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Chapter

Oral Cancer

Xue Xiao and Zhou Wang

Abstract

Oral cancer is a frequent head and neck cancer in developing countries and some developed world. According to the World Health Organization classification 2017, oral cancer influences the anatomical subsites including buccal mucosa, the anterior two-third of the tongue, lip, palate, vestibule, alveolus, floor of the mouth, and gingivae. A variety of premalignant lesions are related with the development of oral cancer, such as leukoplakia, erythroplakia, et al. The predominant histological type of oral cancer is squamous cell carcinoma (SCC). Tobacco and alcohol consumption are regarded as critical etiological factors. Due to the unspecific symptoms in early stage, the majority are diagnosed in advanced stages. Despite the development of medicine over decades, the mortality rate of oral cancer remains high, indicating the importance of optimized treatment and screening strategies.

Keywords: oral cancer, etiology, diagnosis, treatment, prognosis

1. Introduction

Oral cancer is a malignant head and neck disease, and it accounts for 2–5% of cancer types and around 30% of head and neck cancers [1, 2]. According to the World Health Organization classification 2017, oral cancer is defined to tumors in the buccal mucosa, the anterior two-third of the tongue, the lip, palate, vestibule, alveolus, floor of the mouth, and gingivae [3]. Cancers of salivary glands or oropharynx will not be discussed in this chapter.

Oral cancer is distributed high in countries such as India, Pakistan, Taiwan China, and Germany [4]. It is more frequent in men than women [5]. It has a complicated etiology and it is related to many risk factors like tobacco, alcohol, betel nut, human papillomavirus (HPV) infection, et al. Around 90% of oral cancers are squamous cell carcinoma. In early stage of oral cancer, signs are unspecific and not easy to be recognized. As a result, most of the patients are diagnosed at a late stage, dropping down the survival rate from 80–90% to 20–50% [6]. Thus, the prognosis of oral cancer is poor and it is urgent to raise the awareness of public health education. The major management of oral cancer is surgery, supplemented with/without adjuvant radiochemotherapy. However, for better survival, personalized and multidisciplinary treatment strategies are needed.

2. Incidence of oral cancer

Despite the development of modern treatment methods, no significant achievement was reported in the prognosis, survival and mortality of oral cancer. According to the GLOBOCAN 2018 project, there is 354,864 new cases and 177,382

deaths due to oral cancer worldwide [7]. Geographically speaking, oral cancer is highly prevalent in South and Southeast Asia (India, Pakistan, etc.), West, Middle and Eastern of Europe (France, Germany, Hungary, etc.), and Oceania [4, 8, 9]. It is important to notice that the incidence of oral cancer is high in transitioning countries, particularly in India [10]. The incidence rate for the male is higher than female, approximately 10:1 to 2:1 [5, 7]. It is noted that oral cancer patients are usually aged from 50 to 70 years. However, increasing numbers of oral cancer patients have been observed at younger age, possibly due to a distinct etiology and pathogenesis [11].

3. Pathology of oral cancer

More than 90% of oral cancers are squamous cell carcinoma (SCC) arising from the mucosal epithelium, namely oral squamous cell carcinoma (OSCC). A majority of them are moderate to well-differentiated. According to the WHO 2017 classification, eight kinds of subtypes are identified, including basaloid squamous cell carcinoma, spindle cell squamous cell carcinoma, adenosquamous carcinoma, carcinoma cuniculatum, verrucous squamous cell carcinoma, lymphoepithelial carcinoma, papillary squamous cell carcinoma, and acantholytic squamous cell carcinoma [12]. Each different subtype indicates different outcome.

Furthermore, a variety of oral potentially malignant disorders (OPMDs) have been reported to increase the potential of developing into oral cancer. Generally speaking, the common OPMDs, including erythroplakia, leukoplakia, oral submucous fibrosis, oral lichen planus, et al., increase the risk of malignant transformation, and they also serve as premalignant indicators in clinical works [12, 13].

4. Etiology of oral cancer

Numerous studies have demonstrated a multifactoral etiology in the development and carcinogenesis of oral cancer, involving tobacco, alcohol, betel quid, high-risk human papillomavirus (HPV) 16/18, poor nutrition, poor oral hygiene, immune system suppression, bacterial infection, and so on.

4.1 Tobacco

Tobacco is a well-established risk factor for lots of cancers as well as oral cancer. There are more than 80% of oral cancer patients with a habit of tobacco use. All types of tobacco products, for example cigarettes, pipe tobacco, chewing tobacco, contain many carcinogenic molecules, especially nitrosamines, benzopyrenes and polycyclic hydrocarbons, raising the risk of generating cancers. For tobacco smoking, it has a combined odds ratio of 4.65 (95% CI, 3.19–6.77) related with oral cancer [14]. For smokeless tobacco such as paan chewing and gutkha swallowing, it would lead to oral submucous fibrosis (OSMF) and ultimately increase the potential to transform into oral cancer. According to a nested case–control study in India, tobacco chewing was found the most potent high-risk factor linked to oral cancer, with adjusted odds ratios (ORs) of 3.1 for males and 11.0 for females [15].

4.2 Alcohol

Alcohol is also a well-defined significant risk factor for oral cancer [16–18]. An updated analysis based on cohort and case–control studies from 1988 to 2009

shows that, a consumption of 60 g per day or more than 4 drinks per day would raise the risk of oral cancer by 3–9 times when adjusted for smoking and other potential confounding variables [19]. The risk between alcohol and oral cancer is not only dose–response, but also related with the type of alcoholic beverage, meaning those consuming hard liquor or beer have a higher risk than those consuming wine. Besides, a greater significance is observed in both heavy smoker and heavy drinker [18].

4.3 HPV infection

Human papillomavirus (HPV) is a kind of small DNA virus that causes cervix cancer in females and anal cancer in males [20]. As a sexually transmitted pathogen, HPV also infects the human oral cavity in forms of oral sex behaviors and open-mouthed kissing. HPV, especially high-risk subtypes 16 and 18, is reported to have its role in the carcinogenesis of around one-third of oral cancer [21, 22]. Further, oncoprotein p16 is found over-expressed in oral cancer patients with high-risk HPV infection. Meanwhile, the relationship between HPV and oral cancer is not so strong when compared with oropharynx cancer, as studies showed that HPV-16 is found in 10–25% and HPV-18 in 14% of oral cancers [23]. Interestingly, HPV-positive oral cancers generate a more favorable outcome, possibly due to an enhanced anti-virus immune reaction. However, the role of HPV in oral cancer is far from clear [24].

4.4 Others

Besides, carcinogenesis of oral cancer is influenced by other factors namely betel quid chewing [25], poor diet and nutrition such as lack of fresh fruits and vegetables [26], poor oral hygiene [27], oral microbiome alteration [28], and genetic susceptibility [29].

5. Clinical presentations, diagnosis and staging of oral cancer

5.1 Clinical presentations

The most common symptoms of oral cancer patients may include ulceration (57.7%), induration (44.3%), and rupture (14.1%) [30]. However, due to the asymptomatic and unspecific signs, more than half of the patients went to a doctor in advanced stages when the discomforts worsen or appearance of new symptoms. In this situation, patients may present with an enlarged lesion, no improvement after the first treatment, onset of pain, inflexible movement of the tongue, discomfort in the mouth, difficulty in speaking and swallowing, bleeding, neck mass, et al.

5.2 Diagnosis

The physical examination of oral cancer is usually performed by inspection and palpation. The examination lasts around several minutes and does not require special equipment or technique. Dentists are the ideal position to perform examination and alarm suspected changes. Clinical investigation include assessment of primary tumor and the surrounded structures, such as deep muscle invasion, fixation to bone, and cranial neuropathies. Once a suspicious lesion is discovered, it is important for clinicians to perform biopsy, which is the gold standard for diagnosis.

An appropriate imaging detection is a complement of physical examination. It provides proper evaluation for patients. Initial examinations of the primary site are

usually done with computed tomography (CT) scan and/or magnetic resonance imaging (MRI). CT scan is good at evaluating the larynx, neck nodes and invasion of bone or cartilage. In comparison, MRI is preferred in patients concerning tumor involvement of soft tissue, perivascular, perineural, skull base, and intracranial. In addition, dental films or panoramic X-rays can be used in the assessment of cortical bone involvement and ultrasound (US) can be used to evaluate the metastasis of lymph nodes. As distant metastasis evaluation, FDG-PET/CT works more excellent [31]. However, in case of a concerned specific anatomic site, further contrast-enhanced CT and/or MRI should be performed. All the imaging measures mentioned above could help to describe the margins and invasion of the primary tumor, lymph node involvement, local and distant metastasis, thereby providing evidence for clinical TNM (cTNM) staging identification.

5.3 Staging

Nowadays, more and more studies realize that the malignant behavior of oral cancer is not only determined by tumor size but also invasive depth. Based on this, pathologic examination is further performed to identify pT (an actual measurement of unfixed fresh surgical tumor specimens) and/or pN. As an improvement of the previous oral cancer TNM staging algorithm, the eighth edition of American Joint Committee on Cancer (AJCC) Staging Manual highlights depth of invasion (DOI) for T stages and extranodal extension (ENE) for N stages. These alterations improve the discrimination ability of disease-free survival (DFS) between overall stages as well as T categories [32]. A comparison between the seventh and eighth edition is shown below in **Table 1**.

6. Treatment of oral cancer

Treatment of oral cancer patients, especially with invasive condition, is best determined by a multidisciplinary team of medical experts, which may include head and neck surgeons, pathologists, radiation oncologists, chemotherapy oncologists, neuroradiologists, reconstructive surgeons, dentists, nurse specialists and nutritionists. Managements include surgical resection, radiotherapy and chemotherapy, depending on anatomic site and size of the primary tumor, lymph node metastasis and distant metastasis, the patient's risk as well as benefit from the treatment, namely a personalized treatment.

6.1 Surgery

Surgery is the main option for oral cancer patients. There are series of choices: conventional/laser/thermal/robotic surgery, et al. Small tumors located in the anterior part of the oral cavity could be accessed via transoral approach. While for those advanced and/or located in the posterior part of oral cavity, routes of lip-splitting and/or mandibulotomy are suggested. As the first-line treatment strategy, the primary principle of surgery is adequate clearance of tumor and functional preservation (speech, swallowing, deglutition). A positive surgical margin increases the risk of recurrence and generates poor survival outcomes [34]. Thus, complete ablation is demanded, usually a 1-cm macroscopic resection margins around the tumor tissue are suggested for conventional surgery [35–37]. As an adjuvant technique, iodine vital staining supports evidence distinguishing dysplastic or tumorigenic tissues from benign mucosa [38].

However, difficulties of reconstruction come with enough resection margins. The most acceptable reconstruction scheme should take many factors into consideration, including the anatomic site and invasive condition of the primary

	AJCC (7th edition)	**AJCC (8th edition)** [33]
Primary tumor		
Tx: T0: Tis:	Primary tumor cannot be assessed. No evidence of primary tumor. Carcinoma in situ.	The same as the 7th edition. The same as the 7th edition. The same as the 7th edition.
T1:	Primary tumor <2 cm in biggest dimension.	Primary tumor≤2 cm, DOI ≤ 5 mm.
T2:	Primary tumor is 2–4 cm in biggest dimension.	Primary tumor ≤2 cm, 5 mm<DOI ≤ 10 mm; or 2 cm<tumor≤4 cm, and DOI ≤ 10 mm.
T3:	Primary tumor >4 cm in biggest dimension.	Primary tumor>4 cm or any tumor DOI>10 mm
T4: T4a: T4b:	Moderately or very advanced local disease Moderately advanced local disease. (lip) Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face; (oral cavity) Tumor invade adjacent structures only. Very advanced local disease, tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery.	The same as the 7th edition.
Regional lymph node status		
	N	**pN**
Nx: N0:	Regional lymph node cannot be assessed. No regional lymph node metastasis.	The same as the 7th edition. The same as the 7th edition.
N1:	Metastasis to a single ipsilateral lymph node (≤3 cm).	New introduction of negative extranodal extension, based on the 7th edition.
N2a:	Metastasis to a single ipsilateral lymph node (3–6 cm).	Metastasis to one single ipsilateral lymph node (3–6 cm) and extranodal extension (−); metastasis to a single ipsilateral or contralateral lymph node ≤3 cm and extranodal extension (+).
N2b:	Metastasis to multiple ipsilateral lymph nodes (<6 cm)	New introduction of negative extranodal extension, based on the 7th edition.
N2c:	Metastasis to bilateral or contralateral lymph nodes (<6 cm)	New introduction of negative extranodal extension, based on the 7th edition.
N3:	Metastasis to any lymph node (>6 cm)	N3a: Metastasis to one lymph node >6 cm and extranodal extension (−); N3b: Metastasis in one single ipsilateral node >3 cm and extranodal extension (+); or metastasis in multiple ipsilateral, contralateral, or bilateral lymph node, with any extranodal extension (+)
Distant metastasis		
Mx:	Cannot be assessed.	The same as the 7th edition.
M0:	No distant metastasis.	The same as the 7th edition.
M1:	Distant metastasis.	The same as the 7th edition.

Table 1.
A comparison of the 7th and 8th edition of AJCC/TNM staging of oral cancer.

tumor, the general healthy and social economic condition of the patient, and the surgeon team's skills. There are many soft tissue reconstructive techniques such as local flaps, regional pedicled flaps and microvascular free flap, depending on the

defection. For hard tissue defection, autologous bone grafts from the iliac crest, fibula, radius or scapula are common choices.

Elective neck dissection (END) is suggested for all oral cancer patients [37]. It is reported that around 15–30% of cN0 patients have inapparent lymph node invasion (pN) [1], suggesting the importance of prophylactic dissection for N0 patients. Though recent evidence shows that sentinel node biopsy can be a reliable indicator for N0 oral cancer patients, more data is needed to support its function [39]. Additionally, patients with a DOI of more than 4 mm or T2/3/4 stage should undergo neck dissection to improve overall and disease-free survival rate [40].

6.2 Radiotherapy and chemotherapy

For patients with pathologically positive lymph nodes, occult neck metastasis or existence of extra-capsular spread (ECS), radiotherapy should be initiated. Disadvantages of radiotherapy are many which influence the quality of patients, introducing alteration in skin color, oral cavity mucositis, xerostomia, osteoradionecrosis of the mandible, as well as late toxic symptoms such as dysphagia and dehydration [41]. With the development of intensity-modulated radiotherapy (IMRT), side effects are reduced significantly [42].

Chemotherapy has been applied as an adjuvant approach in oral cancer, especially for patients with locally advanced stage. It can be performed before surgery (known as induction chemotherapy), and also as a combination with radiotherapy (known as chemoradiotherapy) before or after surgery which helps effectively controlling the progression of patients with extracapsular extension in lymph nodes and positive resection margin. As a radiosensitizer, cisplatin is the first-line agent to combine with radiotherapy. What's more, the application of anti-programmed cell death-ligand 1 (PD-L1) antibody is found to improve the prognosis of oral cancer patients with metastasis after chemotherapy using platinum [43].

7. Survival and prognosis of oral cancer

With the development of diagnosis and adjuvant therapy, a retrospective database study involving 16,020 cases of oral cancer patients between 1973 and 2014 showed that the 3-year survival rate for early stage patients increased from 78% to 92.9%, and for those with late stage disease increased from 51.9% to 70.3% [44]. Another study including 2082 patients in a tertiary cancer care center from 1985 to 2015 found that the 5-year over survival (OS) rate of oral cancer was 64.4% and disease special survival (DSS) rate was 79.3% [45].

Age, surgical margin clearance, vascular and perineural invasion situation, pT and pN are factors affecting prognosis. Among these, lymph node involvement strongly indicates poor prognosis, especially for those with extracapsular spread [46]. Increased tumor size and advanced tumor stage also have their roles on prognosis [47]. However, tumor differentiation, number of metastasis nodes, ethnicity are found to have no relationship with prognosis. Due to variation in the geography and studied population, more evidence is needed.

8. Screening of oral cancer

More than 50% of oral cancer patients are diagnosed at the state of regional or distant metastasis. Thus, a proper screening is urgently needed for earlier detection and prevention. A primary screening for oral cancer is visual inspection combined

with palpation. Any abnormality that with a history longer than fourteen days should be reevaluated, and a tissue biopsy is required. There are other adjunctive techniques providing subjective interpretations, including toluidine blue staining, brush cytopathology, salivary diagnosis, tissue autofluorescence and chemiluminescence [48]. Alteration of the oral microbial community has its role in predicting oral cancer too, such as the carcinogenic Porphyromonas gingivalis and F nucleatum [49]. Although there is increasing clues showing HPV infection in oral cancer, no screening project has been approved by the U.S. Food and Drug Administration (FDA). Furthermore, a recommendation from the U.S. Preventive Services Task Force (USPSTF) suggested that more evidence is needed to access the value of screening for oral cancer between benefits and drawbacks [50].

9. Conclusion

In spite of advancement of reconstruction surgery and adjuvant therapy in recent decades, oral cancer remains a public social healthy problem because of its high incidence and mortality rate. To better control this malignant disease, the key principle lies in early diagnosis and prevention such as social education about lifestyle. Finally but not lastly, a personalized treatment should be made by a multidisciplinary team for every patient.

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Conflict of interest

The authors declare no conflict of interest.

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