53 Oral cavity cancer

ACKNOWLEDGEMENTS

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The authors acknowledge Professor RJ Shaw , Professor JS Brown and Professor C Butterworth for clinical photographs utilised in this chapter. ACKNOWLEDGEMENTS

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(b) (b) The resection cutting plane with the scapula

treatment for oral cavity cancer. Adjuvant therapy is given based on pathological features of the tumour. Radiotherapy is administered typically via external beam radiotherapy . In high-risk cases, chemotherapy (usually cisplatin-based) is included as a radiosensitiser within the adjuvant regime for suitably fit patients. As outlined in previous sections, the adverse patholog ical features associated with locoregional recurrence and decreased overall and disease-specific survival include ENE, close/involved margins, LVI and PNI. It is these, among other, adverse features that infor m the decision to administer adju vant therapy . While there is no absolute international agreement regard - ing the criteria for radiotherapy , the current consensus is that one major criterion (ENE and/or involved margin [<1 /uni00A0 mm]) or two minor criteria (close margin [1–4.9 /uni00A0 mm], multiple VI/PNI, T3/4) would involved nodes, largest node >3 /uni00A0 cm, L 8 indicate the need for adjuvant radiotherapy . -

Figure 53.15 Series demonstrating the management of a T4 squamous cell carcinoma involving the right anterior /f_l oor of the mouth, mandible and overlying skin. Virtual surgical planning and cutting guides were used to harvest and inset the scapula free /f_l ap.

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Adjuvant chemoradiotherapy

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The landmark RTOG 9501 and EORTC 22931 randomised - trials form the basis for the contemporary role of adjuvant chemotherapy (CRT) in high-risk OCSCC (although only 25% benefit conferred by adding high-dose cisplatin to conventional postoperative radiotherapy (RT), with primary end points of locoregional control and progression-free survival, respectively . Positive surgical margins and extracapsular extension (ECE; now ENE) were used to classify patients as high risk in both studies, while several other criteria unique to each were also investigated. Ultimately , and following several associated long term, subgroup and pooled analyses, these trials provided strong evidence for the use of concurrent cisplatin-based CRT in high-risk patients. Adjuvant chemoradiotherapy

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Biopsy Primary tumour

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Histopathological diagnosis via a formal biopsy is the gold standard prior to further investigation and treatment. An incisional biopsy is preferred. It is important to avoid necrotic areas, and a narrow deep biopsy is more useful than a shallow broad one. Other biopsy techniques such as exfoliative cytol ogy and brush biopsy lack sensitivity and are therefore not commonly employed.

(d) (a) Right ventral tongue SCC. (b) Right soft palate SCC.

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Bone invasion

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Three patterns of bone invasion, namely infiltrative, erosive or mixed, have been described. There is strong evidence that most tumours enter the bone at the point of contact in an erosive fashion, and not via foramina or the periodontal membrane. It is important to point out that cortical erosion as opposed to medullary invasion does not equate to a T4 tumour. Bone invasion

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DIAGNOSIS AND WORK-UP

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These can be summarised as follows: /uni25CF history and examination; /uni25CF biopsy; /uni25CF clinical and radiographic staging investigations; /uni25CF comorbidity and functional status; /uni25CF multidisciplinary team (MDT)/tumour board discussion and treatment plan formulation; /uni25CF pathological staging; /uni25CF adjunctive treatments if appropriate. When a lesion is suspicious for malignancy , a histopatho - logical diagnosis is essential. Prior to this a thorough history and examination of the oral cavity , oropharynx and neck should be completed. Radiographic assessment, in the form of a CT and MRI, is also mandatory . In some centres sentinel lymph node biopsy (SLNB) has become an established technique used f or investi - gation and staging of early oral cancers that hav e no clinical or radiographic evidence for cervical metastases. A positive SLNB necessitates subsequent management of the neck (typi - cally with completion neck dissection). EUA is often used to further assess a tumour, especially in - cases where a biopsy is not possible in the outpatient setting or where the extent of the tumour cannot be properly assessed via clinical examination in an awake patient. An EUA can sup - port trea tment planning and decision making with regards to access, extent of resection and reconstructive plans.
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There is considerable geographical variation in the incidence of oral cancers worldwide, reflecting di ff ering lifestyles and risk factor exposure. For clarity , and in keeping with the 11th revision of the International Classification of Diseases (ICD-11), we will include cancers of the lip, gum, tongue, palate and floor of the mouth as well as the rest of the mouth in oral cavity cancer. Cancers of the nasopharynx, hypopharynx and major salivary glands are excluded. The oropharynx includes the base of the tongue, the soft palate/uvula, the pharyngeal walls and the tonsils. Cancers arising in the oropharynx are discussed separately in Chapter 52 . EPIDEMIOLOGY

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Histological type

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Imaging

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Contemporary cross-sectional imaging techniques are essen - tial in the management of head and neck cancer. They inform treatment decisions and prognosis. CT and/or MRI are the gold standard imaging modalities to stage a tumour of the oral cavity . Plain film radiography and ultrasonography , along with positr on emission tomography–computed tomography (PET - CT) are useful adjuncts. The aims of imaging are as follows: /uni25CF outline the anatomical extent of the primary tumour (T - stage), as well as the ‘resectability’ of the tumour based on its relationship to vital structures; /uni25CF detection of metastatic disease precluding cure; /uni25CF detection of synchronous primary tumours of the lung and upper aerodigestive tract; /uni25CF monitoring of disease response following non-surgical treatment and for detection of disease recurrence. Computed tomography Contrast-enhanced CT (CECT), typically modern multi- detector slice computed tomography (MDCT), is a commonly available staging tool. This o ff ers the advantage of rapidly acquired spatially accurate cross-sectional images. Hard-tissue detail is a particular advantage of CT , relative to MRI; this is particularly important when assessing bony involvement (mandible/maxilla) in oral SCC. CT is also the usual imaging modality for thoracic staging. Magnetic resonance imaging By comparison with CT , MRI has improved soft-tissue contrast resolution and, depending upon specialist radiologist preference, it is frequently the imaging modality of choice for defining the primary extent of oral cavity cancers. Addition ally , it o ff ers more information on perineural spread and bone marrow invasion. T1-weighted ‘anatomical’ images have good spatial resolution, while T2-weighted images preferentially highlight oedema and therefore pathology . MRI has a sensitivity of 82% and specificity of 66.7% for the detection of bone/bone marrow invasion in the mandible. The ability of MRI to detect neck metastases is comparable to that of CT . Positron emission tomography combined with computed tomography PET-CT is not a first-line imaging investigation for head and neck cancer and its use is usually restricted to detection of distant metastases or synchronous tumours, investigation of tumours of unknown primary and post-treatment surveillance. Plain film and panoramic radiographs Plain film or panoramic radiographs can be helpful in defining gross bony involvement during tumour staging; however, their main utility is for evaluation of the dentition to plan essen tial prophylactic dental treatment and highlight infection or inflammation. Ultrasound Ultrasonography is a non-invasive, chair-side investigation that is now most commonly used to guide FNAC sampling of suspi cious lymph nodes. It is operator dependent but in experienced hands is very useful in the detection of lymphadenopathy . It is of limited value in investigation of oral cavity tumours. It has 85% sensitivity and 78.9% specificity for cervical lymphade nopathy . Sentinel lymph node biopsy Sentinel lymph node biopsy (SLNB) has become a recognised technique to support staging of the neck in patients who do not have clinical or radiological evidence of lymph node cancer cells are most likely to spread. SLNB seeks to determine the presence of nodal metastasis within the first draining node(s) and guides the necessity (or otherwise) for further treatment of the neck. There is robust evidence that, in patients with a T1/2 oral cavity SCC, perf orming a prophylactic elective neck dissection as opposed to adopting a ‘watch and wait’ policy leads to 3 superior overall and

disease-free survival. However, not all patients will have nodal metastases and as such provision of a neck dissection for all will inevitably result in overtreatment of a significant proportion. SLNB can be utilised to highlight those patients with occult metastases and who can then proceed to formal neck dissection. Additionally , SLNB may demonstrate unexpected contralateral lymph node drainage that would not otherwise have been identified or treated. Despite its potential 4 benefits, the SLNB technique has a false-negative rate of 14%. To date, evidence providing a comparative analysis of elective neck dissection versus SLNB (where survival is the primary end point) is still lacking. - Imaging

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Immunotherapy

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Antitumour immunotherapy is based on the principle that tumours can sometimes escape immune response/checkpoints owing to adaptations in immune surveillance and the tumour microenvironment. Immunotherapy represents a change in the treatment paradigm. The pathway of the programmed death receptor-1 (PD-1) and its ligand (PD-L1) has become an increasingly important target for immunotherapy in HNSCC. The receptor–ligand interaction is a major mechanism used by tumours to evade the imm une system. Multiple randomised phase III trials have demonstrated that exposure to a PD-1 inhibitor prolongs sur vival in recurrent or metastatic HNSCC. These results, among others, highlight the potential for research assessing the role of checkpoint inhibition in the man agement of HNSCC. Immunotherapy

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Incidence

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There are approximately 350 /uni00A0 000 new cases of oral cavity cancer per year worldwide. The vast majority of these are squamous cell carcinomas (SCCs). In 2015, the estimated age-standardised ratio of oral cavity cancer was 5.8 in men and 2.3 in women per 100 /uni00A0 000. This 2:1 ratio has narrowed recently but still probably reflects the higher consumption of alcohol and tobacco by men worldwide. Two-thirds of all oral cancers occur in low-income countries, with half of those in South Asia. India, for example, has 100 /uni00A0 000 new cases per annum. Rates of oral cancer vary significantly worldwide. High- incidence areas include South East Asia, Papua New Guinea, parts of western Europe (e.g. Portugal and France), parts of eastern Europe (e.g. Slovakia and Hungary), as well as areas in - Latin America (e.g. Brazil). The incidence of oral cancer increases with age, with most cases occurring in those over 50 years. The mean age at presentation is 62 years, with a strong correlation between lo wer socioeconomic class and disease incidence. However, there is an increasing trend for cases a ff ecting younger patients (45 /uni00A0 years or younger), many of whom lack exposure to tradi - tional risk factors. The 5-year survival rate for early-stage cancers is 80%. Despite recent advances, the overall 5-year survival for oral cancer has not markedly improved and remains at 50%. In South Asia, this figure is often below 50%, with a reported 5-y ear survival of 35% in India.

Broad steps necessary for investigation and management • of oral cavity cancers

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Introduction

INTRODUCTION

The oral cavity (Figure 53.1) extends from the mucosal surface of the lips to the junction of the hard and soft palate. It does not include the soft palate, uvula or tonsils, which form part of the oropharynx. Oral cavity cancer is the eighth most common cancer worldwide, with an estimated 350 /uni00A0 000 cases arising annually . While there have been significant advances in the understanding and management of oral cavity cancer, the morbidity and prognosis associated with it have remained largely unchanged. In this chapter, we will outline the aeti ology and epidemiology of oral cavity cancer, as well as risk factors for this disease, and highlight important geographical variations. Additionally , we will explore the in vestigation and management of oral cavity cancer. Lastly , we will outline emerging techniques and technologies utilised in oral cavity cancer treatment.

Learning objectives

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To understand: The epidemiology and aetiology of oral cancer • The cardinal features of malignant lesions of the oral • cavity (signs and symptoms) Learning objectives

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Lymphovascular invasion

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Routine assessment of the chest (as a minimum) for evidence of distant metastasis and/or synchronous lung primary tumours is the norm as part of staging prior to treatment. M0 denotes no distant metastases, whereas M1 signifi es distant metastases present. The presence of any distant metastases automatically places a patient in the stage 4C group, currently without cura tive therapeutic options. M stage

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Patients with a low burden of disease or oligometastatic deposit(s) and a satisfactory performance status can be o ff ered salvage surgery and/or radiotherapy with curative intent. Patients with are eligible for systemic treatment. Current standard of care options depend on previous exposure to platinum-containing c hemotherapy , but include both immunotherapy and palliative chemotherapy regimens. Nonetheless, the poor prognosis for these patients remains. - MANAGEMENT OF RECURRENT AND/OR METASTATIC DISEASE

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Metastases

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As outlined previously , HPV-negative cervical node metastases are associated with decreased overall and disease-specific survival. While skip metastases have been described, most OCSCC metastases occur in levels I and II of the neck. ENE occurs when the capsule is breached and this is now accounted for in the UICC/AJCC eighth edition TNM staging system. Distant metastases are rare in OCSCCs, with reported rates of 2–9%, and are associated most commonly with ENE and bilateral neck disease. Metastases

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Molecular biology

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According to The Cancer Genome Atlas (TCGA), alterations in p53 (83%) and CDKN2A (57%) are the two most frequent genomic mutations noted in HPV-negative cancers of the head and neck (of which oral cancer is an example). This contrasts with HPV-positive tumours, found most frequently in the oropharynx, which have a considerably lower mutational burden and consistently retain p53 ‘wild-type’ status. It is, however, important to note that, as yet, the current standard of care in head and neck squamous cell carcinoma (HNSCC), - including oral cavity cancers, is not based on or influenced by genetic profiling or molecular biology . Molecular biology

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N stage

N stage

The system for describing the anatomy of regional lymph node metastases has been well described previously and is outlined in Figure 53.3 . It divides the lateral neck nodes into five sepa - rate levels, based on their relationship to certain anatomical structures. SCC in the oral cavity and lips tends to metastasise to lymph nodes at levels I, II and III. However, with SCC of the or or oral tongue there is a risk of skip metastasis directly to lymph node levels III or IV , without the involvement of higher level lymph node groups. By contrast, tumours arising in the oro pharynx commonly metastasise to lymph node levels II–IV , as well as retropharyngeal and contralateral nodal groups. In addition to the number , size and location of involved nodes, ENE has now been included as a contributor to nodal staging (Table 53.2). ENE has been reliably shown to be an adverse prognosticator in all oral cavity tumours.

Joint Committee on Cancer (AJCC) tumour–node– metastasis (TNM) staging manual, 8th edition. T category T criteria TX Primary tumour cannot be assessed Tis Carcinoma in situ T1 Tumour ≤ 2 /uni00A0 cm, ≤ 5 /uni00A0 mm DOI T2 Tumour ≤ 2 /uni00A0 cm, DOI >5 /uni00A0 mm and ≤ 10 /uni00A0 mm tumour

> 2 /uni00A0 cm but ≤ 4 /uni00A0 cm, and ≤ 10 /uni00A0 mm DOI T3 Tumour >4 /uni00A0 cm any tumour >10 /uni00A0 mm DOI T4 Moderately advanced or very advanced local disease T4a Moderately advanced local disease: (lip) tumour invades through cortical bone or involves the inferior alveolar nerve, /f_l oor of mouth or skin of face (i.e. chin or nose); (oral cavity) tumour invades adjacent structures only (e.g. through cortical bone of the mandible or maxilla, or involves the maxillary sinus or skin of the face); note that super /f_i cial erosion of bone/tooth socket (alone) by a gingival primary is not suf /f_i cient to classify a tumour as T4 T4b Very advanced local disease; tumour invades masticator space, pterygoid plates or skull base and/or encases the internal carotid artery DOI, depth of invasion (not tumour thickness). Reproduced with permission from AJCC, Chicago, IL, USA. The original source for this material is the AJCC Cancer Staging Manual 8th edition (2017) published by Springer Science+Business Media LLC (springer.com) (Amin MB, Edge SB, Greene FL et al . (eds). AJCC cancer staging manual , 8th edn. New York, NY: Springer International Publishing: American Joint Commission on Cancer, 2017).

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> 2 /uni00A0 cm but ≤ 4 /uni00A0 cm, and ≤ 10 /uni00A0 mm DOI T3 Tumour >4 /uni00A0 cm any tumour >10 /uni00A0 mm DOI T4 Moderately advanced or very advanced local disease T4a Moderately advanced local disease: (lip) tumour invades through cortical bone or involves the inferior alveolar nerve, /f_l oor of mouth or skin of face (i.e. chin or nose); (oral cavity) tumour invades adjacent structures only (e.g. through cortical bone of the mandible or maxilla, or involves the maxillary sinus or skin of the face); note that super /f_i cial erosion of bone/tooth socket (alone) by a gingival primary is not suf /f_i cient to classify a tumour as T4 T4b Very advanced local disease; tumour invades masticator space, pterygoid plates or skull base and/or encases the internal carotid artery DOI, depth of invasion (not tumour thickness). Reproduced with permission from AJCC, Chicago, IL, USA. The original source for this material is the AJCC Cancer Staging Manual 8th edition (2017) published by Springer Science+Business Media LLC (springer.com) (Amin MB, Edge SB, Greene FL et al . (eds). AJCC cancer staging manual , 8th edn. New York, NY: Springer International Publishing: American Joint Commission on Cancer, 2017).

Neck lump

Neck lump

Fine-needle aspiration cytology (FNAC) is the first-line biopsy for the investigation of neck lymphadenopathy . This technique carries a sensitivity of 89–98%. It will help in di ff erentiating between thyroid malignancy , oropharyngeal and oral cavity lesions (utilising HPV diagnostic tests) and lymphoma. Neck lump

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Oral cavity

Oral cavity

All sites in the oral cavity are examined under direct visual - isation. Table 53.4 details the signs and symptoms that are suggestive of a neoplastic process. Figure 53.4 demonstrates the wide clinical presentation of OCSCCs, which range from small areas of (erythro)leukoplakia to larger erosive and cavitated lesions that invade surrounding tissues. Reduced tongue movement, sensory nerve deficit, trismus, otalgia and dysphagia are all in keeping with late-stage disease. Fibreoptic examination is not routinely performed in oral cavity assess - ment but may support assessment of the posterior extent of the tumour. The incidence of synchronous primary tumours of the upper digestive tract is 2.4–4.5%. /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF

TABLE 53.4 Signs and symptoms of oral cavity neoplasm. Signs Symptoms Sensory nerve de /f_i cit Non-healing ulcer (>2 weeks) Chronic otalgia Persistent neck mass/ lymphadenopathy Trismus of unknown aetiology Lesion, pigmentation with progressive increase in size Dysphagia Lesion with associated induration Persistent red or white lesion Non-resolving ‘in /f_l ammatory’ lesion Soft-tissue lesion with associated radiographic changes Unexplained tooth mobility

(c) Figure 53.4 Clinical presentations of oral cavity squamous cell carcinoma (SCC). Note the cardinal features consistent with malignancy; namely speckled appearance, raised rolled edges, contact bleeding and variable ulceration. (c) /uni00A0 Left posterolateral tongue SCC. (d) Right lateral tongue SCC.

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PATHOLOGY OF ORAL CANCERS

PATHOLOGY OF ORAL CANCERS

The vast majority (>95%) of oral cavity cancers are squamous cell carcinomas (OCSCCs). The World Health Organization (WHO) tumour grading system, based on cellular di ff erentia - tion, is routinely used in pathological analysis and diagnosis of OCSCC. The histological parameters routinely described in OCSCC include: /uni25CF histological type; /uni25CF tumour grade/di ff erentiation; /uni25CF pattern of invasion; /uni25CF tumour thickness and DOI; /uni25CF perineural invasion (PNI); /uni25CF lymphovascular invasion (LVI); /uni25CF bone involvement; /uni25CF nodal metastases. PATHOLOGY OF ORAL CANCERS

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Patient selection

Patient selection

As outlined previously , patients’ comorbidities and functional status as well as their social circumstances play a significant role - in their ability to tolerate surgery and rehabilitation. The early involvement of an MDT including physicians, anaesthetists, physiotherapists and dieticians is important particularly in high-risk patients in order to optimise their performance status - preoperatively . The ‘operability’ of a tumour is determined largely by its size and relationship to important anatomical structures of the head and neck. In the AJCC eighth edition TNM staging sys - tem T4b tumour s are those that may be unresectable owing to involvement of or proximity to the skull base, masticator space, ptery goid plates and/or the internal carotid artery . Once the decision has been made that surgery is appropriate, a few key decisions are to be made. These are as follows: /uni25CF airway management; /uni25CF access to the tumour; /uni25CF tumour resection; /uni25CF management of the neck; /uni25CF reconstruction. Airway management Airway management in patients undergoing surgery for OCSCC is largely centred on protecting the airway against acute embarrassment in the perioperative period. The available options are immediate postoperative extubation, overnight intubation/delayed extubation, submental intubation and tracheostomy . The choice of airway is a joint decision made between the anaesthetist and surgeon, and is influenced heavily by the ability to re-establish a patient’s airway quickly should a life-threatening event occur. Immediate postoperative extuba tion is generally reserved for smaller well-lateralised tumours in uncomplicated patients who may not require reconstruction. In selected patients, overnight intubation is considered when tracheostomy is unlikely yet can still be sited on postopera day 1 if warranted; this approach is burdensome on resources given the higher level of care for the first night, but it reduces length of stay via a quicker restoration of speech and swallow . A low threshold for placing a tracheostomy is appropriate in patients having a bilateral neck dissection or previous neck dissection; large resection with reconstruction; and in patients with a di ffi cult airway . Consideration should also be given to placing a tracheostomy in patients having a segmental mandibular resection; lateralised resections involving the floor of mouth and reconstruction; as well as previously irradiated patients. Access surgery The goal in surgical management of OCSCC is to remove the tumour with an adequate margin circumferentially . While most tumours can be removed via a transoral approach, some cannot be resected safely without an access procedure. These might include large maxillary tumours, posteriorly located tumours and tongue base tumours, or patients who have previ ously had surgery and/or radiotherapy . The most commonly used access procedures include the lip-split mandibulotomy (LSM) (Figure 53.5), the mandibular lingual release, the visor flap and the Weber–Fergusson approach (Figure 53.6), w provides excellent access to the maxilla and, if extended infra orbitally , to the periorbital area. Lip-split mandibulotomy This is the most commonly used access procedure and provides excellent access to the posterior oral cavity , tongue base and oropharynx. It involves making an osteotomy in the mandible in order to ‘swing’ it laterally , thereby facilitating access. Care must be taken to ensure that the lingual mucosa does not tear in an uncontrolled fashion towards the tumour resection margin. Sir William Fergusson , 1808–1877, Scottish surgeon, described and published a

modification of the original Weber incision to access the midface. The gold standard in OCSCC is resection with a 1-cm clinical margin circumferentially , vital structures permitting. Mandibular resection Decisions regarding management of the mandible when tumour lies close to, abuts or invades the bone are critical. If there is evidence of infiltrative bone invasion, either segmental or rim resection of the involved mandible is required. Segmental resection involves removing the full height of the invaded section of the mandible such that there is loss of continuity of the lower border. Rim resection or ‘marginal mandibulectomy’ inv olves removing a partial thickness of mandible such that continuity of the lower border remains. A rim resection is sometimes performed when a tumour lies close to but does not definitively invade the mandible, in order to achieve a satisfactory soft-tissue margin. Maxillary resection - Owing to anatomical di ff erences such as thinner bone, the presence of sinuses, tightly adherent palatal mucosa and prox - imity to the orbit and skull base, maxillary resection consid - erations di ff er from those in the mandible. Small tumours of tive the maxillary alveolus can be managed by transoral partial maxillectomy . More extensive tumours involving the floor of the maxillary sinus require wider access by a Weber–Fer gusson incision (Figure 53.6). If the preoperative investigations demonstrate extension of the disease into the pterygoid space or the infratemporal fossa, the prognosis is poor as surgical clearance is di ffi cult or not possible. Tumour extending into the orbit requires simultaneous orbital exenteration or, in some instances, a combined neurosurgical resection. The various methods of maxillary reconstruction can be guided by the extent of resection and tissues involved. Reconstruction seeks to provide an oral seal and restore facial profile and tissue loss, while facilitating a means to achieve dental rehabilitation. Management of the neck In surgical terms, ‘management of the neck’ refers to a neck dissection – elective or therapeutic. In patients with clinical and/or radiographic evidence of cervical metastases, treat - ment of the neck in the form of a therapeutic neck dissection - is indicated (primary radiotherapy is less common). In patients with early-stage disease and in whom there is no clinical or radiographic evidence for cervical metastases, there is now strong evidence showing that patients w ho have an up-front or hich elective neck dissection have better overall and disease-specific - survival relative to patients who have a ‘watch-and-wait’ policy and a therapeutic neck dissection only when a metastasis 5 becomes apparent. SLNB can be utilised as a staging investi - gation to better guide the indications for a neck dissection in the setting of a small tumour where occult metastases may still be present. Over the last 100 years, neck dissections have evolved to achiev e a less radical extent as evidence emerged for the onco - 6 logical safety of more selective or nuanced procedures. For elective neck dissections, a selective neck dissection involving levels I–III of the neck is indicated for the management of 7 OCSCC. A neck dissection is performed not only to stage a disease and aid prognosis, but also for therapeutic purposes as well as informing the need for adjuvant therapy . Additionally , it pro - vides access to recipient vessels within the neck, which may be used in microvascular free tissue reconstruction.

Figure 53.5 Lip-split mandibulotomy. Figure 53.6 Weber–Fergusson approach.

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Figure 53.5 Lip-split mandibulotomy. Figure 53.6 Weber–Fergusson approach.

Pattern of invasion

Pattern of invasion

The pattern of invasion refers to the shape of the advancing front or border of the tumour. Like tumour grade/di ï¬€ erentiation, it is of important prognostic value. The UK Royal College of Pathologists recommends the grading of pattern of invasion into two broad categories: cohesive and non-cohesive. Pattern of invasion

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Perineural invasion

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While there is no clear consensus on the criteria for diagnos ing PNI, it is generally described as being present if at least one-third of the circumference of a nerve is surrounded by tumour cells and/or if deposits of tumour are found in any of the three lay ers of the nerve sheath. PNI is a marker for the biological aggressiveness of a tumour and an independent risk factor for cervical metastases, local recurrence and therefore poorer prognosis. Perineural invasion

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Prognostic stage groupings

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The eighth edition AJCC stage groupings are outlined in Table 53.3 . - -

0.8 0.6 0.4 Cumulative survival T1 0.2 T2 T3 T4 0.0 0 10 20 30 40 50 60 Time (months) No. of patients 0 12 24 36 48 60 T1 429 376 313 262 222 179 T2 564 460 345 276 233 191 T3 377 286 206 180 151 121 T4 422 256 166 133 108 83 Figure 53.2 The in /f_l uence that T stage, and therefore depth of invasion, has on overall survival. (Reproduced with permission from , AJCC, Chicago, IL, USA. The original source for this material is the AJCC Cancer Staging Manual , 8th edition (2017) published by Springer Science+Business Media LLC (springer.com) (Amin MB, Edge SB, Greene FL et al . (eds). AJCC cancer staging manual , 8th edn. New York, NY: Springer International Publishing: American Joint Commission on Cancer, 2017).) IB IA IIA IIB III VA VI VB IV Figure 53.3 Cervical lymph node levels.

Albert Compton Broders , 1885–1964, American pathologist, Minnesota, USA, and Chairman of the Department of Surgical Pathology , The Mayo Clinic, Rochester, MN, USA; for 1 year in 1935 Professor of Surgical Pathology and Director of Cancer Research, University of Virginia, V A, USA.

the American Joint Committee on Cancer (AJCC) tumour– node–metastasis (TNM) staging manual, 8th edition. a N category N criteria NX Regional lymph nodes cannot be assessed N0 No regional lymph node metastasis N1 Metastasis in a single ipsilateral lymph node, 3 /uni00A0 cm or less in greatest dimension and ENE- negative N2 Metastasis in a single ipsilateral lymph node, 3 /uni00A0 cm or less in greatest dimension and ENE- positive; or more than 3 /uni00A0 cm but not more than 6 /uni00A0 cm in greatest dimension and ENE- negative; or metastases in multiple ipsilateral lymph nodes, none more than 6 /uni00A0 cm in greatest dimension and ENE-negative; or metastases in bilateral or contralateral lymph nodes, none more than 6 /uni00A0 cm in greatest dimension and ENE-negative N2a Metastasis in a single ipsilateral or contralateral lymph node 3 /uni00A0 cm or less in greatest dimension and ENE-positive; or metastasis in a single ipsilateral lymph node more than 3 /uni00A0 cm but not more than 6 /uni00A0 cm in greatest dimension and ENE-negative N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 /uni00A0 cm in greatest dimension and ENE-negative N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 /uni00A0 cm in greatest dimension and ENE-negative N3 Metastasis in a lymph node more than 6 /uni00A0 cm in greatest dimension and ENE-negative; or metastasis in a single ipsilateral lymph node more than 3 /uni00A0 cm in greatest dimension and ENE-positive; or metastasis in multiple ipsilateral, contralateral or bilateral lymph nodes, with any ENE-positive N3a Metastasis in a lymph node more than 6 /uni00A0 cm in greatest dimension and ENE-negative N3b Metastasis in a single ipsilateral lymph node more than 3 /uni00A0 cm in greatest dimension and ENE-positive; or metastasis in multiple ipsilateral, contralateral or bilateral lymph nodes, with any ENE-positive ENE, extranodal extension. a Note that a designation of ‘U’ or ‘L’ may be used for any N stage to indicate metastasis above the lower border of the cricoid (‘U’) or be low the lower border of the

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Reconstruction following tumour ablation is a key component in the management of OCSCC. Decision making with regards to reconstruction should not influence the ablative procedure. Notwithstanding the importance of facial aesthetics, preser - vation or restoration of speech, chewing, swallow and oral continence are of paramount importance. The oral cavity is a unique site. It contains hard and soft tissues, including the dentition, is bathed in saliva and is anatomically complex. It ultitude is the opening to the aerodigestive tract and has a m of motor and sensory nerves. Like any defect, reconstruction of the oral cavity should aim to replace resected tissue with similar tissue. The reconstruction ladder (Figure 53.7) is a useful algorithm and can be applied to the oral cavity . Additionally , general reconstruction principles apply: namely , use the simplest method that will meet reconstruction aims, replace lost tissue with similar tissue, consider vascular - ised tissue in a previously irradiated recipient site and alwa ys ve an alternative should your primary reconstruction fail. ha While free tissue transfer (‘free flaps’) has revolutionised reconstruction following ablation of an OCSCC, there are instances, for example owing to patient comorbidities, where a local or regional flap is appropriate. Owing to the extensive and consistent blood supply in the head and neck, local flaps in this region are safe and pre dictable. Smaller defects not requiring substantial soft tissue or bone for reconstruction can be reliably reconstructed with flaps such as, but not limited to, the facial artery m yomucosal (FAMM), nasolabial, buccal fat pad, tongue and palatal flaps Regional and pedicled flaps include tissue(s) from other parts of the head and neck, such as the temporalis and platysma flaps, as well as those from more distant sites such as the latissi mus dorsi, deltopectoral and pectoralis major flaps. Free flaps A free flap is a portion of vascularised tissue harvested from a distant donor site and transferred to an area requiring recon struction where its artery and vein are anastomosed locally , thereby providing an independent blood supply . Most tissue types, including skin, fascia, muscle, tendon and bone, can be tissue can be replaced with similar tissue(s). Soft-tissue reconstruction In oral cavity reconstruction, common soft-tissue flaps used include the radial forearm free flap (RFFF; Figure 53.8) and anterolateral thigh (ALT) flap. Alternative soft-tissue free flaps include rectus abdominis, latissimus dorsi, medial sural artery perforator and lateral arm flaps. The relative merits of these flaps are outlined in Table 53.5 . Composite reconstruction The fibula is the most commonly used bone-containing (composite) flap globally , while the iliac crest (DCIA), scapula (including tip of scapula) and composite RFFFs are also used, each carrying specific pros and cons. Chimeric flaps, where osseous and soft-tissue components are independently mobile (e.g. the thoracodorsal system of free flaps), are advocated for certain complex reconstructions. The relative merits of the more common composite flap donor sites are outlined in - Table 53.6 . Reconstruction by anatomical subsite Soft-tissue reconstruction . Intraorally this includes the tongue, floor of the mouth, buccal and retromolar mucosa as well as the soft palate. As outlined - previously the most commonly used soft-tissue flaps are the RFFF and ALT . The RFFF provides a thin, non-hirsute and pliable flap with a long vascular pedicle and so can be useful where significant bulk is not required. The ALT (Figure 53.9), however, owing to its increased bulk, is far more suited to - tongue

reconstruction where bulkiness is crucial in creating a seal between the oral cavity and soft palate during speech and swallowing. The ALT also facilitates multiple skin paddles and/or muscle components, where necessary .

• Healing by secondary intention • Primary closure • Skin grafting • Local /f_l aps • Regional /f_l aps • Microvascular free tissue transfer Figure 53.7 The reconstruction ladder. TABLE 53.5 Relative merits of common soft-tissue /f_l aps. Donor site RFFF ALT MSAP Donor site +++ ++ ++ morbidity Pedicle length ++++ +++ ++ 18 /uni00A0 cm 12 /uni00A0 cm 10 /uni00A0 cm Quality of ++++ +++ +++ vessels Artery: Artery: Diameter Artery: 3 /uni00A0 mm 1.25 /uni00A0 mm 2.1 /uni00A0 mm Vein: 1.5 (3 /uni00A0 mm if Vein: 2 /uni00A0 mm Vein: cephalic) 2.3 /uni00A0 mm No atherosclerosis Soft-tissue ++ ++++ ++ paddle 12 /uni00A0×/uni00A0 5 /uni00A0 cm 16 /uni00A0×/uni00A0 8 /uni00A0 cm 10 /uni00A0×/uni00A0 5 /uni00A0 cm Two-team +++ ++++ ++++ operating ALT, anterolateral thigh; ELAF , extended lateral arm /f_l ap; LD, latissimus dorsi; MSAP , medial sural artery perforator; RFFF , radial forearm free /f_l ap; TDAP , thoracodorsal artery perforator. TDAP Lateral arm Rectus LD ++ ++ +++ ++ + ++ ++++ + 7 /uni00A0 cm 8.5 /uni00A0 cm 15 /uni00A0 cm 6 /uni00A0 cm; increased with ELAF ++++ ++ ++++ ++++ Artery: 2.7 /uni00A0 mm Artery: Artery: Artery: 2.7 /uni00A0 mm Vein: 3.4 /uni00A0 mm 3.5 /uni00A0 mm 1.5 /uni00A0 mm Vein: 3.4 /uni00A0 mm No atherosclerosis Vein: 4 /uni00A0 mm Vein: 2.5 /uni00A0 mm No atherosclerosis ++++ ++++ ++ +++ Muscle: 35 /uni00A0×/uni00A0 20 /uni00A0 cm 25 /uni00A0×/uni00A0 10 /uni00A0 cm 12 /uni00A0×/uni00A0 5 /uni00A0 cm Muscle: Skin: 18 /uni00A0×/uni00A0 7 /uni00A0 cm 6 /uni00A0×/uni00A0 25 /uni00A0 cm Skin: 13 /uni00A0×/uni00A0 25 /uni00A0 cm + ++ +++ +

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Mandible reconstruction Reconstruction with composite free flaps is now the gold standard for segmental mandibular defects (Figures 53.10 and 53.11). The choice of flap is varied and depends on factors including the site, size and complexity of the defect, patient comorbidities and indeed surgeon training and preference. While it is possible to leave small posterior sites unrecon structed, reconstruction of an anterior defect is particularly important, and challenging, in order to achieve satisfactory function for the patient. The following general principles may help to plan mandib ular reconstruction: /uni25CF reconstruction of the anterior mandible is always more challenging; /uni25CF although the lengths of the bone and pedicle are often cited as factors in choosing the

donor site, the average defect is 6–10 /uni00A0 cm and usually immediately adjacent vessels for microvascular anastomosis mean that these are not usually an impediment; /uni25CF use the curvature of the chosen bony flap to follow the nat ural shape of the mandible, thereby reducing the number of potential osteotomies; /uni25CF in an edentulous case, it may be helpful to slightly reduce the span of the mandibular segment to avoid a resultant class III appearance, where the mandible protrudes beyond the opposing maxilla, giving a very prominent chin position; /uni25CF free bone can become a nidus for persistent infection, par ticularly following radiotherapy . Maxillary reconstruction The main aims of maxillary reconstruction are as follows: /uni25CF restore facial contours and aesthetics; /uni25CF separate sinonasal cavities from the mouth; /uni25CF restore soft palate competence to facilitate speech and swallowing; /uni25CF restore/provide for replacement of dentition. - A classification system for maxillary defects is useful for both treatment planning and discussion with colleagues. The most widely adopted classification is that proposed by Brown and Shaw; this classification considers both the vertical and - horizontal extent of the defect. Classes I–VI (Figure 53.12) describe the increasing size in a vertical dimension, while the horizontal extent is described by the letters a–c. Although not absolute, one of the advantages of this classification system is that it implies management. Class I defects are easy to repair with the only reconstruc - tive requirement being to separate the oral and nasal/antral cavities. Local flaps are often satisfactory , and the RFFF is the most commonly used free flap. Class II defects can be restored in a similar fashion to class I, especially w hen mor e posteriorly - located. However, composite (bone-containing) free flaps are usually required for anterior defects, and class IIc defects, as well as situations where the existing dentition is not adequate to retain a prosthesis. In classes III and IV , support for the contents of the orbit is lost, as well as support for the anterior cheek and alveolus. A prosthesis alone will provide a suboptimal result. The recon - structive goals are to support the orbital contents and facial skin, - ensure bony continuity between the remaining alveolus and zygomatic buttress (ideally su ffi cient to facilitate endo-osseous implant placement), as well as seal the oral and nasal cavities. Therefor e, a composite free flap (e.g. the thoracodorsal free flap) is suitable for fulfilling these requirements.

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(b) (c) (d) Figure 53.10 Management of a right mandibular squamous cell carcinoma utilising virtual surgical planning (VSP) and a /f_i bula free /f_l ap. /uni00A0 (a) Radiographic images demonstrating tumour in the right mandible. /f_l ap with the cutting guide in situ . (d) Final reconstruction clinically and radiographically. (b) VSP highlighting both resection and reconstruction. (c) The /f_i bula free

(c) Figure 53.11 Right mandibular squamous cell carcinoma ablative defect. Orthopantomogram showing the bony defect in the right body/ angle (a) . This was reconstructed with a deep circum /f_l ex iliac artery (DCIA)/iliac crest free /f_l ap. The surface anatomical markings for a right DCIA free /f_l ap are demonstrated with a typical incision (b) . Note the virtual surgical planning cutting guide on the iliac crest bone component and the associated well-vascularised muscle paddle (internal oblique muscle) reconstruction (d) . 1 Vertical component 1 Horizontal component Local flap Pedicle flap Obturator Soft-tissue FF Composite FF Figure 53.12 Maxillectomy defect classi /f_i cation and proposed reconstructions. Note that an updated version was published in 2010, but this diagram provides a useful visual representation of proposed reconstruction according to the class of defect. (Reproduced with permission from Brown JS, Rogers SN, McNally DN, Boyle M. A modi /f_i

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Figure 53.13 A zygomatic implant perforator used to reconstruct a left hemi-maxillectomy defect (courtesy of Prof. C Butterworth). (a) (c) Figure 53.14 Virtual surgical planning. (a) A virtual mandible (green) with an obvious bony defect. overlaid. (c) The /f_i nal reconstruction plan with a two-part (osteotomised) scapula osseous component.

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Regional variations

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Oral cancer is one of the most common cancers in India, 1 with an age-adjusted incidence rate of 20 per 100 /uni00A0 000. The disease accounts for over one-third of all cancers in India. In contrast to western populations, cancers of the buccogingival/ retromolar area account for over 40% of cancers in India and South East Asia, reflecting the commonplace use of the known carcinogens betel quid/gutka, along with smokeless tobacco. In Europe, there is significant variation reflecting the varying cultures and lifestyles, especially between eastern and western Europe. Eastern Europe has one of the highest age-standardised incidence rates of oral cancer world wide, with Hungary recording the highest rates. In these populations, the lateral border of the tongue and the fl oor of the mouth constitute particularly high-risk sites. In the USA, Surveillance, Epidemiology , and End Results (SEER) Program statistics indicate that the age-adjusted rate for oral cancer is 11.2 per 100 /uni00A0 000 per year, while the number of deaths is 2.5 per 100 /uni00A0 000 per year.

Lip Teeth Uvula Tonsil Floor of mouth Nasopharynx Oropharynx Pharynx Hypopharynx Oesophagus Figure 53.1 The oral cavity.

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Risk factors

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Tobacco, alcohol and betel quid (areca nut, catechu, slaked lime wrapped in a piper betel leaf) are long-established risk factors for oral cavity squamous cell carcinoma (OCSCC). There is a dose–response relationship between the use of Guido Fanconi , 1892–1979, Swiss paediatrician, named several conditions, including Fanconi anaemia, a rare genetic disorder of DNA repair leading to bone marrow failure and the development of haematological and solid malignancies typically within early life. Frederick Pei Li , 1940–2015, Boston, MA, USA, and Joseph F Fraumeni Jr syndrome of soft-tissue sarcomas, breast cancer and other malignancies in 1969. tobacco, alcohol and betel quid and the development of oral cancer. Transcriptionally active human papillomavirus (HPV) accounts for only a small percentage (approximately 5%) of OCSCCs, which is in stark contrast to oropharyngeal squa - mous cell cancers (OPSCCs), where 50–70% are caused by HPV . Although HPV-positive SCC has prognostic signifi cance in the oropharynx (see Chapter 52), this survival advantage does not appear to be conferred within the oral cavity . Other risk factors include pr evious exposure to radiation, chronic infection, immunosuppression and hereditary conditions such as Fanconi anaemia and Li–Fraumeni syndrome. , b. 1933, National Institutes of Health, Bethesda, MD, USA, described a familial

Gingiva (gum) Hard palate Soft palate Retromolar trigone Buccal mucosa (lip and cheek lining) Tongue Nasal cavity Oral cavity Larynx Hyoid bone Trachea

Risk factors for oral cavity malignancy /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF Premalignant lesions The majority of oral cancers do not originate from a pre existing lesion. However, there are a group of oral premalignant lesions, or more accurately described potentially malignant lesions, that are mucosal abnormalities from which oral cancer can arise. These lesions include leukoplakia, erythroplakia, erythroleukoplakia, prolifera tive verrucous leukoplakia (PVL), oral submucous fibrosis, oral lichen planus and lupus erythematosus, as well as inherited conditions such as epidermolysis bullosa and dyskeratosis congenita. A leuko plakia is a white patch or plaque that cannot be rubbed o ff , while an erythroplakia is a bright red velvety plaque, neither of which can be characterised clinically or pathologically as any other recognisab le condition. A speckled leukoplakia or erythroleukoplakia is essentially a combination of both; it carries the greatest risk for malignant change. The management of premalignant lesions is challenging, not least because of an inconsistency with nomenclature inter nationally but also because the natural history of these lesions remains unclear. The reported rates of malignant transformation v widely between studies and countries. A systematic review of observa tional studies in 2016 reported that malignant transfor mation in oral leukoplakia could vary from 0.13% to 34.0%. Risk assessment forms the cornerstone of the management of these lesions. Among these lesions, erythroleukoplakia, PVL and dyskeratosis congenita carry the highest risk for malignant transformation. Clinical factors to be considered include size, location and lifestyle exposure to known carcinogens. Biopsy of lesions is advocated for accurate pathological diagnosis

as well as to ascertain the degree of dysplasia (mild, moderate, severe), or indeed the presence of malignancy in a lesion. Summary box 53.2 Factors associated with increased risk for malignant change in pre-existing (dysplastic) lesions /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF malignant or dysplastic lesion does not completely remove the risk of transformation and as such appropriate surveillance regimes are necessary .

Smoking Alcohol Betel quid HPV Hereditary conditions Immunosuppression Chronic infection Potentially/premalignant lesions Female sex 2 Size >200 /uni00A0 mm Non-homogeneous lesion Non-smoker Presence of multiple lesions Location (e.g. lateral border of tongue/ /f_l oor of mouth)

Risk factors

Tobacco, alcohol and betel quid (areca nut, catechu, slaked lime wrapped in a piper betel leaf) are long-established risk factors for oral cavity squamous cell carcinoma (OCSCC). There is a dose–response relationship between the use of Guido Fanconi , 1892–1979, Swiss paediatrician, named several conditions, including Fanconi anaemia, a rare genetic disorder of DNA repair leading to bone marrow failure and the development of haematological and solid malignancies typically within early life. Frederick Pei Li , 1940–2015, Boston, MA, USA, and Joseph F Fraumeni Jr syndrome of soft-tissue sarcomas, breast cancer and other malignancies in 1969. tobacco, alcohol and betel quid and the development of oral cancer. Transcriptionally active human papillomavirus (HPV) accounts for only a small percentage (approximately 5%) of OCSCCs, which is in stark contrast to oropharyngeal squa - mous cell cancers (OPSCCs), where 50–70% are caused by HPV . Although HPV-positive SCC has prognostic signifi cance in the oropharynx (see Chapter 52), this survival advantage does not appear to be conferred within the oral cavity . Other risk factors include pr evious exposure to radiation, chronic infection, immunosuppression and hereditary conditions such as Fanconi anaemia and Li–Fraumeni syndrome. , b. 1933, National Institutes of Health, Bethesda, MD, USA, described a familial

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STAGING

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Staging is required to document tumour size, location and disease extent, as well as to formulate a treatment plan and - facilitate discussion of prognosis with the patient. Additionally , it is an important tool for comparative outcome reporting. The eighth edition of the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) tumour–node–metastasis (TNM) staging manual (Table 53.1) has introduced changes in how oral cavity cancers are staged. The most significant updates for oral cancer are: (i) the inclusion of depth of invasion (DOI) as an element for determining the - T stage of primary tumours and (ii) recognition of extranodal extension (ENE) as a feature necessitating upstaging of nodal disease. This recognition of additional negative prognostic ary factors in the eighth edition should allow improved stratifica - tion of outcomes for patients. - 2 STAGING

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SURGICAL MANAGEMENT

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Surgery , with adjuvant radiotherapy (or chemoradiotherapy) if indicated, remains the mainstay for management of oral cavity cancer. Over time, surgical techniques have evolved to become more refined with a greater emphasis on function-sparing techniques and a move away from more radical procedures. Reconstruction of postablative defects with an associated improvement in quality of life is a cornerstone of the surgical management of oral cavity cancer. This evolution in surgical management has been influenced by an improved understand - ing of tumour biology , more accurate staging investigations and microvascular free tissue transfer reconstruction. Overall and disease-specific survival is largely dictated by tumour biolog y , with features such as nodal metastases with ENE of greatest importance. Notwithstanding this, surgeons can optimise the outcome for patients by considering the following principles: /uni25CF patient selection; /uni25CF key surgical decisions; /uni25CF reconstruction; - /uni25CF multidisciplinary care. SURGICAL MANAGEMENT

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The size and extent of tumours are typically determined by thorough clinical examination (supported by examination under anaesthesia [EUA] where necessary) and by radio - graphic assessment with cross-sectional imaging (e.g. computed tomography [CT], magnetic resonance imaging [MRI]). While the DOI can be estimated radiologically , it remains a pathologically determined feature from a surgically resected specimen. Figure 53.2 illustrates the influence that T stage, and ther efore depth of invasion, has on overall survival. T stage

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The neck

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All levels of the neck must be palpated thoroughly , to assess for lymphadenopathy . However, it is important to note that, along with clinical examination, cross-sectional imaging of the neck is also required. Clinical examination without imaging has a 74% sensitivity for detecting lymphadenopathy . The presence of a neck metastasis decreases a patient’s prognosis by approximately 50%. The neck

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Tumour thickness is measured as the maximum vertical dimension between the tumour surface and the deepest point of invasion. Although frequently used interchangeably with DOI, it is the latter that carries greater importance from a prognostic viewpoint as well as the propensity for metastases. DOI is the distance from the level of the basement membrane of the closest adjacent normal mucosa to the deepest point of the tumour invasion. Tumour thickness and depth of invasion

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