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## Abstract

During the last 30 years the belief that oral/head and neck cancer management is based on team work has been established. The functions of tumor boards and combined clinics is a common contemporary practice with an exceedingly large number of medical, surgical, and other specialties being part of comprehensive, multidisciplinary therapeutic head and neck teams. The basic treatment modalities remain surgery, radiotherapy, and chemotherapy.

Basic surgical techniques have not changed dramatically over the last 30 years. Among the major changes are the variations in the surgical management of the neck of both clinically negative and clinically positive neck patients, as well as the management of the mandible especially in the early invasion of oral squamous cell carcinoma in the mandibular bone. The revolution in the surgical treatment of oral/head and neck cancer is the introduction of reconstructive techniques with both pedicled locoregional flaps and free tissue transfer. These reconstructive techniques allowed for safer and wider resections with adequate disease-free margins and functional reconstruction of the created surgical defects.

Contemporary radiotherapeutic treatment has very little similarities with that of the late 1970s. Modern technology with the institution of new forms of radiation and the application of sophisticated computerized methods have enhanced the therapeutic effectiveness of irradiation with an equal important reduction in the sparing in irradiation of normal surrounding tissues. This has led to an increased therapeutic dose in the tumorous site and a decreased severity of radiation-induced injuries. Alterations in the fractionations have also shown to produce better therapeutic results in selected cases.

The era of methotrexate, the leading chemotherapeutic agent of the 1970s, was followed by the institution of platinum-based chemotherapies with or without the addition of 5 Fu. Adjuvant and neoadjuvant schemes coupled with pre- or postoperative radiotherapy started in the late 1980s and showed a distinct survival benefit over radiotherapy alone. This major breakthrough was followed by the institution of various and diverse chemoradiation regimes tested over a large time period for their survival benefits. The introduction of taxanes and the development of molecular targeted therapies during the last 5 years have revolutionized the concept of chemoradiation. Induction chemotherapy and chemoradiation coupled with epidermal growth factor receptor antagonists proved to have a survival benefit in patients with locally advanced or recurrent squamous cell carcinoma of the head and neck. Other biological agents against tumor angiogenesis or restoring cell apoptosis are being tested in various phase I or II trials.

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Perhaps the most promising noninvasive therapeutic method for squamous cell carcinoma of the oral mucosa is immunotherapy. The clinical applications so far are very limited but the research into these pathways vast and extended.

#### Keywords

Oral squamous cell carcinoma • Head and neck tumors • Oral cavity cancer • Head and neck cancer • Treatment of the oral cavity cancer • Maxillary carcinoma • Chemoradiation • Induction chemotherapy • Targeted therapies • Combined treatments

## 24.1 Introduction

Cancer of the oral cavity comprises nearly 30 % of all malignant tumors of the head and neck. Oral cavity cancers include primary tumors of the lip, floor of the mouth, oral tongue, lower and upper alveolar ridge, retromolar trigone, hard palate, and buccal mucosa. Squamous cell carcinoma represents approximately 90 % of the cases [1], while the remaining 10 % represents rare malignancies (unusual forms of squamous cell carcinoma, minor salivary gland tumors, melanomas, lymphomas, sarcomas) and a variety of malignant tumors of odontogenic origin. Lifestyle, habits, and demographic as well as genetic factors influence geographic variations in the incidence of disease. In North America, common risk factors for the development of cancer of the oral cavity include tobacco and alcohol use. Outside of North America, dietary habits, like chewing beetle, areca nut, and tobacco, represent additional risks for the development of oral cancer. Beyond these risks, there is little evidence linking dietary factors or nutritional deficiencies to the development of oral cavity cancer especially low fruit and vegetable consumption and high fat and/or sugar intake. The highest rates of incidence of cancer of oral cavity are observed in Pakistan, Brazil, India, and France [2]. While the use of alcohol and tobacco independently represents risk factors for the development of oral cavity cancer, the synergistic effect of these risk factors has been well documented. It has been suggested that the use of alcohol suppresses DNA repair following exposure to nitrosamine compounds; however, the exact mechanism of the observed synergy remains poorly defined. Human Papillomavirus (HPV) is strongly associated with the development of oropharyngeal cancer and a small percentage of oral cavity cancers [3]. Over the past 30 years, the proportion of potentially HPV-related oral cancer in the United States has increased, possibly due to changing sexual behaviors especially in the young population. This probably explains the increasing number of patients with oral carcinoma who had never been exposed to tobacco or alcohol.

During the last 30 years, there has been an explosion of accumulated knowledge and evidence in our understanding of the biological phenomenon of oral carcinogenesis as well as in the technological advances in the diagnosis of the

disease in both the histopathological and clinical levels. An equal abundance of knowledge has been achieved in the therapeutic management of the disease from the combined uses of surgery, radiotherapy, and chemotherapy. Despite all these developments, the 5-year overall survival of the disease has remained in the range of 50–60 %. The quality of life though of the patients, which has become a major issue, has undoubtedly improved during these 30 years [4].

## 24.2 Principles of Oral Cavity Cancer Management

The treatment of primary tumors from different head and neck subsites often overlaps. Treatment for oral cavity cancer in general is highly complex, not only because of the variety of tumor subsites, but also because of the anatomic constraints of the head and neck region, and the importance of maintaining organ function after treatment.

The factors that influence the choice of initial treatment are those related to the characteristics of the primary tumor, those related to the patient, and those related to the therapeutic team (Tables 24.1, 24.2, 24.3, 24.4, 24.5, and 24.6) [5]. They are therefore classified under tumor, patient, and treatment factors. In the selection of optimal therapy for oral carcinoma, one should consider these three sets of parameters in primary treatment planning. The ultimate goal of treatment of cancer of the oral cavity is to eradicate disease, preserve or restore form and function, minimize the sequelae of treatment, and finally prevent the development of any subsequent new primary cancers. The tumor factors that affect the choice of initial treatment of oral cancer represent the clinical and histopathological characteristics of the tumor and, more specifically, the anatomical site, size (T stage), location (anterior versus posterior), proximity to bone (mandible or maxilla), status of regional cervical lymph nodes, previous treatment, and histology (type, grade, and depth of invasion). The ability of the patient to tolerate an optimal therapeutic scheme is similarly an important factor influencing the choice of initial treatment. The patient's acceptance of and compliance with the proposed treatment are similarly important considerations in designing an optimal treatment strategy.

**Table 24.1** Staging for tumors of the lip and oral cavity

<b>T (primary tumor size)</b>
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor 2 cm or less in greatest dimension
T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3 Tumor more than 4 cm in greatest dimension
T4a Lip Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face (i.e., chin or nose) <sup>a</sup>
Oral Cavity Tumor invades through cortical bone, into deep extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face
T4b Tumor involves masticator space, pterygoid plates, or skull base and/or encases internal carotid artery

<sup>a</sup>Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify as T4.

Based on data from Ref. [5]

**Table 24.2** Staging for tumors of the nasal cavity and paranasal sinuses

<b>T (primary tumor size)</b>
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
Maxillary sinus
T1 Tumor limited to the maxillary sinus mucosa with no erosion or destruction of bone
T2 Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T3 Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
T4b Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve V2, nasopharynx, or clivus
Nasal cavity and ethmoid sinus
T1 Tumor restricted to any one subsite, with or without bony invasion
T2 Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3 Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
T4a Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4b Tumor invades any of the following: orbital apex, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx, or clivus

Based on data from Ref. [5]

**Table 24.3** Staging for all head and neck sites except the nasopharynx and thyroid

<b>N (regional nodal status)</b>
Nx Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2 Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3 Metastasis in a lymph more than 6 cm in greatest dimension

Based on data from Ref. [5]

**Table 24.4** Staging for head and neck tumors

<b>M (distant metastasis)</b>
Mx Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Based on data from Ref. [5]

**Table 24.5** Stage grouping for all head and neck sites except the nasopharynx and thyroid

Stage group	T stage	N stage	M stage
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
IVA	T3	N1	M0
	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
IVB	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
	T4b	Any N	M0
IVC	Any T	N3	M0
	Any T	Any N	M1

Based on data from Ref. [5]

**Table 24.6** Algorithm of stage status in cancer of the oral cavity

Staging of oral cavity cancer	N0	N <sub>1</sub>	N <sub>2</sub>	N <sub>3</sub>
T <sub>1S</sub>	<b>Stage 0</b>			
T <sub>1</sub>	<b>Stage I</b>			
T <sub>2</sub>	<b>Stage II</b>			
T <sub>3</sub>		<b>Stage III</b>		
T <sub>4a</sub>			<b>Stage IVA</b>	
T <sub>4b</sub>				<b>Stage IVB</b>

**Stage IVC** any T any N when M1

Additionally, the performance status, the previous medical history, and the presence of additional comorbidities should also be taken into consideration. The factors related to the therapeutic team are also important and are related with the experience, dexterity, ability, and availability of technical support of the surgical team and its environment. Expertise in various disciplines including surgery, radiotherapy, chemotherapy, rehabilitation services, dental, and psychosocial support are all crucial in bringing about a successful outcome of the therapeutic program.

For the purpose of providing an overview of treatment strategies in oral cancer patients, it is mandatory to group the oral squamous cell cancers into early-stage disease (stages I

and II; no apparent lymph node involvement) and advanced disease which includes cancer metastatic to cervical lymph nodes (regionally advanced) and locally advanced primary tumors (stages T3 and T4).

### 24.3 Early-Stage Disease

Approximately 30–40 % of patients with oral cavity cancer present with early (stage I and II) disease. In general, these patients are treated with curative intent using either surgery or radiotherapy (RT). Because both modalities result in similar rates of local control and survival, the choice is usually based

upon an assessment of competing morbidities, functional outcomes, and accessibility. One advantage of RT over surgery is the ability to electively encompass areas at high risk for sub-clinical involvement (i.e., cervical lymph nodes). Prophylactic treatment of the clinically negative neck (i.e., no evidence of pathologic lymphadenopathy either by clinical examination or radiographic study) is somewhat controversial. However, in general, prophylactic neck irradiation or lymph node dissection is recommended if the likelihood of neck recurrence at a specific site exceeds 15 %. Generally in tongue cancer, the incidence of nodal metastasis depends upon the stage of the tumor. T1, T2, and T3 tongue cancers are associated with 30 %, 50 %, and 70 % respective incidence of microscopic nodal metastasis. Selective neck dissection can be used to effectively treat clinically positive nodal disease in selected patients [6, 7].

As surgical cures can often be achieved rapidly and with minimal morbidity, surgery has become the gold standard for management of early cancers of the oral cavity. Tumors involving the oral tongue can usually be managed through a transoral approach. While radiotherapy is equally effective for the treatment of early disease, the rates of long-term sequelae including xerostomia, dysphagia, and osteoradionecrosis are unacceptably high. Other advantages of surgery include the duration of treatment. Surgical therapy requires a single intervention, while RT requires daily therapy over a period of several weeks in addition to possible catheter implants and the use of chemotherapy. Therefore, in resectable patients RT is usually reserved for those patients who are unable to undergo surgery [8].

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#### 24.4 Advanced-Stage Disease

Advanced disease (stages III and IV) of the oral cavity is best managed with multimodality therapy. Surgery coupled with preoperative or postoperative RT is often utilized for advanced disease. Although preoperative radiation has been proposed to decrease the tumor mass and therefore increase the “resectability” of the tumor, it is common practice to surgically resect the tumor based on the pre-radiation margins because islands of viable tumor may persist in the initial peripheral margins. Additionally, preoperative radiation is associated with a higher rate of postoperative complications. For these reasons, most centers perform surgery followed by postoperative radiation [9, 10].

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#### 24.5 The Role of Radiotherapy (RT) and Chemoradiotherapy (CRT) as Treatment Modalities in Oral Cancer

The current standard technique for delivery of RT to tumors involving the oral cavity is three-dimensional conformal RT (3D-CRT). As opposed to the historically two-dimensional

planning which relied on simulation X-ray films, treatment planning with 3D-CRT is based upon three-dimensional information that is obtained on simulation CT scans. The radiation dose distribution is shown in three dimensions and doses to the treatment target as well as various organs are more accurately calculated. Modification of beam properties can be performed if needed to produce a conformal dose distribution to the treatment target [11].

Although primary surgical management has been advocated for advanced (T4) oral cavity cancers, recent evidence suggested that primary CRT may be an effective treatment approach for selected patients with T4 lesions, with comparable rates of locoregional control, survival, and complications associated with primary surgical management and postoperative RT [12].

Xerostomia is the most common late side effect of radiotherapy to the head and neck. Compared with conventional radiotherapy, intensity-modulated radiotherapy (IMRT) can reduce irradiation of the parotid glands. Nutting et al. [13] in a randomized controlled trial assessed the hypothesis that parotid-sparing IMRT reduces the incidence of severe xerostomia. The trial compared conventional radiotherapy (control) with parotid-sparing IMRT. The findings from this study showed that sparing the parotid glands with IMRT significantly reduces the incidence of xerostomia and leads to recovery of saliva secretion and improvements in associated quality of life. Over the last few years, IMRT has been implemented in most radiation oncology centers and is becoming a dominant treatment technique for head and neck cancer. With the assistance of advanced computer technology, IMRT is capable of delivering radiation doses that are highly conformal to the target, with rapid dose falloff outside of target volumes. This technique permits high doses of RT to be delivered to tumors which lie in close proximity to critical normal organs [14]. The newest technology, image-guided radiation therapy (IGRT), is being introduced into radiation therapy practice. A CT scanner is incorporated into the linear accelerator, allowing target position verification in the treatment position. The capacity for near real-time imaging during treatment permits tumors to be treated with greater precision and accuracy than is possible with conventional IMRT, further reducing toxicity to normal tissues.

For conventional fractionation RT, the dose for all gross disease (primary and nodal) is 70–72 Gy in 2 Gy fractions over 7 weeks. Subclinical regions of the neck are electively treated to 50 Gy in 25 fractions, while nodal regions with adjacent gross disease may receive 60 Gy in 30 fractions. IMRT also allows for the delivery of smaller radiation doses to the major salivary glands, thus reducing the risk of permanent post-irradiation xerostomia.

Most oral cavity tumors as with the majority of head and neck cancer typically present with advanced-stage locoregional disease (stage III or IV) for which local and regional control with surgery and/or radiation has been the mainstay

treatment. After the publication of the trials on larynx preservation strategies in both Europe and the United States [15, 16], there was a rapid proliferation of non-site-specific trials to further investigate organ preservation protocols in the treatment of advanced head and neck squamous cell carcinoma. Over 70 divergent randomized trials compared traditional locoregional treatments of surgery and radiation versus locoregional treatment plus chemotherapy. Unfortunately, this enthusiasm was plagued by small sample sizes and a lack of statistical power to confidently detect even modest effects on survival, leading to mixed results and an obscured clinical picture [17–19].

Concomitant CRT may represent an acceptable alternative in selected advanced stages of oral cancer patients. In addition to the optimal combination of drugs, the role of altered fractionation RT schedules is also under active study [20]. Two main strategies of altered fractionation have been explored in order to increase the effective dose of RT delivered without magnifying toxicity. Hyperfractionation that delivers smaller doses of RT twice daily (1.1–1.2 Gy fractions compared to conventional daily 1.8–2.0 Gy fractions) allows higher doses of RT to be administered (thereby improving local control) without a significantly higher risk of late complications [21].

Because delayed long-term toxicity of normal tissues is dependent on the size of the individual fractional dose, decreasing the size of each radiation fraction should permit utilization of higher total doses without increasing late morbidity [22]. In practice, multiple daily treatments with smaller than conventional fraction sizes are given over approximately the same treatment duration. Typically 1.1–1.2 Gy/fraction two fractions per day to total doses of 74–80 Gy have been employed. Accelerated fractionation RT schedules deliver the total dose of RT in shorter treatment duration. This seems to reduce the rapid tumor repopulation that is thought to occur during treatment interruptions [21].

A benefit for hyperfractionated compared to conventional fractionation RT in patients with locally advanced head and neck cancer has been shown in at least three prospective, randomized trials [22–24] and in meta-analyses of these trial data [15, 21].

Even in the absence of chemotherapy, significantly higher local control rates have been documented with both strategies compared to conventional fractionation RT alone, although demonstrating a survival benefit from either approach has been more difficult [25]. Taken together, these data support the view that accelerated treatments using split-course RT schedules or reduced total doses do not improve locoregional tumor control or overall survival. Accelerated treatments that employ continuous (rather than split-course) RT schedules, without compromising the total dose, improve local control [22]. However, whether the added mucosal toxicity is justified by meaningful gains in survival remains an

open question. Altered fractionation RT is considered by some to represent a standard approach for patients who are receiving RT alone as definitive treatment for oral cancer.

However, it is important to clarify that the indications for postoperative RT directed to the primary site are different from the indications for postoperative radiation directed at the neck. The goal of a surgical excision is to achieve a complete resection of the tumor with tumor-free margins. In cases where there are positive or close margins (tumor within 5 mm of the surgical margin), surgical re-resection is usually recommended. In cases where a re-resection is performed, if there remains evidence of microscopically positive margins, radiation directed at the primary site should be considered. In cases where there is neck disease that is N2 or greater, or the histopathological characteristics of the primary tumor demonstrate an aggressive behavior [26], radiation therapy to the neck is warranted, usually administered with concurrent chemotherapy [27, 28].

Definitive RT, usually administered with cisplatin-based chemotherapy, is the treatment of choice for patients with potentially resectable locoregionally advanced oral cancer who desire organ preservation, for those who have surgically unresectable disease, or who are medically inoperable. Although direct comparative data are lacking, combined use of chemotherapy and RT appears to produce similar locoregional control and survival rates as does surgery, while providing the opportunity for function preservation [25].

Chemotherapy can be administered before, at the same time, or after locoregional treatment corresponding to induction, concomitant, or adjuvant chemotherapy. There are several other potential advantages to giving neoadjuvant rather than postoperative (adjuvant) chemotherapy. These include the delivery of chemotherapeutic drugs through an intact vasculature which is optimal to enhance its therapeutic effectiveness before surgery or radiation. The neoadjuvant treatment is more likely to treat micrometastases, thus diminishing the chances of developing gross metastatic disease. Finally, the reduction in tumor size and healing prior to definitive RT may improve functional outcomes.

The response to chemotherapy may be an important predictor of survival, as various studies have shown that patients with a good response to induction chemotherapy have a better overall survival [4, 29, 30]. A thorough meta-analysis of randomized trials showed that adding cisplatin concurrently to radiotherapy improved progression-free survival (PFS), overall survival (OS), and organ preservation, but only approximately 50 % of patients survived more than 5 years [31]. Moreover, radiation-cisplatin regimens induce severe acute and late morbidity [32]. These observations inspired the search for alternative therapy approaches.

A greater benefit (8 %) was observed in trials that gave CT concomitantly to RT. Effect of concomitant CT on survival did not differ significantly between the group of trials

with postoperative RT or curative RT with conventional or altered fractionation. No significant difference was also seen between mono- and poly-chemotherapy. In the poly-chemotherapy group, the effect of chemotherapy was not significantly different between the different subgroups: with cisplatin or carboplatin (platin) and 5-fluorouracil (5-FU), with either platin or 5-FU, or with neither [31, 33]. As might be expected, the proportion of deaths not due to head and neck cancer increases progressively with age from 15 % in patients less than 50 to an impressive 39 % in patients 71 and over. The survival benefit resulting from the addition of CT to RT is confirmed to be around 4 %. This benefit is larger for concomitant CT, whereas there was no clear evidence of a benefit for induction and adjuvant CTs. Another important issue is that the benefit of concomitant CT appears to be similar irrespective of whether the RT is given conventionally or using altered fractionation. Finally, the magnitude of the benefit of concomitant CT is less in older patients, a feature that has also been observed with altered fractionation compared to conventional RT in head and neck cancer [21] and also when combining anti-EGFR agents (cetuximab) with radiotherapy [34–36]. One strategy to improve the efficacy of treatment is to add molecular targeted agents to classical chemoradiotherapy regimens. Cetuximab, the first targeting strategy to demonstrate survival advantage for patients with HNSCC, has emerged in the context of epidermal growth factor receptor (EGFR) biology [34, 37]. In a recent meta-analysis, the comparison of the benefit associated with concomitant versus induction CT was examined. It is interesting that both the indirect and the direct comparisons were consistent on survival, event-free survival, and locoregional failure, showing a clear advantage in favor of concomitant CT [38, 39].

Combining cisplatin or cetuximab with radiation improves OS of patients with stage III or IV head and neck carcinoma. Cetuximab plus platinum regimens also increase OS in metastatic head and neck carcinoma. The Radiation Therapy Oncology Group launched a large phase III trial to test the hypothesis that adding cetuximab to the radiation-cisplatin platform improves PFS [40]. Of 891 analyzed patients, 630 were alive at analysis (median follow-up, 3.8 years). Cetuximab plus cisplatin-radiation, versus cisplatin-radiation alone, resulted in more frequent interruptions in radiation therapy (26.9 % vs. 15.1 %, respectively), similar cisplatin delivery (mean, 185.7 mg/m<sup>2</sup> vs. 191.1 mg/m<sup>2</sup>, respectively), and more grade 3–4 radiation mucositis (43.2 % vs. 33.3 %, respectively), rash, fatigue, anorexia, and hypokalemia, but not more late toxicity. Adding cetuximab to radiation-cisplatin did not improve outcome, and hence, the authors stated that should not be prescribed routinely. This large phase III trial stemmed from strong previous phase III data showing that combining cisplatin or cetuximab concurrently with radiation improved PFS and OS of patients with locally

advanced head and neck carcinoma and that adding cetuximab to platinum-based chemotherapy improved OS of patients with recurrent or metastatic head and neck carcinoma. Therefore, it was disappointing to discover that adding cetuximab to the radiation-cisplatin platform had no significant impact on PFS, OS, LRF, or DM [40]. This study reported conflicting findings from a number of previous studies on the same subject. More specifically, in a phase III study in locally advanced HNSCC, it was demonstrated that cetuximab increased OS when combined with radiotherapy alone, while not enhancing local toxicities [37]. In addition, following a proof-of-concept study in the recurrent metastatic setting, the Erbitux in First-Line Treatment of Recurrent or Metastatic Head & Neck Cancer (EXTREME) study showed that addition of cetuximab to platinum-based chemotherapy with fluorouracil improved OS, PFS, and response rates [35, 41]. Both studies attempted to intensify treatment in the locally advanced setting by incorporating cetuximab into concurrent chemoradiotherapy regimens in unselected populations. RTOG-0234 was a randomized phase II study in the postoperative setting in patients with high-risk pathologic features. It was designed to select one of two chemoradiotherapy regimens for further testing against standard high-dose cisplatin-based chemoradiotherapy in a phase III trial [42]. The two chemoradiotherapy regimens, docetaxel–radiation–cetuximab triplet and weekly cisplatin–radiation–cetuximab triplet, were compared in terms of disease-free survival (DFS) to the historical cohort treated with chemoradiotherapy in RTOG-9501 [27]. Both arms performed better than historical RTOG-9501 results, and the docetaxel arm appeared better than the cisplatin arm. RTOG-9501 randomly allocated high-risk postoperative patients to either radiation alone or radiation with concurrent high-dose cisplatin. No significant impact on distant control was noted, although the addition of cisplatin did increase acute severe adverse events [43]. However, the EXTREME trial was conducted in an unselected population and showed improvement in survival, even though the cetuximab-sensitive population was diluted as a result of the lack of a predictive test. Such a synergistic effect of cetuximab with chemotherapy did not emerge in RTOG-0522, possibly because of a lack of feasibility of the cisplatin–cetuximab–radiation triplet [40].

Postoperative RT with or without concomitant chemotherapy is reserved for those cases in which the risk of recurrence is high. Defining the “high-risk” patient has been the topic of controversy. This decision is made after a careful evaluation of the various patient and disease factors. The findings can be summarized as follows: extracapsular extension and/or microscopically involved surgical margins are the only risk factors for which the impact on survival of adding chemotherapy to RT is statistically significant. There is a trend toward improved survival in favor of CRT in patients who had stage III and IV disease, perineural infiltration, vascular embolisms, and/or

clinically enlarged level IV and V lymph nodes secondary to tumors arising in the oral cavity or oropharynx. The differences though were not statistically significant. Patients with two or more histopathologically involved lymph nodes without extracapsular extension did not seem to benefit from the addition of CT. The problem with CRT in head and neck cancer is that the schedules are often rather toxic and associated with a substantial morbidity which in turn influences the compliance with treatment. Obviously this morbidity is to some extent outnumbered by the benefit of the combined treatment, resulting in an improved survival, but we must not forget that many patients do not comply with treatment, and patients who do not fulfill a planned course of RT due to morbidity with the interacting drug are in fact in a worse situation condition than the ones who are treated with RT alone.

## 24.6 Site-Specific Treatment

The anatomic boundaries of the oral cavity extend from the skin–vermilion junction of the lips to the junction of the hard and soft palate above and to the line of circumvallate papilla of the tongue below. Specific sites of tumor origin include the lips, floor of the mouth, oral tongue, lower alveolar ridge and retromolar trigone, upper alveolar ridge and hard palate, and the buccal mucosa [44]. The maxillary sinus carcinomas will also be included.

## 24.7 Lip Cancer

The lip is the most common primary site within the oral cavity, accounting for approximately 25 % of cancers at this site. The majority of lesions occur on the lower lip and 95 % occur in males [45] (Fig. 24.1). Basal cell carcinomas (BCCs) may arise from the skin and cross the vermilion border to invade the lip, while squamous cell cancers (SCCs) most frequently develop at the vermilion margin. BCCs are more common on the upper lip. The similar local control and cure rates that can be achieved with surgery or RT in stage I lower lip tumors make either treatment acceptable. Surgery is the treatment of choice for early-stage lesions and is preferred because of better cosmetic results and lower morbidity rates compared to RT. Defects that involve less than two-thirds of the lip usually can be closed primarily. Defects involving two-thirds of the lip can be reconstructed with full thickness pedicled flaps (“Abbe or Estlander”) from the upper or lower lip [46]. Many reconstructive options are available for defects larger than two-thirds of the lip, ranging from local nasolabial flaps to hair-bearing free flaps. The facial artery musculomucosal flap has shown application and success in upper and lower lip reconstruction [47]. Radiation



**Fig. 24.1** Clinical photograph of a 60-year-old male with an ulcerated lesion in the middle part of the lower lip. A biopsy revealed a moderately differentiated squamous cell carcinoma

therapy is generally reserved for recurrent tumors, for nodal disease, and for patients who cannot tolerate surgery.

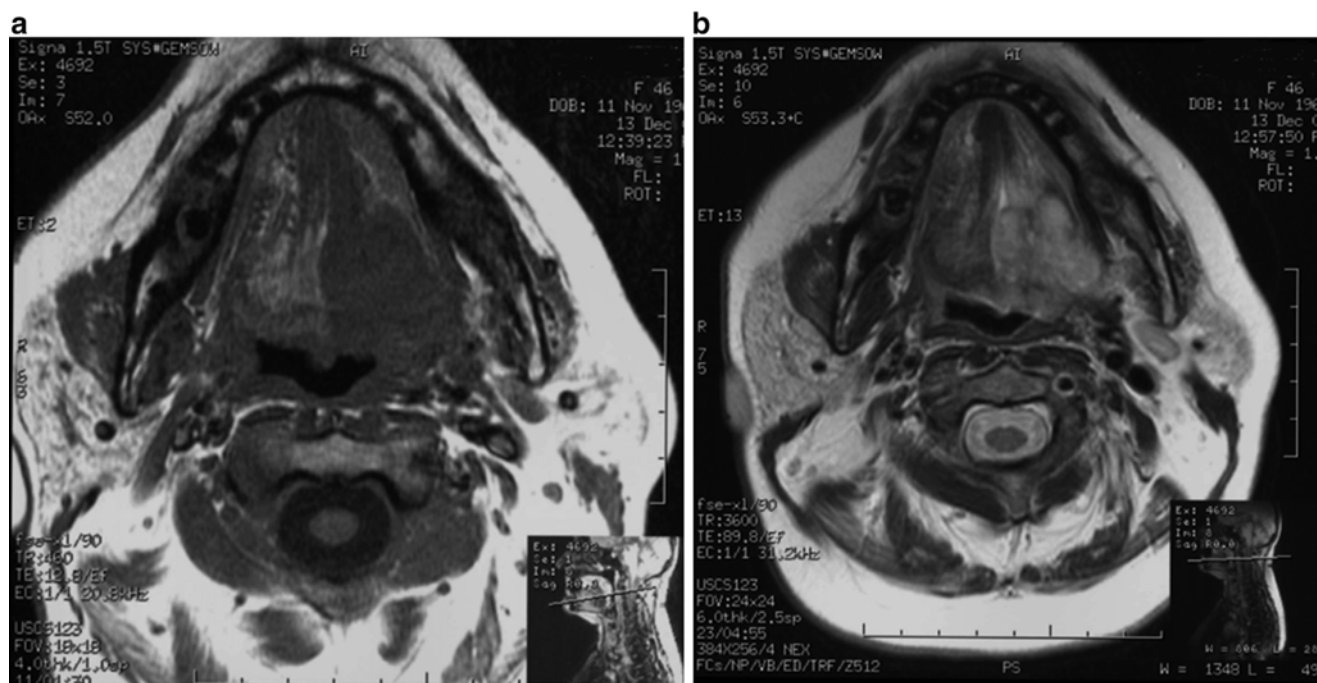
Maximum tumor thickness is a predictor of metastatic spread to the regional nodes and is therefore important for treatment planning and assessment of prognosis in patients with squamous cell carcinoma [48, 49]. Among patients who have a clinically negative neck, those with T2 or larger tumors that are treated surgically should undergo ipsilateral neck dissection [49]. Upper lip and commissure tumors are more aggressive, tend to grow more rapidly, ulcerate sooner, and metastasize earlier than those of the lower lip. Carcinomas in these sites may give regional metastases to preauricular and submandibular nodes.

## 24.8 Oral Tongue Cancer

The incidence of tongue cancer exceeds all other sites in the oral cavity, excluding lip cancer, accounting for almost 30 % of oral cancer patients. The median age for patients with SCC of the tongue is 60, and, similar to other disease sites, the male to female ratio is 3:1. Cancers of the mobile tongue have a high incidence of occult and clinical cervical lymph node metastases.

Tongue cancer has been considered to have a more aggressive course in younger patients. However, more recent studies have found no difference in staging or survival among patients under the age of 40 as compared to a group of patients aged 60–70 [50, 51]. Those receiving neck dissection for prognostic or therapeutic purposes have significantly better 5-year survival rates than those who do not receive a





**Fig. 24.2** Squamous cell carcinoma of the tongue in a 48-year-old female patient. The MRI shows the lesion extending and occupying the right side of the tongue. T1 weighting (a) and T2 weighting (b)

neck dissection as part of their primary treatment. Surgery is recommended for small, anterior, and well-lateralized lesions. Radiation therapy is preferred for large T1 lesions and for T2 tumors where resection would result in impairment of normal speech and/or swallowing (Fig. 24.2).

Most stage I and II lesions can be resected via an intraoral approach with ample surgical margins. Due to the small size of these early tumors in relationship to the usual bulky mass of the tongue, most T1 and T2 cancers of the oral tongue can be excised without permanent speech or swallowing deficits. Excision usually entails a partial glossectomy (Fig. 24.3).

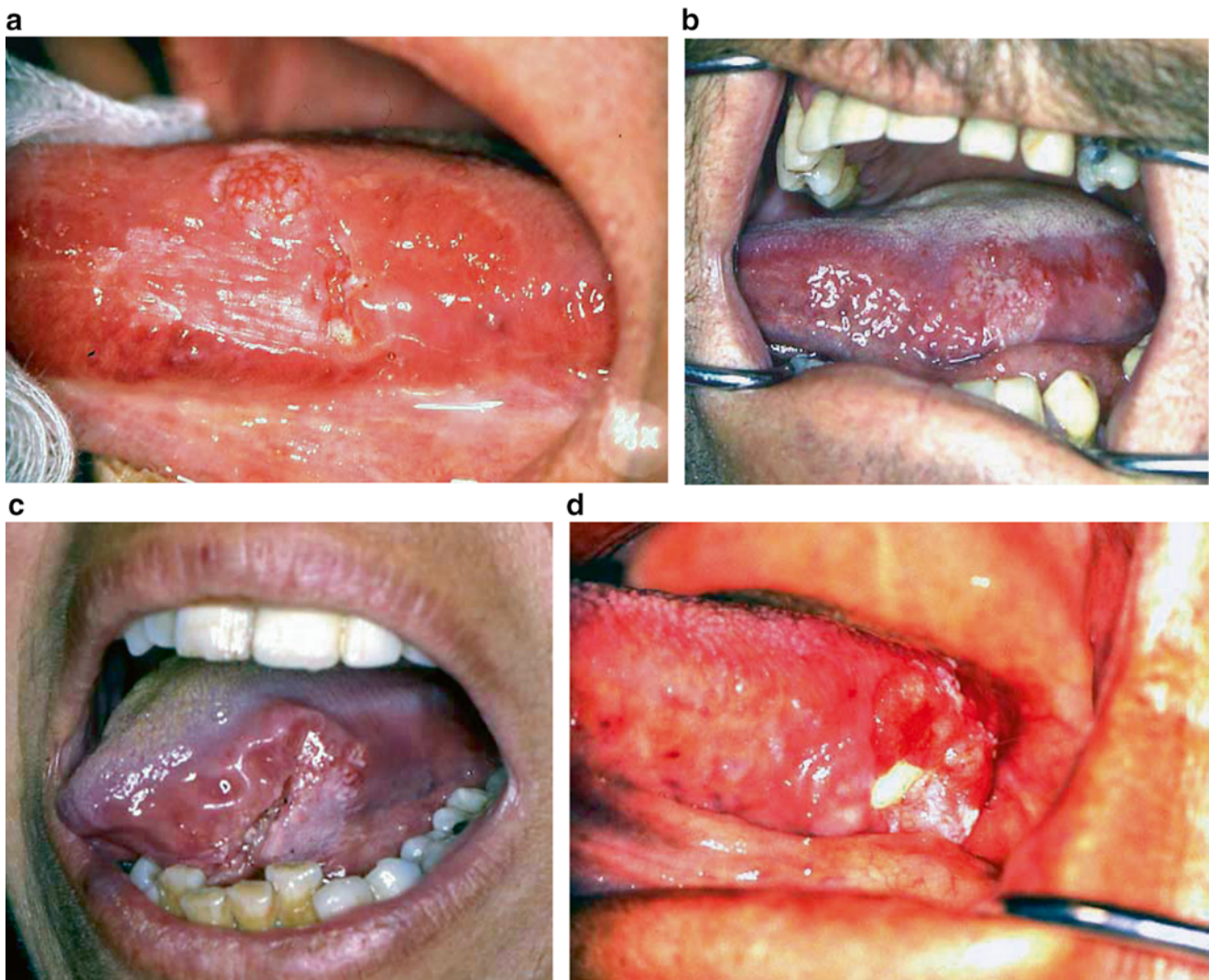
Adequate margins (greater than 1 cm) and elective treatment of the clinically negative neck are extremely important in the treatment of early tongue cancer. The 5-year survival rate, in patients with stage I or II disease, after appropriate surgical treatment, approaches 90 %.

Elective neck dissection is recommended in patients with T2-4 tumors and a clinically negative neck because of the high incidence of occult cervical nodal disease [52–54]. More than 25 % of patients undergoing elective neck dissection will be found with pathologically node positive (N+) [53]. The staging information provided by the neck dissection is crucial for defining necessity for and type of postoperative additional treatment.

It is more difficult to define the role of elective neck dissection in patients with T1 disease and a clinically negative neck. There are no randomized trials examining this issue. The 5-year survival rates for patients undergoing synchronous (prophylactic) neck dissection, no dissection, or a meta-

chronous dissection (at the time of clinical neck recurrence) are 81, 60, and 45 %, respectively. This finding supports the concept that prophylactic neck dissections offer improved survival compared to the “wait and see” policy and emphasizes the need for a more aggressive approach to the neck at primary tumor presentation [55]. The best pathologic predictors for the presence of occult neck metastases are depth of invasion above 5 mm, depth of muscle invasion, double DNA aneuploidy, and poor histologic differentiation. It is therefore recommended that elective neck dissection must be considered in patients with T1N0 cancer undergoing surgical treatment of the primary who have aneuploid tumors, depth of muscle invasion  $>4$  mm, or a poorly differentiated cancer [55].

As oral cavity cancer rarely metastasizes to neck level V, a radical or modified radical neck dissection of all five nodal levels is not necessary for patients with N0 neck. Selective neck dissection of levels I–III (“supraomohyoid neck dissection”) is the procedure of choice for elective neck dissection of the neck. Most of the relatively small numbers of isolated metastasis to level IV are from primary tumors of the tongue, which are known to produce “skip metastases.” Thus, an “extended supraomohyoid neck dissection” of levels I–IV is recommended for elective treatment of the neck in tongue cancer in patients with T2 and above and N0 necks [56]. A number of recent prospective multi-institutional studies have demonstrated that sublevel IIB is rarely involved with isolated metastasis from oral cavity primary tumors, except from some tongue cancers [57–61]. Thus, it is justifiable to



**Fig. 24.3** (a) Clinical photograph of a 69-year-old female patient. On the left border of the tongue there is a well-demarcated speckled lesion, indurated on palpation. There is also an area of leukoplakia. The patient had noticed the change on the left tongue border for the first time about 3 months earlier. A biopsy revealed a well differentiated oral squamous cell carcinoma. (b) An early, T1 carcinoma of the middle third of the tongue in a 65-year-old male smoker patient. A slightly raised, erythematous superficially ulcerated area can be noted. (c) Clinical photograph illustrating an ulcer in the left anterior two-thirds of the tongue in a

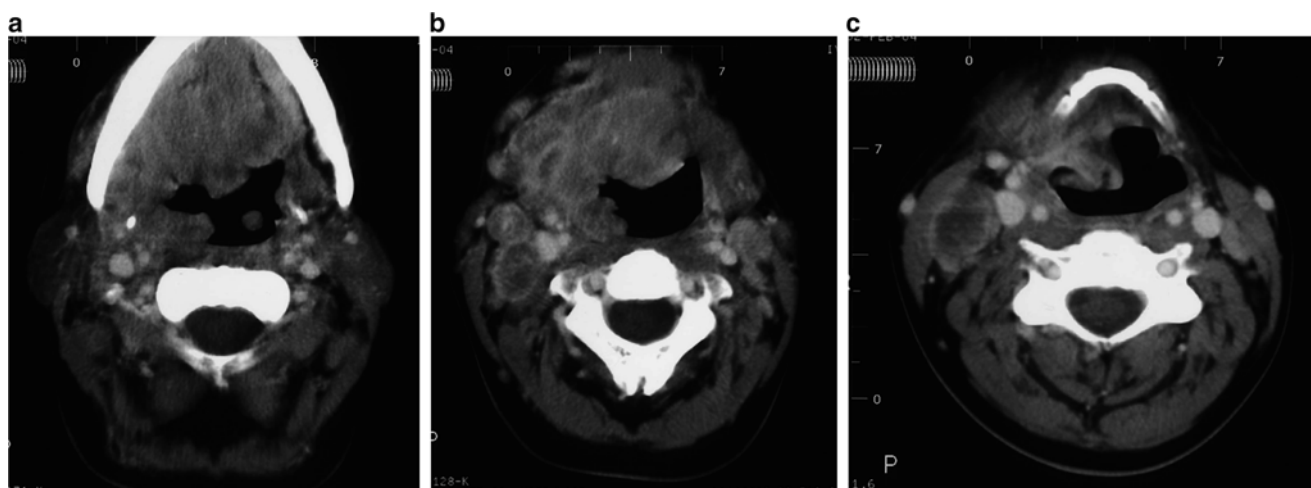
43-year-old female patient. She had no tobacco or alcohol habits. The lesion measured 4.3 cm in its widest dimension. This carcinoma is therefore staged as T3. A submandibular lymphadenopathy was detected. Incisional biopsy showed a deeply invasive squamous cell carcinoma. (d) This photograph shows a non-healing ulcer in the posterior third of the tongue corresponding to a T2 squamous cell carcinoma. The patient, a 55-year-old male was a smoker and reported a history of regular alcohol consumption. No regional lymph nodes were palpable

omit dissection of sublevel IIB in elective treatment of most cases of oral cavity cancers. In this way injury to the spinal accessory nerve is avoided [62].

It is recommended that elective neck dissection is performed for all patients with T2 or larger tumors if surgery is used to treat the primary tumor [54]. Ipsilateral neck dissection is generally sufficient for most T1/T2 tumors. However, bilateral node dissection should be considered for patients with anterior or midline lesions, as well as for those with more advanced-stage disease (Fig. 24.4).

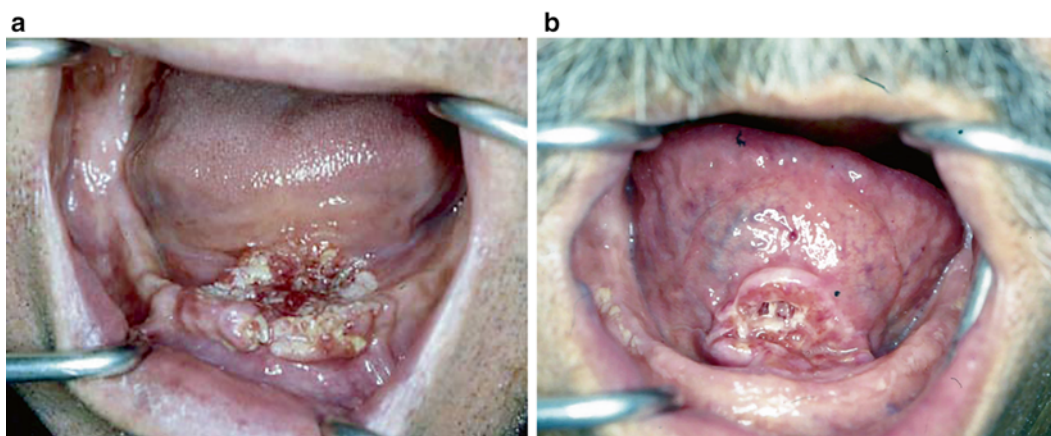
## 24.9 Floor of Mouth Cancer

The floor of the mouth is rich in neural and vascular structures including the lingual and hypoglossal nerves, the submandibular duct, and the sublingual glands. SCCs of the floor of the mouth are aggressive oral cavity neoplasms. They typically present as painful infiltrative ulcerative lesions that may bleed (Fig. 24.5). The lack of any substantial fascial barrier means that early tumors of the floor of mouth can quickly invade into the underlying structures and



**Fig. 24.4** Squamous cell carcinoma of the tongue in a 55-year-old male patient. The CT shows the lesion occupying the entire musculature of the left side of the tongue. Regional node metastases are also present. (a) At the level of the floor of the mouth. (b) At the level of the

base of the tongue. Multiple nodal metastases with central necrosis can be seen. (c) At the level of the hyoid bone. A large nodal block can be seen under the sternocleidomastoid muscle



**Fig. 24.5** (a) Clinical photograph of a 67-year-old edentulous male patient with a heavy smoking history. A carcinoma of the floor of the mouth is noted. The lesion extends also toward the alveolar ridge of the

anterior mandible. (b) An ulcerated lesion in the floor of the mouth in a 76-year-old male smoker can be seen. The lesion also extends toward the ventral side of the tongue

metastasize to the first echelon lymph node basin (neck levels I and II). They have a high incidence of cervical nodal metastases which are detectable clinically in 30–60 % of patients at presentation. The incidence of occult cervical metastases is also high [63].

Treatment approaches include surgery and RT. Due to the risk of radiation-induced bone necrosis, surgery is usually the preferred treatment approach in operable patients. Local control of these tumors can be difficult because of their proximity to the mandible and the lack of a good mechanical barrier to tumor spread at this site. Surgery is generally preferred with an emphasis on negative margins, which can be technically difficult without rim mandibulectomy due to the

proximity of and/or occult invasion into the mandible. The outcome of surgical treatment for patients with cancer of the floor of the mouth varies directly with tumor size and the status of the surgical margins. In early-stage T1 and T2 disease, the 5-year survival can be higher than 80 % [63, 64].

Due to the high incidence of occult nodal disease in all but the earliest superficial carcinomas (i.e., those limited to less than 5 mm invasion) of the floor of the mouth, prophylactic neck dissection is recommended at these sites [52, 63]. For T1 or T2 lesions, an ipsilateral supraomohyoid (levels I–III) dissection is generally advocated as the surgical procedure of choice; bilateral selective dissections are indicated for more anterior/midline lesions [65]. Because of the density

of neurovascular structures in the floor of the mouth, frequent metastasis occurs to the sublingual, submandibular, and level II lymph node basins.

Postoperative radiation (in some cases, with concomitant chemotherapy) is indicated for patients who have positive resection margins (if not re-resected), mandibular bone erosion, or pathologically positive lymph nodes after elective neck dissection. Postoperative RT should also be considered if there is vascular or perineural invasion in the primary tumor [66]. For resectable tumors in nonsurgical candidates, RT (usually a combination of external beam RT and brachytherapy) achieves similar local control rates [66].

## 24.10 Tumors Invading the Mandible

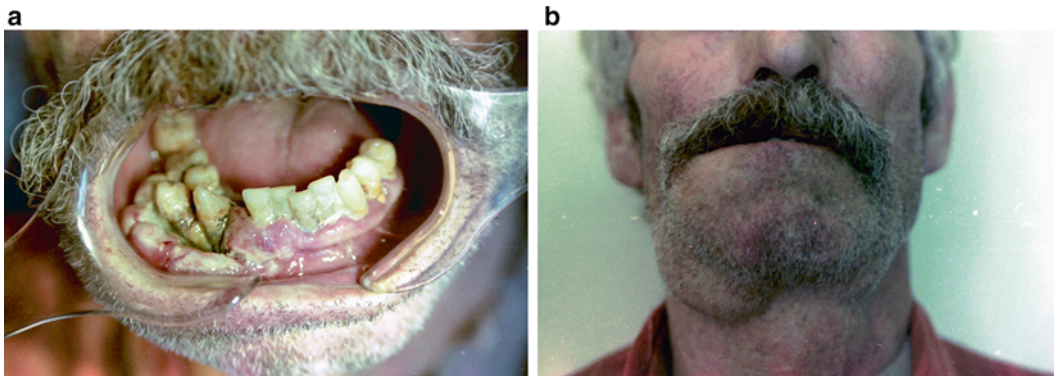
Tumors within the oral cavity may invade the mandible and gain entrance into the mandibular canal through several routes. Not uncommonly, SCC of the oral epithelium will travel along the surface mucosa until it approaches the attached gingiva where the tumor cells may come into contact with the periosteum of the mandible. This can be done in both dentate and edentulous patients. In the dentate patient, tumor cells demonstrate a tendency to migrate into the dental sockets because this area represents a pathway of minimal resistance. In edentulous patient, tumor cells will migrate onto the occlusal surface of the alveolus and enter the mandible through dental pits, which are cortical bone defects at the location of prior dentition. SCCs of the floor of the mouth may also extend to invade the neighboring mandibular bone. Less commonly, tumor may enter the mandible through mental or mandibular canals. Finally, adjacent tumor may erode through the cortical bone directly into the mandibular canal (Fig. 24.6).

Plain radiography has been used in the past for the diagnosis of tumor invasion of the mandible. The introduction of orthopantomogram or panoramic radiography, CT, and MRI

scans has increased the accuracy of preoperative imaging and staging (Fig. 24.7). Significant debate still exists regarding the optimal modality or combination of modalities recommended for preoperative assessment of mandibular invasion by oral SCC. While CT is a very accurate method for identifying gross bone invasion, prior work has suggested that bone invasion may be missed in as many as 27 % of patients with preoperative CT scans [67]. The CT scan renders an excellent view of both the soft tissue and bone of the mandible; however, it has several limitations, the most significant being artifacts caused by dental amalgams and prosthetic metal bridgework. Dental amalgams commonly create a shadow leading to artifact that can obscure invasion of the mandibular cortex. Additionally, the CT scan may misleadingly detect defects in the cortex secondary to irregular tooth sockets or periapical lesions of inflammatory origin.

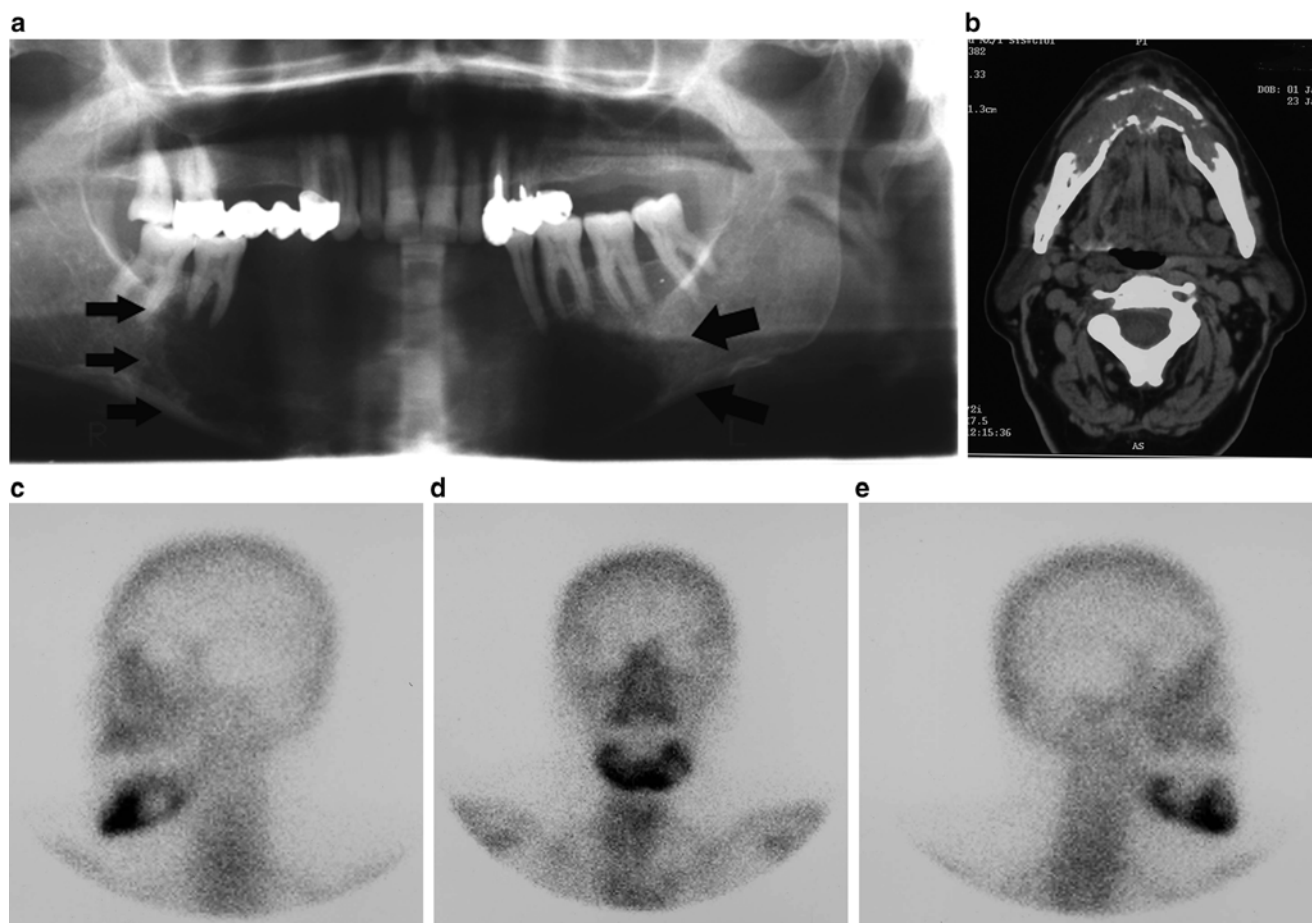
In light of these shortcomings, several investigators have reported on the use of a Dentascan. The Dentascan was introduced in the early 1980s to assist oral maxillofacial surgeons in planning for osseointegrated implants. The Dentascan images are derived by reformatting standard axial CT scans in two views, panelliptical and parasagittal. This reformatting permits assessment of the buccal and lingual cortices. The diagnostic accuracy of the Dentascan is high, yielding a sensitivity of 95 % and a specificity of 79 % with a positive predictive value of 87 % and a negative predictive value of 92 % [68]. The Dentascan is therefore an accurate method for preoperative evaluation of mandibular invasion in patients with SCC of the oral cavity (Fig. 24.8).

While the CT scan and Dentascan may offer excellent methods for assessing bone, MRI offers the advantage of imaging soft tissue and potentially the medullary bone space. Several studies have examined the use of MRI in assessing mandibular invasion and it has been concluded that MRI is superior for evaluating the medullary space of the mandible [69] but inadequate for assessing mandibular invasion. Shaha [70] examined the value of various studies including



**Fig. 24.6** (a) Clinical photograph of a 58-year-old male patient with a large (T4) squamous cell carcinoma of the right mandibular parasymphysis. The patient, a heavy smoker and alcoholic, reported a 2 years

presence of the tumor which had completely invaded the mandibular bone. (b) There was a marked regional lymphadenopathy with fixation of the nodes in the mandible



**Fig. 24.7** Squamous cell carcinoma of the anterior part of the mandible in a 60-year-old female. (a) Orthopantomogram showing the lesion to extend from the right premolars area of the mandible to the left one (arrows). (b) CT of the mandible shows the extensive distraction of the

osseous architecture of the mandible extending to the buccal and lingual cortical bone. (c, d, e) Bone Scan with Tc 99 m shows a pathological uptake of the radionuclide in the anterior part of the mandible. The uptake corresponds to the extent of the lesion

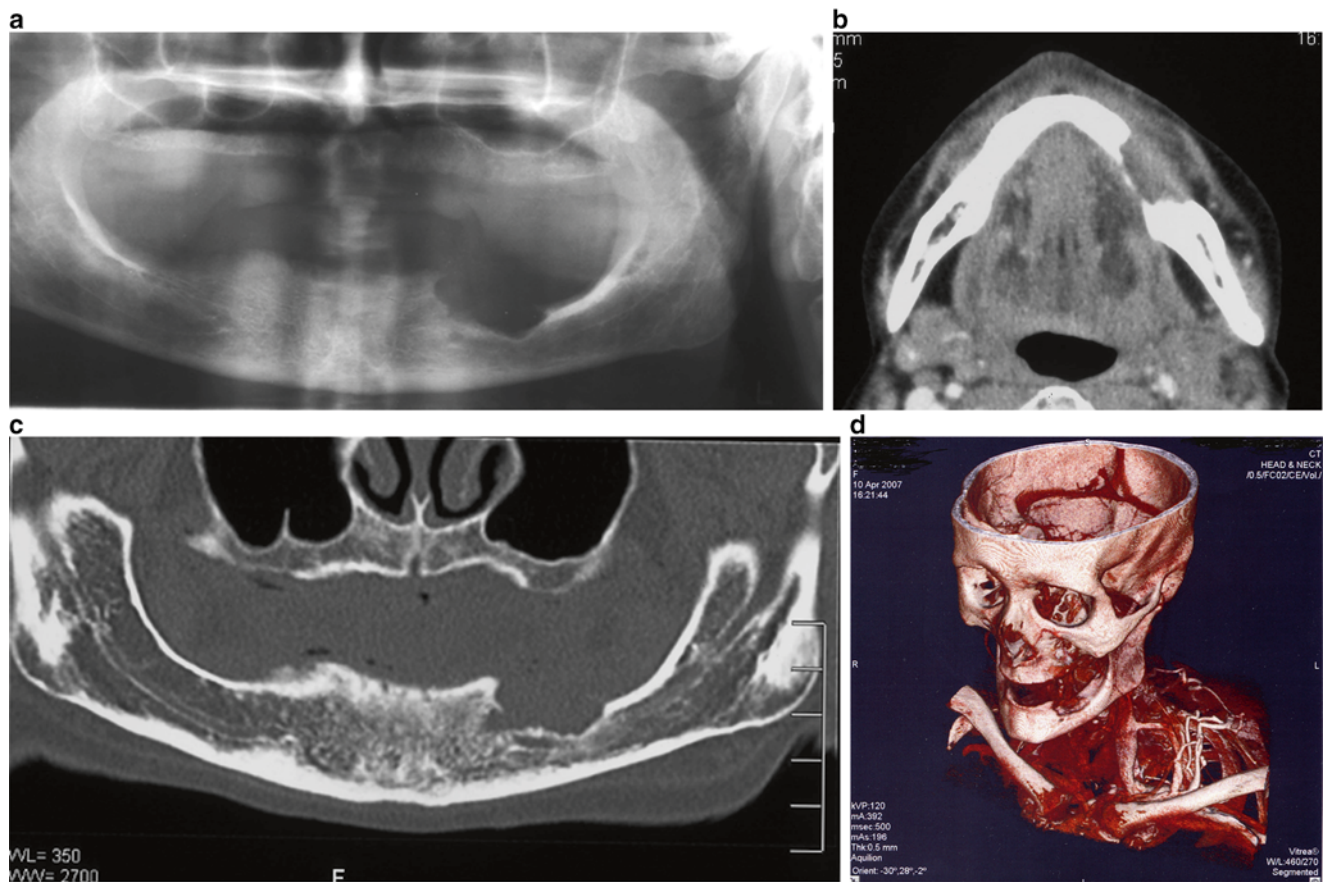
panoramic X-rays, dental films, routine mandible films, bone scans, CT scans, and MRI and found that CT scanning was not very helpful mainly because of the presence of irregular dental sockets and artifacts. Many suggest that clinical evaluation is the most accurate in determining the presence of bone invasion and the optimal method of resection, marginal versus segmental [71].

Most centers consider the combination of a CT scan and a panoramic X-ray acceptable for preoperative imaging of the mandible and maxilla; however, the most accurate measure of bony invasion is determined clinically at the time of surgery. Unless there is frank invasion of the bony cortex, periosteal stripping followed by frozen section examination at the time of surgery is often the most reliable measure of bone invasion. Recent studies have shown that technetium (Tc) 99 m bone scintigraphy in the form of planar views or as SPECT provides a high diagnostic accuracy for mandibular invasion by oral SCC of the alveolus in both edentulous and dentate patients [72, 73].

Among all investigations and evaluations of the extent of disease in the oral cavity in relation to involvement of the

mandible, the best investigation continues to be routine clinical evaluation and intraoperative evaluation of the proximity of the tumor to the inner border of the mandible. Even though the tumor may not involve the mandible directly, a marginal mandibulectomy may be necessary for appropriate oncologic margins and resection of part of the mandible due to close proximity. This decision is best made using clinical judgment.

Tumors invading the mandible can be managed either with a marginal resection or a segmental resection. The decision regarding the optimal method of tumor resection is largely dependent on the degree of invasion. It has been suggested that tumor invasion of the periosteum or cortical bone, without invasion of the medullary cortex, can be appropriately managed with a marginal resection. Tumors that erode into the medullary canal, however, require a segmental resection. It has been shown that once a tumor gains access to the medullary canal, tumor may travel through the canal via the neurovascular bundle. The inability to obtain frozen section assessment of the mandible intraoperatively represents a management dilemma because decalcification of the



**Fig. 24.8** Squamous cell carcinoma of the left body of the mandible in a 68-year-old male patient. (a) The orthopantomogram shows a lytic lesion in the left body of the mandible extending to the inferior dental canal. (b) The CT shows complete destruction of the entire width of the

mandibular body. (c) The Denta Scan CT depicts the erosion of the cortical bone and the extension of the tumor to the medullary part of the mandible. (d) Three-dimensional reconstruction of the CT of the mandible

mandible specimen in preparation for definitive histopathological analysis can take as long as 2 weeks.

The periosteum is relatively resistant to cancer invasion. With the exception of the tooth sockets, the periosteum acts as a dense barrier to the invasion of adjacent tumor. In spite of the protective periosteum, aggressive and long-standing tumors erode the periosteum and invade the adjacent mandible through a variety of pathways. Two distinct histological patterns of tumor invasion have been identified. The first pattern is referred to as *infiltrative* and is characterized by fingerlike projections of tumor which advance independently and invade the cancellous spaces without the intervening connective tissue layer and possess very little osteoclastic activity. The second pattern is referred to as *erosive*. In contrast to the infiltrative pattern, the erosive pattern is characterized by a broad front with a connective tissue layer and active osteoclast activity. The significance of the erosive and infiltrative patterns has been demonstrated in several reports, and it has been demonstrated that patient survival is significantly impacted by the pattern of invasion [74]. It has been suggested that the pattern of invasion is a reflection of the biologic aggressiveness of the tumor and may impact the approach to ablative therapy. While most tumors that invade the mandible mandate postoperative

external beam radiation, some have suggested that superficially invading tumors may not benefit from postoperative radiation. Given the aggressive behavior of the infiltrative pattern of invasion, we recommend postoperative RT for all patients with this pattern of bone invasion.

While the superficial invasion of the periosteum or cortical bone may be managed with a marginal mandibulectomy, once the tumor has eroded into the medullary cavity and mandibular canal most advocate a segmental resection. Determining the presence of bone erosion and the extent of bone erosion represents an ongoing clinical dilemma. The poor predictability associated with preoperative imaging has led many to rely on preoperative clinical assessment as the primary method for determining the presence of mandibular invasion. Several groups have studied this issue and found that clinical evaluation of mandibular bone erosion is more sensitive than radiographic evaluation; however, radiographic assessment may be more specific and provide a higher reliability index [75].

There are a few studies reviewing the impact of clinical assessment alone in determining the extent of mandibular invasion. This likely represents the difficulty in quantifying a clinical exam. However, most agree that clinical assessment

for invasion is paramount. Several studies have evaluated the role of periosteal stripping as an indicator for tumor invasion of the mandible and found that periosteal stripping at the time of resection represented an accurate predictor of the presence of mandibular invasion [76]. Without clear preoperative evidence of mandibular invasion, a marginal resection followed by periosteal stripping and inspection is an adequate approach. In the event that microscopic evidence of invasion at the rim is discovered, the marginal mandibulectomy is converted into a segmental mandibulectomy.

### 24.11 Lower Alveolar Ridge and Retromolar Trigone Cancer

The retromolar trigone is a small mucosal space that begins at the third molar of the mandible and extends cranially to the maxillary tuberosity. It is directly continuous with the buccal mucosa, upper and lower gingiva, maxillary tuberosity, anterior tonsillar pillar, soft palate, and the floor of the mouth (Fig. 24.9).

Squamous cell cancers arising in the retromolar trigone and lower alveolar ridge comprise approximately 10 % of all oral cancers and exhibit the same 3 or 4:1 male predominance of other head and neck cancers. The presenting symptom is typically pain, which is exacerbated by chewing.

Treatment options include RT and surgery. The local recurrence rate is higher with these tumors than for other sites in the oral cavity due to microscopic extension to the mandible and maxilla (for retromolar trigone tumors). In addition, the probability of occult regional lymph node metastases is higher than with most other oral cavity tumors, with the exception of tongue cancer and floor of mouth cancer [69]. Thus, elective neck dissection is usually recommended for patients with a clinically negative neck.

Surgical treatment involves wide local excision. Marginal or horizontal “rim” mandibulectomy may be required in order to achieve tumor-free margins. Due to the normally thin overlying mucosa and the close proximity to the mandible, alveolar ridge and retromolar sites have a propensity for early invasion of this bone, as well as the maxilla for retromolar trigone lesions [77, 78]. Consequently, lesions that are clinically staged T1/T2 and treated with rim mandibulectomy may become pathologic stage T4 after histologic confirmation of bony invasion. Segmental or composite resection is reserved for those tumors that are deeply invasive or that wrap around the mandible [67]. In addition, segmental mandibulectomy may be necessary for early-stage lesions in the thin, edentulous mandible in order to achieve negative margins.

It is extremely important to determine the true invasive margin, which may extend grossly or microscopically beyond the tumor front [69]. Determining this invasive margin is challenging. For oral cavity lesions in general, computed tomography (CT) scans may be helpful for identifying bone invasion. The sensitivity of CT scan for bone involvement of the retromolar trigone is approximately 50 % with a negative predictive value of 60 %; however, the positive predictive value is approximately 90 %. It has been concluded that while the CT scan is accurate when bone erosion is clearly identified, its negative predictive value is unacceptably low and therefore an inaccurate indicator of bone invasion at the retromolar trigone. In one report of 127 patients with oral cavity or oropharyngeal carcinoma treated with composite (segmental) resections, CT scan findings suspicious for bone invasion and primary tumor location (alveolus, retromolar trigone, tonsil, and sulcus) were the only independent variables that predicted for the presence of bony invasion [72, 77, 79]. However, in one report, preoperative CT scan failed to identify bone invasion in one-half of



**Fig. 24.9** (a) Squamous cell carcinoma of the left retromolar area of the mandible in a 47-year-old male patient. The lesion was diagnosed after a dental extraction when the tooth socket failed to heal after 6 weeks. (b) Clinical photograph of a ulcerative lesion in the right retromolar trigone of a 52-year-old male patient. The superficial ulceration

after biopsy proved to be a moderately differentiated squamous cell carcinoma. (c) Clinical photograph illustrating a carcinoma of the alveolar ridge in a 60-year-old partially edentulous female patient. The patient reported an ill-fitting denture that produced diffuse local pain

retromolar trigone lesions that histologically invaded bone [80]. Potential reasons for this low sensitivity include the thickness of CT sections, the lack of bone windows and coronal imaging, and the presence of distortion from dental artifact.

A resection margin of at least 1 cm in all directions is recommended [81]. At least for tumors involving the retromolar trigone, the optimal extent of surgery is controversial [63, 82]. In addition to stage, outcomes are dependent on the presence of bone invasion, deep infiltration of the masticator space, nodal involvement, and treatment modality [78, 83, 84].

Among the patients with stage I and II disease, survival exceeds 75 % at 5 years. In a later series of 99 patients treated with definitive RT or surgery followed by RT, local control rates were better in surgically treated patients (approximately 71 vs. 48 %) [83, 85]. Among all patients treated for stage I–III disease (RT or surgery plus RT), 5-year rates of cause-specific and overall survival were 70 and 58 %, compared to 57 and 42 % for those treated for stage IV disease. Notably, in multivariate analysis, both cause-specific and overall survival were significantly better in the group undergoing RT in addition to surgery.

For early lesions of the lower alveolar ridge and retromolar trigone, selective neck dissection in levels I–III is recommended as tumors are characterized by early invasion of the mandible and high rates of regional metastases.

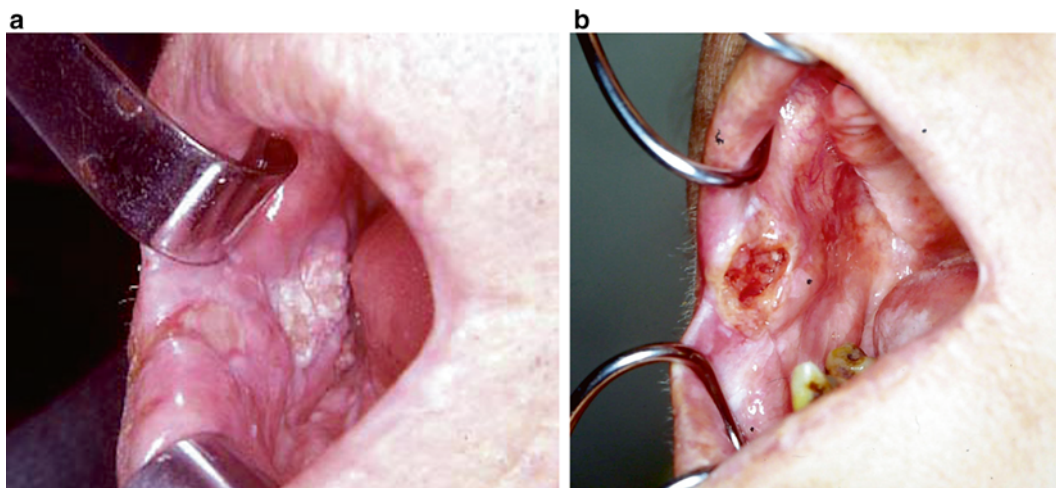
## 24.12 Tumors Invading the Buccal Mucosa

Buccal cancer comprises less than 10 % of oral cavity cancers, and when it occurs, it commonly arises from a preexisting leukoplakia [86, 87] (Fig. 24.10).

SCCs arising within the buccal mucosa are notable for their locoregional aggressiveness. For early-stage disease, treatment with either surgery or definitive RT is reasonable, although in most circumstances surgery is favored. Surgical treatment can be compromised by anatomic difficulties in obtaining adequate margins. For locally advanced but resectable tumors, surgery followed by postoperative RT is the treatment of choice.

The principles of management of buccal cancer are no different than those of other subsites within the oral cavity. Surgical therapy is the preferred method of management. In early disease, surgical excision can usually be accomplished transorally. The buccal space has poor anatomic boundaries and it is difficult to obtain a clear surgical margin. Even patients with early-stage disease have potential microscopic invasion through the buccinator muscle into the buccal fat and buccal space.

Although more aggressive surgery including exenteration of the buccal space and parotidectomy may improve surgical results, the resulting disfigurement and morbidity of these procedures may be considerable. Tumors that invade the buccinator muscle and tumors that present with nodal disease or with poor prognostic features should be managed with postoperative radiation therapy. Negative surgical margins are paramount, and in an effort to achieve this goal, careful preoperative planning is essential to determine the extent of the tumor. While early tumors of the buccal mucosa commonly present as an irregular mucosal mass, more than half of buccal tumors will present as deeply invasive tumors that may track along the parotid duct, masseter muscle, or into the palate. The proximity of the buccal mucosa to the parotid duct requires that the duct be traced retrograde and sampled to ensure a negative margin.



**Fig. 24.10** (a) Squamous cell carcinoma developed in a preexisting leukoplakia of the right buccal mucosa in a 56-year-old male smoker patient. (b) Deep ulcerative lesion in right buccal mucosa and the corner of the mouth in a 56-year-old female patient



Deeply invasive lesions may break into the buccal fat pad. When this occurs, it is advisable to resect the entire fat pad because negative surgical margins in this area are difficult to confirm. The rich lymphatic network, characteristic of the buccal region, and the high rate of lymph node metastasis mandate that the neck be carefully evaluated and, in most cases, treated. Smaller tumors can usually be managed through a transoral approach; however, more advanced tumors may require a midline labiotomy incision. Cancer of the buccal mucosa is a highly aggressive form of oral cavity cancer that is associated with a high rate of locoregional recurrence and poor survival.

Surgery is generally preferred for managing small lesions. The tumor can usually be excised using a transoral approach. Five-year survival rates are approximately 75 % for patients with stage I disease and 65 % for patients with stage II lesions [88–90]. However, local recurrence rates with surgery alone are high, particularly with surgical margins less than 2 mm [88, 89, 91].

Treatment of the clinically negative neck is controversial. Elective neck dissection is not routinely recommended in all patients. For those with small (T1) lesions, cervical lymph node metastases occur in less than 10 % and the neck can be observed. Selective neck dissection of levels I–III should be considered for larger lesions [89].

### 24.13 Upper Alveolar Ridge and Hard Palate Cancer

Malignant neoplasms of the upper alveolar ridge and hard palate comprise approximately 5 % of oral cavity malignancies and have a male to female ratio of 8:1. Only about two-thirds of hard palate malignant neoplasms are SCCs; the remainder are minor salivary gland carcinomas and other

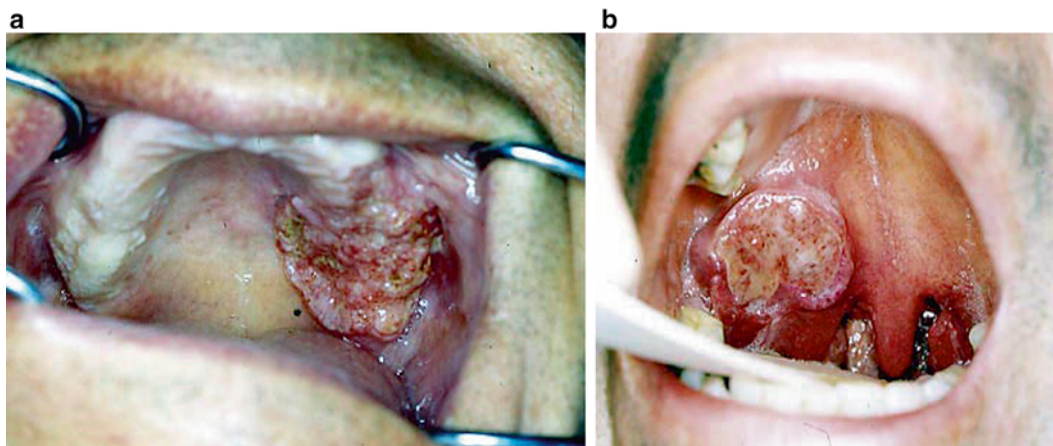
rare malignancies. Unlike other areas of the oral cavity where SCC makes up the overwhelming majority of pathology, the palate is rich in minor salivary glands and therefore is the site of both benign and malignant salivary gland tumors (Fig. 24.11).

Most upper alveolar ridge and hard palate SCCs are managed with primary surgery. RT can be used for small, superficial lesions, or tumors with extensive involvement of the hard and/or soft palate. Combined modality therapy provides better locoregional disease control than single modality therapy [83, 84]. Postoperative RT (in some cases with concomitant chemotherapy) is indicated for patients with positive resection margins, bone erosion, or pathologically positive lymph nodes after elective neck dissection [83, 84]. Others recommend that postoperative RT also be considered if there is vascular or perineural invasion in the primary tumor [66].

The principles of management of tumors of the palate are similar to those of mandible; obtaining tumor-free margins is essential to achieving a good outcome. Lateral tumors may represent a risk to invasion and perineural spread via the palatine or trigeminal neurovascular bundle. The depth of invasion will dictate the extent of the surgical resection. Superficial lesions of the palatal mucosa are best managed with a wide surgical resection including the underlying palatal periosteum. The periosteum serves as an early barrier to spread; however, as tumors become more invasive, tumors can vertically invade the nasal vault or maxillary sinus.

Tumors of the hard palate rarely metastasize to the neck and therefore a neck dissection is rarely warranted in the absence of demonstrable regional disease. One exception is when there is tumor erosion through the posterior or posterior lateral maxillary sinus into the pterygopalatine fossa.

Most lesions of the upper alveolar ridge and hard palate are managed with primary surgery. Lesions with extensive involvement of the hard and/or soft palate can also be initially



**Fig. 24.11** (a) A large, T3 squamous cell carcinoma of the alveolar ridge and the palatal mucosa in a 72-year-old male edentulous patient. (b) Exophytic ulcerative tumorous lesion in the hard palate in a 63-year-

old female patient. The lesion extends to the soft palate causing dysphagia to the patient

treated with primary RT. In patients initially treated with surgical resection, the 5-year survival rates are 70 and 45 % for patients with stage I and II disease [92].

Selective neck dissection with removal of level I–III nodal groups is adequate for early disease of the hard palate in patients with clinical positive nodes at presentation. If disease extends beyond the hard palate, however, elective treatment of the neck is indicated even in No neck patients.

#### 24.14 Maxillary Sinus Cancer

Paranasal sinus cancer is rare, accounting for just 3 % of upper aerodigestive tract malignancies [93]. The incidence is higher in males than in females (2:1) with a peak incidence at 50–59 years of age. Lesions of the maxillary sinus are most common, followed by the ethmoid, sphenoid, and frontal sinuses. These tumors are generally slow-growing and tend to remain asymptomatic until late in the course. As a result, most patients present with locally advanced disease. SCCs constitute the majority of paranasal malignancies (45–80 % of cases). This is followed by malignancies of salivary gland origin, of which adenoid cystic carcinomas predominate [94–96], followed by adenocarcinomas and mucoepidermoid carcinomas. The most common symptoms in patients with paranasal sinus cancer include facial or dental pain, nasal obstruction, and epistaxis [97]. Oral symptoms (e.g., ill-fitting dentures) occur in 25–30 % of patients. Pain with unilateral nasal obstruction or ocular symptoms can be seen in 50 and 25 % of patients with antral-ethmoidal disease, respectively (Fig. 24.12).

A classic triad of facial asymmetry, palpable/visible tumor in the oral cavity, and visible intranasal tumor occurs in 40–60 % of patients with advanced disease. At least one of these signs is present in 90 % of cases [98].

As disease progresses, symptoms and signs depend upon the involved site. The bony structures between the nasal cavity, sinuses, orbits, and cranial vaults are thin and offer little resistance to cancer spread (Fig. 24.13).

Regional nodal metastases are uncommon, occurring in less than 20 % of patients, lower if they have adenoid cystic tumors [94, 99–102]. The incidence of lymph node involvement increases as tumors extend locally to adjacent sites, especially with extension into the oral cavity. The retropharyngeal nodes comprise the first echelon lymphatic drainage for sinus malignancies. Other regional nodes that may be involved with lymphatic spread are the periparotid and level Ib nodes. Patients with clinically positive nodes will have their necks treated with surgery and/or radiotherapy. Much more controversial is the strategy to be adopted for patients with a NO neck. Some authors stress the indication for prophylactic neck treatment, whereas others recommend a wait and see policy especially in patients with small sized or his-

tologically low-grade tumors. In order to investigate this controversial issue, Cantu et al. [103] performed a retrospective study of patients with tumors of the maxillary sinus. The study included 704 consecutive patients with malignant tumors of the paranasal sinuses seen over a 35-year period. Tumor site was classified as maxillary or ethmoid sinus. The series of 704 study patients included 305 patients with tumors of the ethmoid sinus (43.3 %) (ethmoid sinus group) and 399 with tumors of the maxillary sinus (56.7 %) (maxillary sinus group). Eighty patients underwent an orbit exenteration. Surgical resection achieved clean margins in 545 cases (77.4 %); there was macroscopic residual disease in 38 cases (5.4 %) and close margins or microscopic residual disease in 121 cases (17.2 %). The surgical procedure that achieved the highest rate of clean margins was anterior craniofacial resection (88 %). Lymph node recurrences (66 overall) were mostly observed in the maxillary sinus group, with a cumulative incidence significantly higher (12.5 %) than for the ethmoid sinus group (4.3 %) ( $P = .001$ ). They concluded that nodal metastases from malignant tumors of the ethmoid sinus are very rare, either at presentation (1.6 %) or during the postoperative follow-up period (4.3 %). Moreover, most subsequent neck metastases appeared together with a recurrence of the primary tumor. Therefore, in their opinion, in ethmoid sinus malignancies there is no indication for prophylactic treatment of the neck. The problem is more intriguing for maxillary sinus malignant tumors. In non-squamous cell carcinomas, the rate of neck metastases at presentation in this series was very low (6 %). In addition, subsequent nodal metastases were rare. The rate of neck metastases at presentation for SCC was 10.3 %. The percentage of cervical metastases was much higher in T2 tumors than in T3 or T4 tumors. However, among 31 patients who developed node metastases during follow-up, only 1 presented with unresectable nodes, whereas 30 underwent neck dissection with or without radiotherapy and were successfully salvaged [103].

There is no consensus as to optimal treatment for early-stage tumors. Traditionally, surgery has been the primary treatment modality for paranasal sinus cancers involving the maxillary or ethmoid sinuses. However, the limitations of surgery alone are obvious given the frequent presentation of advanced disease [104].

Both surgical technique and the overall approach to management have evolved to incorporate into the decision-making process the histology and tumor size as well as location in relation to the adjacent critical structures. In many cases of maxillary and ethmoid sinus SCC, for example, aggressive local therapy includes en bloc craniofacial resection with or without orbital exenteration, followed by reconstruction and adjuvant RT.

RT may be used, particularly for T1 tumors of the ethmoid, sphenoid, and frontal sinuses, with acceptable results



**Fig. 24.12** (a) Clinical photograph of a 63-year-old male patient. The patient reported an 18 months history of progressive pain and swelling of the left eye causing visual disturbances. Clinical examination showed a painful mild exophthalmus with proptosis of the left eye and ptosis of the upper lip. (b) Intraoral examination of the same patient revealed a swelling of the left alveolar ridge of the maxilla with expansion and parts of ulcerations of the overlying mucosa. The edentulous patient reported a progressive inability for his denture to fit in place. Radiographic examinations and intraoral biopsy showed an extensive

squamous cell carcinoma of the left maxillary sinus invading the orbital content and extending to the nasal cavity. (c) The patient during chemoradiation. A marked erythematous reaction of the skin of the left middle third of the face caused by radiotherapy is evident. (d) Chemoradiation also produced a stage IV mucositis. (e) Three months after chemoradiation improvement of the clinical signs and symptoms occurred. (f) Clinical photograph of the patient 3 years after chemoradiation. The patient shows a complete response and remains tumor free. (g) Intraoral photograph showing complete response to the treatment

[105, 106]. However, in practice, RT is rarely used as the sole modality of treatment except for cancers of the frontal and sphenoid sinuses, which are unsuitable for en bloc surgical resection.

Regardless of the surgical margin status, adjuvant postoperative RT optimizes local control. However, even with aggressive surgery and adjuvant RT, the results of treatment for most paranasal sinus cancers are poor with local control rates from 50 to 60 %, and 5-year survival rates ranging from 30 to 60 % [105–113].

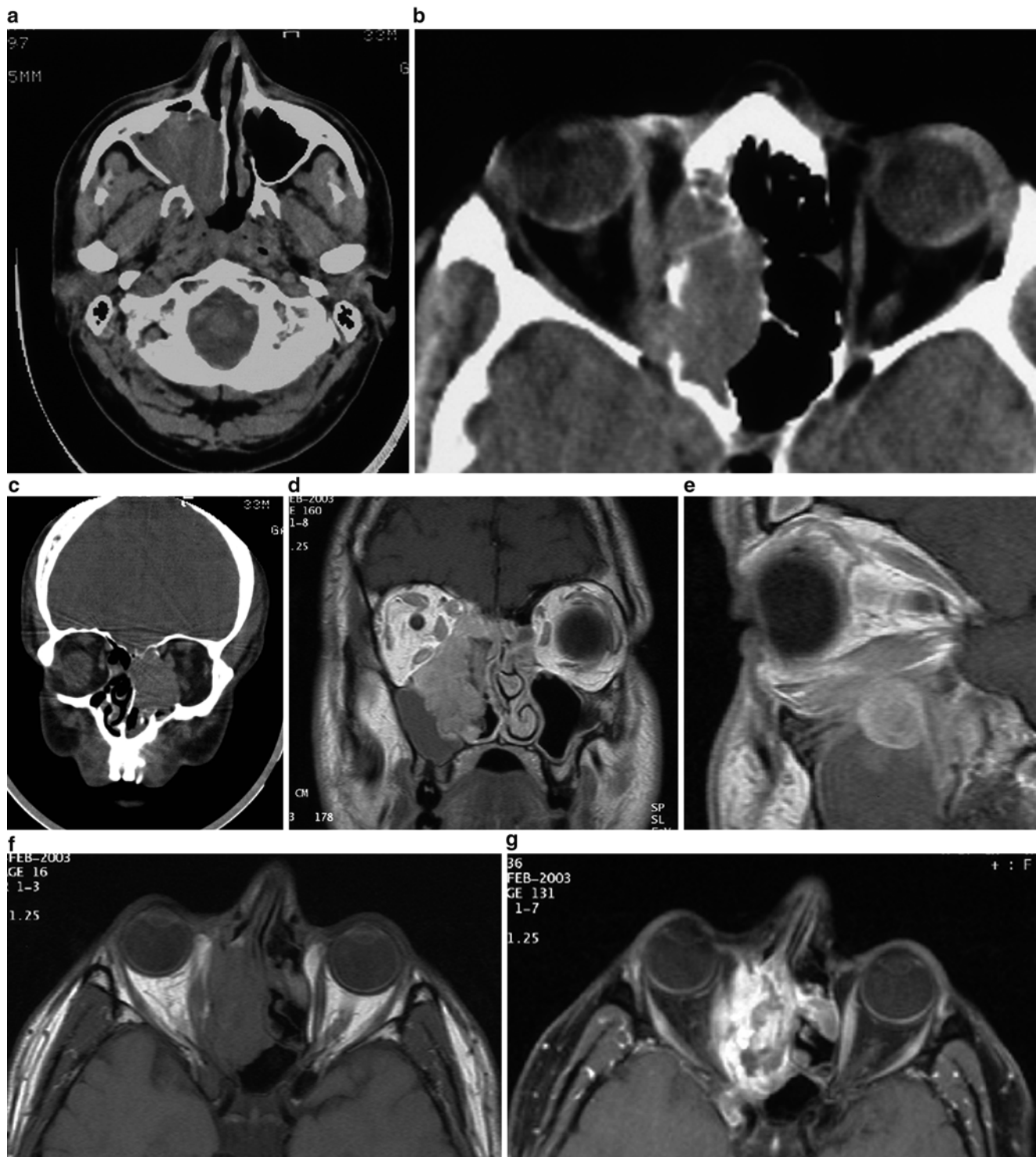
Preoperative RT has been explored as a means of making these lesions more amenable to surgical resection [99, 114]. However, given the inherent bias in these nonrandomized studies, it is unclear whether preoperative is superior to post-

operative RT in enhancing local control and improving outcome.

The use of postoperative RT and concomitant chemotherapy should be considered in patients with pathologically positive lymph nodes, particularly in cases with adverse prognostic factors such as multiple metastatic lymph nodes or any node with extracapsular spread.

## 24.15 Conclusions

If one wants to summarize the most notable developments of the last 30 years in the therapeutic management of oral squamous cell carcinomas that have been incorporated into



**Fig. 24.13** Squamous cell carcinoma of the right maxillary antrum extending in the homolateral orbital cavity, the anterior ethmoids, and the nasal cavity in a 72-year-old male. (a) CT shows the lesion occupying the right maxillary sinus. The lesion is confined within the maxillary sinus cavity and does not erode the wings of the sphenoid bone. (b) The lesion occupies the anterior ethmoids and erodes the thin lateral

orbital wall. (c) Coronal section showing the extension of the tumor into the right orbital cavity. (d) In the MRI (coronal T1 weight imaging) the tumor extends to the entire right middle third of the face. (e) Sagittal T1 weighting image showing the tumor eroding the right orbital floor and extending into the content of the orbital cavity. (f, g) T1 and T2 weighting images of the tumor invading the anterior ethmoids

everyday clinical practice, he should definitely point out the following key issues.

During the last 30 years the belief that oral cancer management is based on team work has been established. The functions of tumor boards and combined clinics is a common contemporary practice with an exceedingly large number of medical, surgical, and other specialties being part of comprehensive, multidisciplinary therapeutic head and neck teams.

The basic treatment modalities remain surgery, radiotherapy, and chemotherapy. Basic surgical techniques have not changed dramatically over the last 30 years. Among the major changes are the variations in the surgical management of the neck of both clinically negative and clinically positive neck patients, as well as the management of the mandible especially in the early invasion of oral squamous cell carcinoma in the mandibular bone. The revolution in the surgical treatment of oral cancer is the introduction of reconstructive techniques with both pedicled locoregional flaps and free tissue transfer. These reconstructive techniques allowed for safer and wider resections with adequate disease-free margins and functional reconstruction of the created surgical defects.

Contemporary radiotherapeutic treatment has very little similarities with that of the late 1970s. Modern technology with the institution of new forms of radiation and the application of sophisticated computerized methods have enhanced the therapeutic effectiveness of irradiation with an equal important reduction in the sparing in irradiation of normal surrounding tissues. This has led to an increased therapeutic dose in the tumorous bed and a decreased severity of radiation-induced injuries in the neighboring unaffected by the disease normal tissues. Alterations in the fractionations have also shown to produce better therapeutic results in selected cases.

The era of methotrexate, the leading chemotherapeutic agent of the 1970s, was followed by the institution of platinum-based chemotherapies with or without the addition of 5-Fu. Adjuvant and neoadjuvant schemes coupled with pre- or postoperative radiotherapy started in the late 80s and showed a distinct survival benefit over radiotherapy alone. This major breakthrough was followed by the institution of various and diverse chemoradiation regimes tested over a large time period for their survival benefits. The introduction of taxanes and the development of molecular targeted therapies during the last 5 years have revolutionized the concept of chemoradiation. Induction chemotherapy and chemoradiation coupled with epidermal growth factor receptor antagonists proved to have a survival benefit in patients with locally advanced or recurrent squamous cell carcinoma of the head and neck. Other biological agents against tumor angiogenesis or resulting in the restoration of cell apoptosis are being tested in various phase I or II trials with promising results.

## Message Box

- In the course of the next decade: oral cancer in nonsmoker nondrinkers will increase.
- The differences in the ratios between males and females will tend to equalize.
- Surgery will remain the prime modality in early (stage I and II) disease.
- Molecular prognosticators will be used to determine optimal treatment.
- Postoperative chemoradiation will remain the treatment of choice for “aggressive” early (stage I and II) disease.
- Organ preservation treatments will prevail in advanced (stage III and IV) disease.
- Surgery will remain the treatment of choice for locoregional salvage surgery.
- The use of stem cells and biomechanical engineering will complement reconstructive surgery.

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