factor, duration of time under anaesthesia appears to be predictive of postoperative surgical complications and length of hospital stay. In a retrospective study of 157 patients by Boruk et al., 10 patients were found to develop major complications in the postoperative period [10]. In this study, they estimated the odds of having a complication (major or minor) increased by 0.6 % with every minute of anaesthesia [10].

In view of the available evidence, it is reasonable to conclude that all patients with major head and neck problems do not require routine postoperative admission to the ICU. However, those who do, require a level of care consistent with the extensive nature of surgery, and co-morbid conditions that often accompany diseases of the head and neck. A decision to admit to the ICU requires close cooperation and active communication between the surgical team, the anaesthetist and the intensivist.

Co-morbid Conditions

The literature is expanding on factors associated with increased risk of mortality and postoperative complications [11–13]. Many of these factors can be identified before surgery, making them particularly important targets for preventative measures. With improved safety of operative techniques, the relative risk of complications associated with the surgery is substantially less compared to risk associated with pre-morbid conditions. Multiple studies have established the importance of frequently encountered patient factors [13, 14]. These include age, American Society of Anesthesiologist (ASA) physical status, and albumin. The odds of 30-day mortality double for every decade after 70 years of age; an increment in the ASA status roughly doubles postoperative death rate, and a drop in preoperative albumin level to <30 g/L is associated with an OR of 2.5 for 30-day mortality [13, 14].

Major co-morbidities identified in head and neck patients include hypertension, diabetes mellitus, cardiac disease, excessive alcohol intake, and a history of protracted and heavy smoking. These co-morbid conditions are believed to be a better predictor of patient outcome than staging of cancer [15]. Age is an important issue

in head and neck surgery [1]. As expected, medical morbidity and mortality is increased in the elderly, but this is more so as a result of concurrent illness in patients rather than age alone. The impact of co-morbidity is greater in older than in younger patients, although it affects both. When complications occur, they are more severe in older patients and are associated with a higher mortality and costs [1].

Several instruments are available to quantify co-morbidity in patients planned for head and neck surgery. These include the adult co-morbidity evaluation 27 (ACE-27), Charlson index (CI) and cumulative illness rating scale. ACE-27 has been validated extensively in HNC for the purpose of predicting survival [16], complications [17], functional outcome [18], and quality of life [19]. CI too has been evaluated by several authors and has been found to be a significant predictor of postoperative complications among head and neck patients [20, 21]. In addition, ICU scoring systems (e.g. APACHE II) [22] have been used to predict immediate surgical complications, but have not been adopted widely. The Revised Cardiac Risk Index (RCRI), derived from using rigorous statistical methodology, is another useful measure that is robust, but guidelines on the action to undertake once the risk estimates are obtained are lacking [23]. Some head-to-head comparison [24] of disease-specific and general indices suggest that all these instruments have similar prognostic ability, whereas others have shown ACE-27 to be most successful in stratifying HNC patients with prognostic ability comparable to that of nodal staging [25].

Patients with HNC have a risk profile not dissimilar to those with vascular disease, which predisposes them to atherosclerotic disease and its complications. Some patients with pre-existing coronary artery disease and stents *in situ* need to discontinue antiplatelet therapy, exposing them to substantial risk of stent closure in the postoperative period. Although interest in and hope for revascularization was high 5 years ago, the weight of evidence subsequently has suggested no benefit of prophylactic revascularization in patients before major surgery [26].

The presence of chronic obstructive pulmonary disease (COPD) is associated with an increased risk of pneumonia and respiratory failure in the postoperative period [26]. The severity of the underlying lung disease and the magnitude of risk is roughly correlated. As many as 75–80 % of patients undergoing surgery for HNC have a history of smoking and a significant proportion have COPD [2]. Among these, 10 % have severe disease. Patients with undiagnosed obstructive sleep apnoea (OSA) are also likely to develop postoperative complications if the condition is not recognized and managed appropriately. Patients at risk can be identified preoperatively by the STOP-BANG questionnaire, which has been validated for use in head and neck patients [27]. Evidence is mounting to suggest a link between HNC treated with either primary surgical resection [28] or radiation therapy [29] and the development of OSA.

Postoperative Complications

The most dreaded complication after head and neck surgery is airway compromise and bleeding (or haematoma formation). However, the commonest complications post-surgery are either respiratory or cardiovascular.

Bhattacharya and Fried's seminal work published in 2001 remains widely quoted even though nearly half of all patients included in their case series were postoperative after a thyroid or parathyroid operation [30]. Among 3309 patients undergoing a primary head and neck procedure, the authors reported an overall mortality of only 3.55 %. Death occurred in 12.6 % of those who experienced a complication compared with 1.71 % mortality in patients without a complication. Postoperative pneumonia was common, occurring in 3.26 % of patients and was associated with a mortality of 10.94 %. The majority of deaths occurred during the first 3 days after surgery, and among these, more patients died from medical rather than surgical complications. These data were similar to the findings reported earlier by Downey et al. [6], who retrospectively evaluated the need for an ICU after HNC surgery at a single, large, specialized cancer centre. Only 1.5 % of patients in this case series required ICU admission. Approximately two-thirds (29/43) of patients developed respiratory or cardiovascular complications; of these about 25 % died [6].

A recent analysis of patients admitted postoperatively to an ICU in the Netherlands has added to the knowledge base in this area [31]. In this large dataset of >28,000 patients admitted to the ICU postoperative after elective cancer surgery, 3.1 % (888 patients) were admitted after a major head and neck procedure. In this group, the commonest co-morbidity was COPD (~12 %) followed by diabetes mellitus (~9 %). The incidence of postoperative pneumonia was ~1 % and the rate of cardiac dysrhythmias was 1.5 %. Overall, the hospital mortality in this case series was 3.3 %, exceeded only by patients with colorectal malignancy, oesophageal surgery, and pancreatic (and/or biliary) surgery [31]. Postoperative pulmonary complications were the focus of a recent retrospective study of patients undergoing major head and neck surgery at a tertiary care centre in Canada [32]. In this case series, ~45 % developed one or more complications; the most common was postoperative respiratory failure. Development of pulmonary complication was associated with higher mortality (12.7 % vs. 1.7 %), and longer ICU and hospital length of stay (LOS).

The aforementioned studies have shaped our current understanding of the postoperative course of patients after head and neck surgery. Without doubt, patients who suffer medical complications do badly, but to identify them preoperatively remains a major challenge. The primary means of assessing risk is through history and a clinical examination. Needless to say, history must be elicited carefully.

Head and Neck Malignancy

HNC, or cancer of the upper aerodigetive tract, is an uncommon malignancy comprising only 3 % of all malignancies in the USA [33]. In many parts of the world, particularly France and India, HNC is a major cause of death. The most common pathology is that of a squamous cell carcinoma (SCC), comprising >90 % of all malignancies of the upper aerodigestive tract. Treatment includes radiotherapy and chemotherapy but surgery has been the mainstay of management for >30 years. Surgery as definitive treatment is preferred for oral cavity lesions whereas radiotherapy and/or chemotherapy are favoured for oropharyngeal or laryngeal disease, unless local spread is extensive.

Risk factors most commonly associated with HNC include smoking, alcohol consumption, human papillomavirus (HPV) infection and Epstein–Barr virus infection [34]. Among these, smoking and alcohol consumption are important in terms of additive risk for oral and oropharyngeal cancer.

Severe Soft Tissue Infections of Head and Neck

Infections of potential spaces of the head and neck may be associated with airway compromise, jugular septic thrombophlebitis, aspiration pneumonitis, lung abscess, mediastinitis or, in the worst case scenario, septic shock with multi-organ failure. An understanding of the anatomical boundaries, interconnections, clinical manifestation and microbiology are crucial to the management of these serious infections [35].

Submandibular Space Infections

In submandibular, lateral pharyngeal and retropharyngeal space infections, the portal of infection is the oral cavity and thus antibiotic therapy invariably is directed towards organisms commonly found in the mouth. Although severe infection in any deep spaces of the head and neck can affect airway patency, submandibular space infection is more commonly associated with a compromise of the airway. As a result, such patients require early airway involvement of the critical-care team and placement of a definitive airway. Not all patients require intubation, but if an initial course of close observation is pursued, it should be carried out in an environment in which frequent monitoring and airway intervention is possible [36].

Infections in the submandibular space are typically odontogenic in nature and arise from the spread of periapical abscesses of the mandibular molars, most typically the second or third molars where bone is the thinnest [35]. Other pathological processes that involve the submandibular space include sialadenitis, mandibular or lingual malignancy, laceration of mouth floor, lymphadenitis, and foreign bodies. The distinguishing feature of submandibular space infection is a rapidly spreading woody inflammation with or without overlying cellulitis. A striking aspect of the physical examination is the protruding tongue, which is forced outwards due to internal pressure and limitation imposed by fibres of the deep cervical fascia. At times, the whole floor of the oropharynx is elevated and tender to touch. Multivariate analysis has identified some independent risk factors associated with severe complications after submandibular space infections [37, 38]. These include anterior visceral space involvement, bilateral neck swelling, presence of diabetes mellitus, and other co-morbidities.

Over the past decade or so, the proportion of deep space infections arising from an odotogenic source has increased relative to other types of infections [39]. Odontogenic infections are associated with poor dental hygiene and low socioeconomic status. In a single-centre observational study, 144 patients with an odontogenic infection treated in a tertiary care ICU had indicies of socioeconomic disadvantage that were significantly worse than the rest of the ICU patients [40].

Lateral Pharyngeal Space Infections

Infections involving the lateral pharyngeal space can develop from a variety of sources but most commonly follow a pharyngitis or tonsillitis. Often, the infection yielding a portal of entry into the lateral pharyngeal space is minor or may even have resolved by the time symptoms of the deep space infection appear. The classical clinical signs are dysphagia, trismus and ipsilateral pain extending up to the jaw or pain referred to the ear. Complications of lateral pharyngeal space infection include laryngeal oedema, sudden death, carotid artery involvement or suppurative jugular vein thrombophlebitis (Lemierre syndrome) [41].

Retropharyngeal Space Infections

The retropharyngeal, danger and prevertebral spaces are a common pathway for extension of head and neck infections into the thorax. Although separated by fascial planes, these spaces are considered as a unit because of their anatomical proximity and their propensity for spread beyond the head and neck. Suppurative adenitis of deep cervical lymph nodes in children, trauma from oesophageal instrumentation, and foreign bodies are causes of retropharyngeal abscesses.

The most lethal complication of retropharyngeal and danger space infection is descending necrotizing mediastinitis. Infections, if untreated, can spread into the pleural, pericardial and the retroperitoneal space. Debridement and appropriate antibiotics are the foundations of treatment for mediastinitis, which even if treated effectively can be associated with a high mortality [41].

Infections of the prevertebral space are primarily haematogenous in nature and their microbiology is markedly different to other infections of the head and neck discussed so far. Complications arise from spread to the epidural space with cord compression, spread to the vertebrae or disc with mechanical instability of the spine, loculation of pus at distant sites, and ongoing bacteraemia. Initial coverage for Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* is recommended.

ICU Management: General

Anticipating, recognizing and treating complications is integral to operative success. Optimal management requires ongoing close cooperation between the surgical team and the critical-care team.

Patient Position

Nosocomial pneumonia is the most frequent problem in the postoperative period of patients undergoing a major head and neck procedure [30]. The recognized

pathogenetic sequence is abnormal oropharyngeal colonization and subsequent aspiration. Bacterial colonization of the stomach and gastric reflux might also play a part in the pathogenesis of lung infection. Approximately 20 years ago, studies using radio-labelled gastric contents showed that reflux could be reduced and aspiration could be avoided by positioning patients in a semi-recumbent position [42, 43]. A subsequent clinical study indicated the risk of nosocomial pneumonia to be the highest among ventilated patients receiving enteral feeds in the supine position [44]. A recent meta-analysis of three randomized trials (337 patients) confirmed that the odds of developing clinically proven pneumonia were significantly lower among ventilated patients in the semi-recumbent 45° position compared to the supine position (OR 0.47; 95 % CI 0.27–0.82) [45].

Not surprisingly, an elevated head position (angle >30°) has become a standard of care for all mechanically ventilated patients in the ICU [46]. It stands to reason that the same concept can be extrapolated to prevent pneumonia in postoperative head and neck patients, although these patients have additional factors that contribute to nosocomial infections. The semi-recumbent position is one of the simplest and most cost-effective preventative measures in healthcare.

Analgesia and Sedation

Patient comfort and safety are two important priorities of analgesia and sedation in critically ill patients [47]. Analgesia and sedation are provided in the postoperative period by means of a pharmacological agent. Opioids are time-honoured, valuable and powerful analgesics for the management of moderate-to-severe postoperative pain. The efficacy of different opioids is similar as far as clinically relevant outcomes are concerned. However, evidence suggests that more sophisticated methods of administration, such as patient-controlled analgesia (PCA) may improve pulmonary outcome. The most commonly used opioids for intravenous (i.v.) PCA are morphine, fentanyl or hydromorphone. The common setting for administration of these drugs is summarized in Table 12.1. In general, the depth of analgesia should be adapted to the needs of individual patients. Management of patients is best guided by simple clinical scales [48, 49], although there is no consensus on how frequently pain and sedation scores should be evaluated. Whereas there is some agreement on what constitutes an acceptable level of pain relief, the same is not true of sedation. Recent data from clinical trials have shown that sedation of ICU patients with benzodiazepines might contribute to confusion or overt delirium [50, 51].

Table 12.1 Commonly used opioids in intravenous patient-controlled analgesia (PCA)

Drug	Demand dose	Lockout interval	Basal infusion rate[a]
Morphine	1–2 mg	5–10 min	<0.5 mg/h
Hydromorphone	0.25–0.5 mg	5–10 min	<0.4 mg/h
Fentanyl	10–50 mcg	5–10 min	<50 mcg/h

[a]Basal infusions are recommended only in opioid-tolerant patients

Patients receiving sedatives and opioids are also at risk of excessive sedation, respiratory depression, nausea and vomiting. These side-effects are likely to be most evident in elderly patients or those with renal or hepatic dysfunction, although large individual variations are known to occur. Opioids suppress hypoglossal activity, thereby diminishing the activity of genioglossus muscle during inspiration, while concomitantly decreasing the responsiveness of upper airway muscles to hypercapnia. Consequently, patients with known OSA have a higher frequency of apnoeic episodes postoperatively [52]. Patients with nasal obstruction, tonsillar or adenoidal hypertrophy, or those with upper airway surgery appear to have an increased risk of complications in the immediate perioperative period.

Postoperative delirium is a common complication of head and neck surgery because of the high prevalence of certain risk factors (e.g. age, cognitive decline, alcohol use). Patients who become agitated are at increased risk of self-harm [53, 54], increased length of ICU and hospital stay, increased costs, and a higher all-cause mortality. The relationship between delirium and increased mortality is independent of age, illness severity, and whether or not these patients receive mechanical ventilation in the ICU. The confusion assessment method for ICU (CAM-ICU) [55] is an objective scoring system for delirium, which complements the Richmond agitation–sedation scale [56] for use in ICU patients. A scoring system to identify patients at-risk of postoperative delirium is probably more useful but it has not been validated in head and neck surgery patients [57].

Given the high prevalence of alcohol consumption, it is prudent to screen all patients preoperatively for current alcohol intake using the standard CAGE questionnaire. In general, the severity of withdrawal symptoms is proportional to the duration and amount of alcohol intake, with patients who have experienced delirium tremens or seizures being at the highest risk. Symptom-triggered approach with early introduction of benzodiazepines is preferable at the onset of withdrawal symptoms. The α-2 agonists, clonidine and dexmetetomidine, have been used for alcohol withdrawal in the ICU. These agents have little effect on respiratory function but have several useful cardiovascular effects, including blunting of the tachycardic and hypertensive response of patients emerging from effects of prolonged alcohol intake. α-2 agonists have also been shown to reduce behavioural and autonomic responses after termination of conventional sedation and facilitate extubation [58]. In a separate study by Reade et al. [59] dexmetetomidine was compared with haloperidol for treating patients deemed otherwise ready, but were not extubated because of agitated delirium. Patients receiving dexmetetomidine went onto extubation earlier compared with those receiving haloperidol [59].

Venous Thromboembolism Prophylaxis

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are important causes of morbidity and mortality among surgical patients. Guidelines for thromboprophylaxis are well established and based on the results of several randomized trials [60]. In contradistinction to these guidelines, chemoprophylaxis is not

recommended routinely for patients undergoing head and neck surgery, including HNC surgery [61]. The generally low incidence of perioperative DVT or PE (0.1–2.5 %) in head and neck surgery patients [62–65] and the risk of bleeding or related complications means that chemoprophylaxis targeted to a high-risk group is a better strategy. Chemoprophylaxis for low-risk, ambulatory (or day care) patients is not justified and currently is not recommended.

Several patient-specific risk factors for venous thromboembolism (VTE) have been identified in surgical patients [26]. These can either be elicited from history or more formally in the form of a risk stratification scale [66]. Among patients with multiple risk factors who are undergoing a major procedure that is likely to result in prolonged immobilization, VTE prophylaxis is considered reasonable. A disproportionately high number of VTE events have been recorded among patients undergoing microvascular flaps, implying that this group of patients should also be managed as a high-risk group. The American College of Chest Physicians guidelines recommend the use of pneumatic compression devices, unfractionated heparin (UFH) or low-molecular weight heparin (LMWH) for prophylaxis [67]. If prophylaxis is used, it should commence within 2 h of completion of surgery to be effective [67]. For pneumatic compression to be effective, the compression device must be worn for at least 90 % of the duration of immobility [68].

A recent meta-analysis of clinical trials on ICU patients has confirmed a beneficial effect of chemoprophylaxis with UFH compared with placebo in reducing the risk of DVT, but more importantly, the statistical analysis showed a decreased risk of PE with the use of LMWH compared with UFH (RR 0.62; 95 % CI 0.39–1.00; $p=0.05$) [69]. Although rates of major bleeding were not significantly different, it is worth noting that the effects of UFH can be easily quantified and reversed, if needed.

Nutrition

Nutrition has long been recognized as the second most important factor in predicting long-term prognosis in HNC. Whereas the National Institute for Health and Clinical Excellence (NICE) guidelines provide the best framework for a multidisciplinary approach to nutritional management of patients, the most comprehensive guidelines have been issued recently by the Clinical Oncological Society of Australia (COSA) [70]. COSA guidelines have provided a grade A recommendation for inclusion of a dietitian in the multidisciplinary team looking after HNC patients, and for dietary intervention during treatment to maintain or improve nutritional status. The European Society of Parenteral and Enteral Nutrition (ESPEN) guidelines on enteral nutrition (EN) recommend preoperative nutritional supplementation for 10–14 days prior to surgery in patients with BMI of <18.5 kg/m^2, or those with weight loss of >10–15 % in past 6 months [71]. This is applicable to preoperative head and neck patients as well.

Standard polymeric fibre feeds are recommended for use postoperatively with an aim to deliver ≥30 kcal/kg/day. Postoperative tube feeds should commence within

24 h with consideration given to individual patients, depending on the extent of the surgical procedure performed and other priorities identified by the multidisciplinary team. This recommendation is supported by a recent meta-analysis, which showed that early EN (within 24 h) compared to standard care was associated with a significant reduction in mortality and rate of pneumonia among adult ICU patients [72]. The optimal method of tube feeding remains unclear. Evidence does not favour post-pyloric feeds over the standard nasogastric feeds [73].

The role of parenteral nutrition (PN) in critically ill adults has been clarified recently by two large multi-centre trials [74, 75]. Published in 2011, the EPaNIC trial did not find any benefit with the addition of PN to deliver calories up to a desired goal in patients who were already receiving some EN [74]. Therefore, sick ICU patients who tolerate some enteral feeds in the first 24–48 h may not derive any additional benefit from rapidly reaching a pre-specified but empirical nutritional target. A second trial (Early Parenteral Nutrition trial) was designed to study a small subset of ICU patients with relative contraindications for early EN (within 24 h of ICU admission) [75]. In this trial, early PN commenced on day 1 of ICU was compared with standard care; no difference was observed in 60-day mortality between the early PN group and standard care group in which nutritional therapy was started on day 3. Early PN resulted in significantly fewer days of invasive ventilation but no change in the ICU or LOS. In other words, starting PN within 24 h of admission in ICU patients who are not ready to be fed enterally is not associated with improvement in mortality. One salient finding of the early PN study was that the rate of central line infection in patients receiving PN was comparable to that in the EN arm of the study [74].

Diabetes is a common co-morbid condition among head and neck patients and is considered a risk factor for several postoperative complications, such as infections, cardiac and metabolic problems, and delirium. Although a review has focused on the postoperative care of the diabetic patient, it has not addressed the issue of diabetic patients undergoing head and neck surgery [76]. In general, targets for glycaemic control among the critically ill have been clarified recently by a large multi-centre, randomized trial NICE-SUGAR [77]. Contrary to the prevailing view at that time, the study showed an increased risk of mortality and adverse effects (hypoglycaemia) among patients randomized to the strict glycaemic control arm (4.5–6.0 mmol/L) [77]. Consequently, the currently recommended insulin therapy is targeted to achieve blood glucose levels of 6.0–10.0 mmol/L.

Antibiotic Prophylaxis

The efficacy of antibiotic prophylaxis for reducing surgical site infection (SSI) has been clearly established. Patients who receive prophylaxis within 1 h or 2 h before the surgical incision have lower rates of SSI compared with those who receive antibiotics sooner or later than this window [78, 79]. In general, antimicrobial selection for SSI prophylaxis is based on type of surgery, safety, bactericidal activity and cost.

Elective procedures of the head and neck are predominantly clean or clean-contaminated. Clean procedures include thyroidectomy and lymph node dissections.

Table 12.2 Antimicrobial prophylaxis for head and neck surgery patients

Type of surgery	Pathogens	Antimicrobial prophylaxis	Usual adult dose
Clean		None	
Clean with placement of prosthesis	S. aureus, S. epidermidis, Strep. species	Cefazolin	<120 kg: 2 g i.v. >120 kg: 3 g i.v.
		OR cefuroxime	1.5 g i.v.
		OR clindamycin	600–900 mg i.v.
Clean – contaminated	Anaerobes, enteric Gram-negative bacteria, S. aureus	Cefazolin	
		PLUS metronidazole	500 mg i.v.
		OR cefuroxime	1.5 g i.v.
		OR ampicillin- sulbactam	3 g i.v.
		OR clindamycin	900 mg i.v.

Clean-contaminated procedures include all surgeries involving an incision through the oral or pharyngeal mucosa. These range from parotidectomy, submandibular gland excision, tonsillectomy, adenoidectomy and rhinoplasty, to complex procedures, such as tumour debulking and mandibular fracture repair. The infection rate among patients undergoing complex head and neck procedures in the absence of antimicrobial prophylaxis is high (24–78 %); infection rates are markedly lower with prophylaxis (5–38 %) [80].

Most infections arising after clean-contaminated head and neck procedures are caused by microorganisms residing in the oral cavity. These include anaerobic bacteria, and therefore postoperative SSI are polymicrobial [81, 82]. The predominant oropharyngeal organisms include various streptococci (aerobic and anerobic), other anaerobes, including Bacteroides species (but not *B. fragilis*), Peptostreptococcus species, Fusobacterium species, Veillonella species and, rarely, Enterobacteriaceae, and Staphylococcus species.

Antimicrobial prophylaxis is not warranted for patients undergoing clean procedures of the head and neck [83, 84]. A single preoperative dose of cefazolin (or clindamycin in the setting of β-lactam allergy) is reasonable in the setting of prosthetic material placement, although data on the efficacy of this practice have not been clarified. Prophylaxis with antibiotics is recommended routinely for most other head and neck procedures [80], although randomized trials have not shown any benefit in the setting of adenoidectomy, tonsillectomy or septoplasty [85, 86]. A reasonable regimen for patients undergoing surgery includes a cephalosporin (cefazolin or cefuroxime) plus metronidazole or ampilcillin-sulbactam. Clindamycin is an alternative for patients with β-lactam allergy (Table 12.2).

In general, repeat antibiotic dosing after wound closure is not necessary. In a systematic review of controlled trials, no difference was seen in the rate of SSI with a single dose compared with multiple dose regimens given for less than or more than 24 h [87]. For cases in which perioperative antibiotic coverage is required beyond the period of surgery, the duration should be <24 h.

Errors in the selection and timing of prophylactic antibiotics remain a major concern. Among 34,133 patients undergoing major surgery in the USA, an antimicrobial was administered within 1 h before incision to only 56 % of patients, and antimicrobials were discontinued within 24 h of surgery in only 41 % of patients [88].

ICU Management: Specific

Patients with active head and neck pathology or those who have undergone surgical or radiation treatment for HNC are at increased risk of adverse airway events. These need to be recognized and managed appropriately.

Airway

A number of head and neck procedures involve the upper airway. When airway compromise is not an issue, most procedures are routine and largely uneventful [89]. All patients with airway compromise should be considered as having a potential difficult airway for which well-established guidelines now exist [90]. Unfortunately, there is no universal recipe for the management of the airway for head and neck procedures. Each procedure requires an appraisal of the urgency of the procedure, size and site of lesion, level of obstruction, and degree of airway compromise [89].

The recently published report of the Fourth National Audit Project of the Royal College of Anaesthetists and Difficult Airway Society (DAS) identified serious airway complications occurring during anaesthesia in the ICU and in the emergency department [91]. In the presence of head and neck pathology and after maxillofacial or major neck surgery, a number of airway-related complications were encountered. Approximately 70 % were associated with obstructive lesions within the airway [91].

Early fibre-optic intubation by an experienced anaesthetist or tracheostomy by an experienced surgeon is a reasonable consideration in patients with a threatened airway. Patients with airway compromise are easily identified in the presence of tachypnoea and stridor, but should be recognized even in the presence of subtle signs, such as an inability to lie down flat in bed or silent breathing with adoption of the sniffing position while sitting upright. Routine endotracheal intubation in these patients is complicated by trismus, distorted anatomy, immobility of soft tissue structures, friability and bleeding, or in the worst case scenario, complete obstruction of the airway after anaesthetic induction. Awake fibre-optic techniques are suitable for oral cavity, oropharyngeal and tongue base lesions, but might be unsuitable for lesions in the larynx in which the fibrescope has to pass through the mass.

Inhaled induction techniques in which spontaneous ventilation is maintained have been used for potentially difficult airways. However, such an approach is not without its problems. A reduction in airflow, increased collapsibility of airway, increased work of breathing, and reduction in functional residual capacity can impair the onset and depth of anaesthesia and preclude placement of an endotracheal or nasotracheal tube, as required.

Following major head and neck surgery, the risk of upper airway obstruction remains high and the optimal postoperative airway management remains controversial. Bilateral neck dissections, use of bulky reconstruction flaps, resection of mandible, tongue or floor of mouth carry the greatest risk. It is uncertain if the risks of tracheostomy outweigh anticipated airway problems in the postoperative period. Cameron and colleagues used an old dataset to derive a clinical score to guide clinical decision-making that reliably identified the need for elective tracheostomy at the time of the initial procedure [92]. The score was validated in their sample of 148 major head and neck procedures and indicated a variable positive and negative predictive value, depending on the cut-off threshold used. The scoring system has since neither been refined nor applied widely, but remains a useful adjunct to clinical judgement.

Airway Devices

Humidity is important throughout the postoperative period to prevent drying of secretions and blockage of the airway, particularly in patients with a fresh tracheostomy or tracheostoma. Tracheostomy reduces the risk of glottic damage compared with long-term use of a tracheal tube, and is particularly important if slow resolution of oedema or inflammation is anticipated. Elective tracheostomy should be considered in patients with HNC in whom either the location or the extent of cancer precludes translaryngeal tube placement. Wherever possible, a tracheostomy tube with suction above the cuff should be considered. Two randomized trials [93, 94] and a meta-analysis [95] have shown that endotracheal tubes (ETT) equipped with subglottic suction significantly reduced the incidence of ventilator-associated pneumonia (VAP) in patients ventilated for $\leq$3 days without a corresponding increase in adverse events. A recently published randomized trial has extended these observations to a group of mechanically ventilated patients who required a tracheostomy in the ICU [96]. In this study involving only 18 patients, the researchers were able to show a significant reduction in the incidence of VAP (56 % vs. 11 %; $p=0.02$) with the use of tracheostomy tubes with a suction port above the cuff [96].

Tracheostomy care has traditionally been provided by surgical teams that performed the procedure, but this has changed with the introduction of newer techniques [97] and with the growing recognition of the complex needs of tracheosomy patients. Tracheostomy insertion has implications for communication, swallowing, airway management and overall nursing care, thereby justifying the need for involvement of a multidisciplinary team. In 2009, Garrubba et al., conducted a systematic review of multidisciplinary care for ward-based tracheostomy patients [98]. They identified three studies and concluded that time to decannulation, LOS and adverse events were better with a tracheostomy team compared with the standard approach. A more recent, second systematic review also confirmed a reduction in total tracheostomy time after the introduction of tracheostomy teams [99].

Postoperative Care

Scheduled administration of steroids is a common practice. Steroids reduce inflammatory oedema but have no direct effect on oedema arising from mechanical trauma or venous obstruction. The evidence suggests that all steroids are equally efficacious, provided they are given in equivalent doses. When considered for use, steroids should be continued for ≥12 h [100]. Single-dose steroids given immediately before extubation are ineffective.

The perioperative use of β-blockers in naïve patients undergoing non-cardiac surgery is controversial since the publication of the POISE study [101]. In this large multicentre trial, patients >45 years of age randomized to receive metoprolol perioperatively had fewer MIs (4.2 % vs. 5.7 %; p = 0.05; NNT 67) but an increased rate of stroke and overall mortality. A metaanalysis of clinical trials on the same topic published within a month of the POISE study showed a reduction in the risk of nonfatal MIs in the postoperative period [102]. In fact, trials showing a beneficial effect of intervention were the ones that studied β-blockers in high-risk patients. Other studies showing benefit without any adverse events were ones that used a lower dose of β-blockers compared with the POISE study. These controversies notwithstanding, patients with an indication for β-blockers or those already on the drug derive a benefit, if they are continued on the drug throughout the surgical period [103].

Extubation in ICU

Many patients are transported to the ICU intubated and are extubated after what is deemed as a suitable period of observation. In 2012, the DAS—acknowledging the lack of large randomized trials of extubation practices—released a set of guidelines for the management of tracheal extubation on the basis of expert opinion [104].

Extubation in the ICU is an elective process even if intubation of the trachea was undertaken during an emergency. Planning for tracheal extubation is a critical component of a successful airway management strategy, particularly when dealing with patients with a difficult airway. This involves assessment of the airway and general risk factors. Extubation is considered 'low risk' if the airway anatomy was normal at induction and remained so until the end of surgery with no complications supervening. 'At-risk' extubation, on the other hand, is one in which an airway or a general risk factor has been identified. However, evaluating these risks in a patient whose airway is still protected is a more subtle task. While reliable anatomical predictors of inability to perform effective mask ventilation and intubation have been identified, the same is not true for answering the question, 'Is it safe to remove the tube?'

Whereas oedema of the tongue and pharyngeal structures is easily visualized, laryngeal oedema is more difficult to assess and quantify, especially in the presence of an ETT. If the tube is small compared with the size of the airway, as is frequently the case with upper airway pathology, direct laryngoscopy to visualize the degree and anatomical distribution of oedema is helpful. However, the degree of interobserver agreement is only modest [105]. A quantitative cuff leak test can be used

along with laryngoscopy (direct or video-assisted) to increase the predictive value of assessment [106]. The discriminatory power of this test depends on the method and cut-off values chosen. Choice of a higher cut-off value minimizes the risk of false-negatives (presence of leak = negative test) may be valuable in patients in whom difficult tracheal intubation is expected. In a systematic review and a meta-analysis, Ochoa et al. [107] concluded that whereas a negative test is not necessarily reassuring, a positive cuff-leak test should alert the clinician about the risk of upper airway obstruction. This test has been validated only in patients who have received mechanical ventilation for 48 h rather than those ventilated overnight. The test itself requires measurement of expired tidal volumes after six complete respiratory cycles while on an assist-control mode or control mode of ventilation with the ETT cuff deflated. A leak volume of 10–25 % (~100–130 ml in a 70 kg adult) of the expired tidal volume before cuff deflation is considered safe for extubation.

With the exception of tube exchangers to guide and expedite reintubation, no other specific tool or procedure to increase safety at extubation has gained widespread acceptance or has been adopted in clinical algorithms [108]. Airway exchange catheters (AEC) are long, thin, hollow tubes made of semi-rigid polyurethane and are supplied with 15 mm connectors compatible with anaesthetic circuits and Luer lock connectors for use with jet ventilation. They can be inserted through the tracheal tube before extubation because they can be used as a guide over which a tracheal tube can be passed, should reintubation become necessary [109]. They can also be used to oxygenate patients' lungs. In a recent review, Duggan et al. reported that oxygen insufflation might be associated with a significant risk of barotrauma [110]. The authors therefore concluded that priority be given to reintubation over attempting oxygenation and ventilation through the lumen of the catheter. To enhance safety, the recently published DAS guidelines suggest that an AEC should not be inserted beyond 25 cm, but this only applies to orally intubated, adult patients [104].

Extubation failure after a well-planned extubation is uncommon, but it is relatively more common in critically ill patients. In the presence of head and neck pathology and after maxillofacial or major neck surgery, the rate of tracheal reintubation has been reported to vary between 0.7 and 11 %. Conditions, such as obesity, OSA, rheumatoid arthritis and other cervical spine pathologies also carry a significant risk of extubation failure. This usually follows loss of upper airway patency because of oedema, soft tissue collapse, laryngospasm, bleeding, secretions, or collapse of upper airway structures. A few investigators have reported that ICU patients requiring reintubation for respiratory failure have a higher mortality (30–53 %) than patients reintubated because of airway obstruction (7–17 %), suggesting that weaning failure may carry a higher mortality compared with extubation failure [111]. One explanation to account for this difference is that patients who fail extubation because of airway obstruction are reintubated earlier than those who fail because of respiratory complications [108], and time to reintubation is a well known independent risk factor for mortality in this group [111].

In this context, it is reasonable to consider extubation in the operating theatre to ensure availability of equipment and, most importantly, availability of the surgical team, in case a surgical airway is required.

Conclusion

Care of the critically ill head and neck patient poses many challenges many of which arise as a result of the primary disorder, but increasingly because of associated co-morbidities and complications of treatment. Some, more often than not, complicate airway management, and pose a significant threat to life. These need to be recognized by the primary surgical team and the anaesthetist in a timely manner, and treated appropriately. A multidisciplinary approach is essential to achieve high quality care.

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Future Directions in the Management of Non-melanoma Skin Cancer

13

Gerard Adams and Sandro V. Porceddu

Introduction

The current and future management of non-melanoma skin cancer (NMSC)—predominantly basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)—represents a significant public health problem worldwide. Australia has one of the highest rates of skin cancer in the world, with data showing that NMSC is five times more common than all other cancers combined [1]. The sun-exposed head and neck (HN) is the most common location, with incidence rates continuing to rise 3–10 % per year. Although BCC is more common, the vast majority of NMSCs are localized and easily treated with simple excision. However, 5 % are considered high-risk (nearly always SCC) and metastasize to regional lymph nodes with the potential for distant spread [2].

Campaigns to reduce sun exposure may mitigate this rising incidence in the future. However, the risk of NMSC (mainly SCC) has been shown to be raised significantly in conditions in which immunity is suppressed, either naturally (e.g. chronic lymphocytic leukaemia (CLL) [3], infection with human immunodeficiency virus (HIV) [4] or iatrogenically (e.g. organ transplant recipients [5], treatment for rheumatoid arthritis [6]). With more people with these conditions surviving, as well as an ageing global population, the rates of NMSC are likely to remain high, with, perhaps, even an increasing rate of high-risk disease.

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NMSC already represents the most expensive cancer burden on the Australian Health system [7]. The predominant treatment is surgery, as it is generally curative and provides histopathological information. Modalities, such as radiotherapy, topical treatments and photodynamic therapy, are used when surgery is not the preferred option [8]. Issues surrounding current management are dealt with elsewhere in this book. This chapter examines how management of NMSC might alter in the future, with an emphasis on high-risk SCC of the HN.

Operable Disease

Adjuvant Chemotherapy in High-Risk Disease?

As with other cancers, modern management aims to stratify patients into high- and low-risk groups. Research is aimed towards intensifying treatment in the higher-risk group in the hope of improving control or de-escalating treatment in the lower-risk groups with the aim to maintain high control rates, yet minimize toxicity and improve quality of life for survivors.

The current focus of treatment intensification in high-risk groups with cutaneous HNSCC (cHNSCC) is centred on the addition of chemotherapy. High-risk features include size (>2 cm), deep invasion (4–6 mm), incomplete excision, presence of perineural invasion (PNI) and/or lymphovascular invasion, recurrent disease, poor differentiation, location (ear or lips), and immunosupression [9]. Currently consensus is lacking on what role, if any, the addition of adjuvant chemotherapy plays in management. Advocates for adding chemotherapy point to the improved survival when adjuvant high-dose cisplatin-based chemoradiotherapy is used, compared with to radiotherapy alone in the postoperative management of mucosal HNSCC (mHNSCC) [10, 11]. However, those cautious about chemotherapy point to the paucity of data on its use for cHNSCC [12, 13], as well as the fact that many patients with this disease are elderly, have significant co-morbidities or hearing impairment, which would preclude the use of these chemotherapy regimens, especially without clear evidence of benefit.

In order to investigate the role of adding chemotherapy, the Trans-Tasman Radiation Oncology Group (TROG) is currently accruing to a multicentre, randomized phase III trial in which patients in the investigational arm receive chemotherapy with weekly carboplatin (area under the curve [AUC] 2), in addition to the standard postoperative radiotherapy. This trial, viz. TROG 05.01 Post-Operative Skin Trial (POST) NCT00193895, is outlined in Fig. 13.1. The use of weekly carboplatin (AUC 2) is a pragmatic choice, as this regimen is better tolerated than the high-dose cisplatin regimens used for mHNSCC, and hence more appropriate for this population. Also, the investigators have evidence of similar results using this regimen and weekly low-dose cisplatin—a regimen used for those unable to tolerate high-dose cisplatin—in postoperative mHNSCC [14]. As of March 2013, a total of 307 of the required 350 patients had been accrued. When the results of this trial are available, clinicians may have a better idea about the role of chemotherapy in

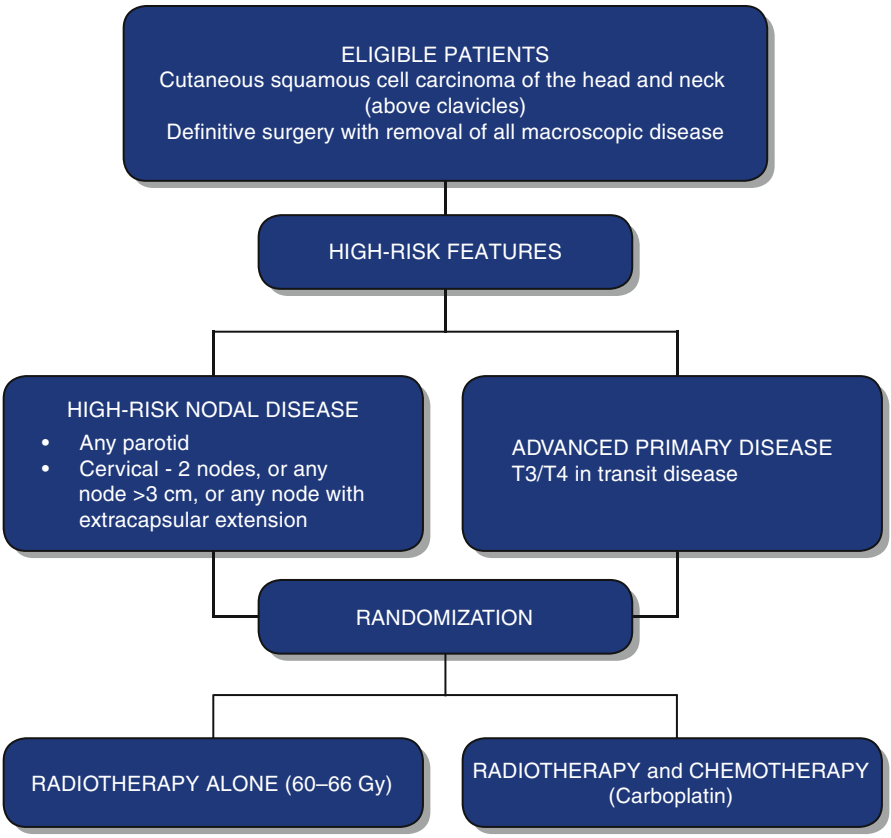

Fig. 13.1 Schema for Trans-Tasman Radiation Oncology Group phase III randomized controlled trial of postoperative concurrent chemoradiotherapy versus postoperative radiotherapy in high-risk cutaneous squamous cell carcinoma of the head and neck. TROG 05.01 Post-Operative Skin Trial

addition to radiotherapy in the management of high-risk cHNSCC, although further studies may be required to optimize the chemotherapy regimen or better characterize the high-risk factors.

De-intensification—Reducing Extent of Surgery (or Radiotherapy) in Lower-Risk Disease?

Apart from treatment escalation in high-risk groups, efforts are under way to de-intensify treatment in lower-risk groups. Metastatic involvement of the parotid gland lymph nodes from cHNSCC is in itself considered to be a high-risk feature and would fulfil the requirements of entry into the POST study (Fig. 13.1).

Current best practice includes parotidectomy (with attempt to preserve facial nerve function, if appropriate), a neck dissection (with levels according to possible primary

Table 13.1 Summary of published series showing the rates of clinically occult neck lymph nodes in patients undergoing neck dissection for cutaneous squamous cell carcinoma metastasizing to the parotid gland

Study	Study period	Total	cN+	cN0	ND in cN0	pN+ after ND
Kirke et al. [16]	1999–2008	81	30	51[a]	34	5/34 (15 %)
Audet et al. [17]	1970–2001	56	6	50	24	4/24 (17 %)
Dona et al. [18]	1983–2000	74	9	65	43	7/43 (16 %)
Ying et al. [19]	1982–2003	41	6	35	27	12/27 (44 %)
O'Brien et al. [20]	1987–1999	73	19	54	37	13/37 (35 %)

cN+ clinically node positive, *cN0* clinically node negative, *ND* neck dissection, *pN+* pathologically node positive
[a]clinically and radiologically negative

sites) followed by adjuvant radiotherapy [15]. Adjuvant radiotherapy to the parotid bed is almost always required because of the inevitable close margins, especially if the facial nerve is preserved. The rationale for elective neck treatment has arisen from multiple studies showing a significant rate of occult disease in the cervical nodes in patients undergoing neck dissection for cHNSCC that has metastasized to the parotid [16–20]. These studies were carried out in both Australia and North America and are summarized in Table 13.1. The rate of occult neck disease ranged from 15 to 44 %. This wide range may reflect the small sample size of each retrospective, single-institution study, or alternatively, it may reflect differences in case selection, utility of staging investigations or treatment philosophy between centres. Nevertheless, all these factors point to the need for some form of elective node treatment. However, only one study, by Kirke and colleagues from Brisbane, specifically addresses the rate of occult nodes in a group with 'clinically and radiologically' negative necks [16]. None of the other studies mention the use of imaging to assess the neck. Indeed the starting point of most studies pre-dates the routine use of modern imaging techniques, the use of which will inevitably reduce the rate of occult disease.

Routine preoperative imaging with computed tomography (CT) scans is now commonplace, and so the incidence of occult neck disease may not be as high as some of the earlier reports suggest.

If postoperative radiotherapy is required for the parotid bed, many radiation oncologists will also treat the surgical bed, albeit to a lower dose. However, if the rate of occult neck disease is closer to 15 % then the routine use of neck dissection and adjuvant radiotherapy is likely to represent overtreatment for the majority, especially given the known detrimental effects on long-term quality of life when radiotherapy and neck dissection are combined in patients with mHNSCC [21, 22]. This forms the rationale for the current DROPNECK study under way in Brisbane, which attempts carefully to select a group of patients with clinically and radiologically negative necks in whom neck dissection can be eliminated safely and the elective neck treatment delivered in conjunction with the adjuvant radiotherapy to the parotid bed. This low-risk group is limited to those with nodes of <6 cm, no dermal infiltration, immunocompetent patients, and patients not requiring vascular flap reconstruction. This is a single-arm safety study with the primary end-point being the rate of neck node failure as the site of first relapse. The policy will be deemed

safe if this rate is found to be ≤7 % at 2 years. A careful follow-up schedule has been established and early stopping rules are in place to terminate the study if it becomes apparent that this primary end-point is unlikely to be met.

Studies such as this can help identify a cohort of patients with lower risk in whom treatment can be de-intensified. Indeed, there may be a cohort who may be best managed with surgery and limited neck dissection without the need for radiotherapy. If such studies take place it is important that outcome measures include quality of life and cost-effectiveness, as well as standard clinical measures.

Extending the Radiotherapy Fields with High-Risk Perineural Invasion?

PNI in cHNSCC is a marker for poor outcome even with aggressive surgical and radiotherapy approaches [23]. The trigeminal (V) and facial (VII) are the most likely to be involved. In addition to the characteristic signs and symptoms, magnetic resonance imaging (MRI) can help define the extent of involvement and help plan surgery [24].

Radiotherapy is indicated after resection, usually targeting the involved primary site with a generous margin as well as 'chasing' the involved nerve. Crossover of disease from one nerve to another can occur, and this might even involve switch inside (e.g. left to right) for disease close to the midline [25].

There are also interconnections between named nerves (subdivisions of V and/or VII) on the same side that might help facilitate spread [26].

Adjuvant radiotherapy requires knowledge of the course of the relevant cranial nerves. Whereas their courses are well known [27], precise knowledge of boundaries between subdivisions and/or degree of overlap at the level of the skin is unknown. Variation exists between oncologists as to the boundaries used to demarcate fields. The choice of boundaries, such as midline [28], may be pragmatic because of limiting toxicity rather than potential routes of spread.

Fortunately, modern radiotherapy can be delivered more conformally to the shape of the target volume using intensity-modulated radiotherapy (IMRT). This will allow extension of the treatment fields to target the areas at risk while sparing low-risk tissue, thus minimizing toxicity.

However, much is still unknown about the precise pathways of spread as well as the individual variation in anatomy. Although further research is required, work is ongoing to establish consensus guidelines along similar lines to those already in common use for nodal HN volumes [29]—in order to allow a more standardized approach to radiotherapy for this uncommon clinical scenario.

Improvements in Staging

As already discussed, staging of cHNSCC involves a CT scan and an MRI scan if there is a suggestion of PNI. Whereas functional imaging, typically with [18 F] fluorodeoxyglucose positron emission tomography (FDG-PET) has an established role

and changes management in both mHNSCC [30] and advanced melanoma [31], the role of functional imaging with NMSC is less well established. Routine use of FDG-PET is not recommended with BCC because of its low risk of distant spread. However, there have been reports of metastatic BCC identified by FDG-PET [32]. Similarly, there have been reports of FDG-PET being used in the staging of cHNSCC; [33] however, high-quality evidence about its role in cSCC is lacking. This probably reflects the tendency to perform lymph node dissection followed by radiotherapy in all high-risk tumours, especially in cases of cHNSCC.

However, as focus shifts towards identifying subgroups with lower risk that may benefit from less aggressive locoregional treatment, it is likely that FDG-PET will be used more. Yet, it is important that well-designed studies are developed to try to evaluate its utility in this setting rather than simply assuming that the benefits in mHNSCC and melanoma are automatically transferred. There is a danger that routine use of FDG-PET may result in over-treatment of some patients, especially if the DROPNECK study outlined above identifies a group in which clinical assessment and CT are able to identify a group that might be safely spared routine neck dissection.

Efforts are under way in Brisbane to establish a study in which patients not eligible for DROPNECK, and thus who are planned for parotidectomy and neck dissection, undergo a FDG-PET as well as diagnostic CT before surgery. Given the consistent management approach, this study will be able to provide information on the sensitivity, specificity and clinical usefulness of FDG-PET in the management of this group of patients. This is a similar approach currently being used in the Merkel PET Phase II 'MP3' study discussed in an earlier chapter on Merkel cell carcinoma [34].

It is hoped that results of this FDG-PET cHNSCC study and the DROPNECK study will drive further research that will ultimately result in improvements in managing patients with operable cHNSCC.

Inoperable or Metastatic Disease

Chemoradiotherapy

Whereas most patients with locally advanced tumours are able to undergo curative intent surgery, a small proportion present with inoperable disease. Results with radiotherapy alone have been disappointing in this group. However, evidence has emerged showing favourable results in a small cohort of inoperable patients treated with primary chemoradiotherapy [35]. In this prospective single-centre phase II trial, 14 patients were treated with cisplatin 40 mg/m^2 or carboplatin (AUC2) concurrently with radiotherapy to a total dose of 70 Gy in 35 fractions. Encouragingly, all but one patient was able to complete radiotherapy with 42 % also receiving the planned chemotherapy. Toxicity was acceptable and the complete response rate was 57 % (8/14) with a further 2 (14 %) achieving a complete response after surgical salvage. The 3-year overall survival rate was 54 % [35].

Given the previous poor outcomes in this group, this study should form the basis of further research in order to further define the role of chemoradiation as the initial

management in cHNSCC. Similar to mHNSCC, over time there may be an increasing use of this modality to downstage tumours that are operable at presentation but where the long-term functional or cosmetic outcomes are improved by initial chemoradiation.

Targeted Therapies

As stated earlier, there is no evidence for the use of conventional cytotoxic chemotherapy as a sole agent with cHNSCC [12, 13] Therefore, current research continues to focus on the role of targeted therapies in advanced disease.

Targeting the epithelial growth factor receptor (EGFR) has recently shown some success. Both large molecule antibodies (cetuximab) [36] and small molecule tyrosine kinase inhibitors (TKIs), such as gefitinib [37], have had moderate success in treating locally advanced or metastatic SCC. Targeting the EGFR in both these phase II studies of patients with either locally advanced or metastatic cSCC showed response rates of ~70 %. While encouraging for further research, it is not yet clear how durable the response is and whether response is related to levels of receptor expression or mutations in downstream proteins.

A different pathway has been identified in advanced BCC. In 2009, a phase I study by Von Hoff and colleagues showed that an oral inhibitor of the hedgehog pathway had anti-tumour effect in metastatic BCC [38]. Further studies have shown objective response rates of 30–40 % when this drug (vismodegib) is used in inoperable or metastatic BCC [39].

Also, in a randomized phase III trial of vismodegib versus placebo, established BCCs were more likely to regress and new BCCs were less likely to occur in patients with the basal cell nevus syndrome who were on active treatment. However, 54 % of patients discontinued the drug due to toxicity (mainly loss of taste, hair and weight, and muscle cramps) [40].

The clinical role of vismodegib, although clearly an active drug, needs to be better defined, given its toxicity. An active research programme is under way targeting the hedgehog pathway with the hope that other drugs might be identified that may be clinically useful for the rare phenomenon of advanced or metastatic BCC [41].

Key Points

- NMSC will remain an important health issue in the future.
- Current research is aimed at methods of escalating treatment in high-risk disease (chemoradiation) or de-intensifying treatment in lower-risk patients (reducing the extent of surgery and/or radiotherapy fields).
- Concurrent definitive chemoradiation is likely to become the treatment of choice in suitable patients with inoperable disease.
- Functional imaging with PET scanning may become useful in tailoring treatment to individual patients.
- Targeted drugs will have an increasing role in the management of advanced SCC and BCC.

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