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Tongue cancer: An overview and current update

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Abstract

Introduction: Oral cancer is a prevalent malignancy and, due to frequent mechanical stimulation, the incidence of squamous cell carcinoma of the tongue ranks first among neoplastic cancer cases and continues to increase.

Objective: To analyze the literature on the characteristics of tongue cancer, particularly its epidemiology, etiology, classification, diagnosis and treatment.

Methodology: For the literature review, it was performed with electronic exploration by search engines such as: PUBMED, SCOPUS and Google Scholar, with the keywords "Tongue cancer, incidence, etiology, epidemiology, classification, diagnosis, and treatment", based on a specific selection regarding the dates of 2015-2022.

Results: The incidence of tongue cancer occurs in the posterolateral portion, with 66% of tongue carcinomas, while, in the ventral and anterior side, in 20%. Its etiology as a fundamental factor for the appearance of tongue cancer are heavy smoking and alcohol consumption, which have a synergistic effect. The American Joint Committee on Cancer (AJCC) classification provides the tumor-lymph node-metastasis (TNM) staging system as a resource for physicians. Diagnostic studies should include a clinical examination, along with biopsy studies, surgery and computed tomography of the neck. The most popular treatment is surgery combined with postoperative radiotherapy and chemotherapy are of choice.

Conclusions: The occurrence of malignant neoplasms in the tongue is becoming more common every day, so it is important to perform recurrent clinical examinations in patients who smoke and consume alcohol, for early detection and to provide a better diagnosis and treatment to the patient.

Keywords: Tongue cancer, squamous cell carcinoma (SCC), oral cavity carcinoma

1. Introduction

Tongue cancer was first described in 1635 by Read A. and currently ranks sixth of all neoplasms. Malignant tumors of the oral cavity represent 6% of all cancers and 30% of head and neck cancers. Carcinoma of the tongue is second only to carcinoma of the lip and has a male to female ratio of 2:1, with a higher frequency in Caucasians than in African Americans [1]. Head and neck tumors are typically characterized by a peak incidence in the elderly and a strong correlation with chronic exposure to risk factors such as smoking and alcohol abuse. In this regard, the adult-elderly age has a central role in allowing the accumulation of a sufficient rate of genetic alterations to promote carcinogenesis [2]. Oral tongue squamous cell carcinoma (OTSCC) is the most common malignancy of the oral cavity. OTSCC is increasing in incidence [3,4], and has an aggressive clinical behavior with a relatively poor forecast [5].

Head and neck squamous cell carcinoma (HNSCC), which is a disease that causes serious harm to humans, is highly associated with alcohol consumption, smoking and betel nut chewing, as is human papillomavirus infection [6].

Most cases of squamous cell carcinoma (SCC) of the tongue occur on the lateral border. Dorsum of tongue affection is very rare, especially in the midline. This lesion may be overlooked or misdiagnosed as a more common benign lesion or an oral manifestation of systemic disease [7]. It is defined as a cancer occurring in the anterior two-thirds of the tongue, extending from the apex of the tongue anteriorly to the circumvallate papillae posteriorly.

It can spread secondarily to the base of the tongue, floor of the mouth, gum, jaw, among others, but is defined by its origin in the oral tongue^[8]. Survival is clearly related to tumor stage, being 60-70% for stages I-II, but dropping to 30-40% for stages III-IV. Tumor location, size and depth are the main factors that determine the risk of cervical involvement^[1]. In the literature it is described as extremely important to be aware of this disease, to know how to recognize its signs and symptoms, as well as to be informed of the risk factors in order to be able to provide an adequate treatment plan depending on the type of involvement and degree of progression. The objective of the study is to analyze the information in the literature on the characteristics of tongue cancer, particularly its epidemiology, etiology, classification, diagnosis, and treatment.

2. Materials and methods

Articles on the subject published through the PubMed, SCOPUS and Google Scholar databases were analyzed, with emphasis on the last 5 years. The quality of the articles was evaluated using guidelines, i.e., identification, review, choice and inclusion. The quality of the reviews was assessed using the measurement tool for evaluating systematic reviews. The search was performed using Boolean logical operators AND, OR and NOT. The search was performed using Boolean logical operators AND, OR and NOT; with the keywords: "tongue cancer ", "incidence", "etiology ", "epidemiology ", "diagnosis ", "treatment ". The keywords were used individually, as well as each of them related to each other.

3. Results & Discussion

3.1 Epidemiology

Tongue cancer is usually caused by squamous cell carcinoma. It rapidly migrates to adjacent structures and travels through the bloodstream and invades other organs, an event that will severely affect the patient's quality of life and facial appearance^[9]. The incidence of tongue neoplasia is higher among older patients. It is characterized by being highly malignant, with high rates of local recurrence and cervical lymph node metastasis^[10]. However, about 5% of patients with head and neck cancer are diagnosed before the age of 45 years. The incidence in this subgroup appears to be steadily increasing, a trend that contrasts with that observed in the general population^[2]. Most cancers occur at the lateral border, making dorsal involvement very rare, with an incidence of 2.9 to 5.0%; in the dorsal midline it is even rarer and accounts for less than 1% of tongue carcinomas^[7]. Sixty-six percent occur in the posterolateral portion, while the ventral and anterior aspect is affected in approximately 20%. Mobile tongue tumors have a high incidence of regional lymph node metastases, between 15-75% depending on the initial stage of the primary tumor. In early stages, the incidence of occult metastasis ranges between 20-40% according to different surgical series. Up to 3-5% debut with bilateral lymph node involvement and 15-20% present with contralateral lymph node metastases^[1]. Smoking in the USA has decreased in recent decades and, with it, the incidence of many types of head and neck cancer^[11, 12]. However, head and neck cancers, oropharyngeal squamous cell carcinoma and squamous cell carcinoma of the oral tongue are on the rise. These occur primarily in the youngest birth cohorts: those under 50 years of age^[13]. The increased incidence of SCC among the young has been attributed to human papillomavirus (HPV) infection, however, for OTC, no single cause has been identified^[14].

The oral lesion is highly malignant and with a high frequency in the oral cavity. The incidence of tongue cancer averages 60 years in patients. The majority of tongue cancers occur in the posterolateral portion with 66%, while the ventral and anterior aspect is affected in approximately 20%. Tobacco use has decreased in recent decades and, with it, the incidence of many types of head and neck cancer, however, SCC of the oral tongue is on the rise.

3.2 Etiology

A large number of epidemiological studies have shown that lifestyle factors, such as smoking, alcohol consumption, low weight and some consumption of vegetables, among other fruits, are associated with oral cancer^[15, 16, 17, 18]. OTSCC is the most common carcinoma of the oral cavity and, according to a recent analysis of the Surveillance, Epidemiology, and End Results database, patients with OTSCC are more likely to experience cause-specific mortality than patients with SCC of the other oral subsites^[19]. In the elderly, males account for more than 70% of cases; this percentage drops to 50-65% below the age of 45 years. This difference has increased the evidence when considering that the majority of young, non-smoking, non-drinking patients are female^[2]. The two most important independent risk factors for the development of SCC on the tongue are heavy smoking and alcohol consumption, which have a synergistic effect. Cigarette smoke contains known carcinogens, mainly nitrosamines and polycyclic hydrocarbons^[20, 21, 22, 23]. A variety of suspected risk factors have also been proposed, such as chronic irritation, poor oral hygiene, viral infection, occupational exposure, malnutrition, diets low in fruits and vegetables, as well as genetic factors^[24, 25]. Also, human papillomavirus, in particular HPV-16, has been suggested as an etiologic agent for the development of a subset of squamous cell carcinoma, especially at the base of the tongue and tonsillar area in younger individuals compared to the HPV-negative counterpart^[1].

A major factor in the development of tongue cancer is heavy smoking and alcohol consumption, which have a synergistic effect. Other suspected risk factors could be chronic irritation, poor oral hygiene, viral infection, occupational exposure, malnutrition, diets low in fruits and vegetables, among other factors. Oral squamous cell carcinoma OTSCC is the most common carcinoma of the oral cavity. In addition, human papillomavirus, particularly HPV-16, has been indicated as an etiologic agent for the development of a subset of squamous cell carcinoma.

3.3 Classification

The traditional tumor (T), lymph node (N) and metastasis (M) staging system has been the cornerstone for clinical staging of OTSCC, although it has been widely criticized for its low prognostic value, especially in early stage cases^[26, 27]. Recently, the eighth edition of the American Joint Committee on Cancer staging manual (AJCC) has been published^[28], which includes numerous changes and modifications to the TNM system that differ from the previous 7th edition (AJCC). For OTSCC, the most significant change in the 8th edition was in the tumor category by incorporation of depth of invasion. In addition, extranodal extension (ENE) was added to the lymph node category^[29]. OTSCC is the most common and aggressive SSC of the oral cavity. The most clinically relevant parameter in the classification of OTSCC is the tumor-lymph node-metastasis (TNM) staging system, which evaluates tumor size, lymph node status and distant

metastasis. However, for early OTSCC, the clinical behavior of many cases is unpredictable according to the current TNM classification only TNM-I^[30].

3.3.1 TNM System

The American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC) provide the TNM staging system as a resource for physicians to stage different types of cancer according to certain standards. This system is updated every 6 to 8 years to include advances in our understanding of cancer.

In the TNM system, each cancer is assigned a letter or number to describe the tumor, nodes, and metastases.

“T” refers to the original (primary) tumor.

“N” refers to the lymph nodes (nodes). Indicates whether the cancer has spread to nearby lymph nodes.

“M” refers to metastases. Indicates whether the cancer has spread to distant parts of the body.

Most types of cancer have their own version of this classification system, so the letters and numbers do not always mean the same thing for each type of cancer. Some cancers also have special groups that are different from other cancers.

3.3.2 Grouping to Establish the Stage

Once the values for T, N and M are determined, they are combined to assign an overall stage. For most cancers, the stage is a Roman numeral from I to IV, where stage IV is the highest and means the cancer is most advanced. Sometimes stages are subdivided, using letters such as A and B.

3.3.3 Other Factors That May Affect the Stage

For some types of cancer, T, N and M values are not the only factors that determine stage. Some of the factors that can be considered are: grade, cell type, tumor location, and tumor marker levels^[31, 32, 33].

The American Joint Committee on Cancer AJCC and the International Union for Cancer Control provide the TNM staging system as a resource for physicians to stage different types of cancer according to certain standards. Recently, the eighth edition of the AJCC staging manual was published, and it includes numerous changes and modifications to the TNM system, the most significant change, was in the tumor category by incorporating depth of invasion. In addition, extranodal extension was added to the lymph node category.

3.4 Diagnosis

OTSCC is the most frequently diagnosed type of cancer in the oral cavity and has been recognized as a distinct subsite primarily for two reasons. First, the tongue is the only part of the oral cavity with a rich lymphatic network and consists of muscles not encapsulated by fascia or bone that could restrict the spread of a tumor. Second, OTSCC is associated with a worse prognosis than carcinomas in other locations in the oral cavity^[34].

The symptoms of early stage oral cancer are atypical and are often mistaken for a bite or mild stabbing pain. Consequently, several patients with oral cancer already have intermediate or advanced stage disease at the time of initial diagnosis and, therefore, have missed the optimal window for treatment. Tongue cancer should be predicted and diagnosed as early as possible; therefore, it is crucial to elucidate the molecular mechanisms underlying its etiology and pathogenesis^[10]. Clinically, SCC of the dorsum of the tongue can be difficult to suspect because it may resemble other lesions such as median

rhomboid glossitis, granular cell myoblastoma, amyloidosis, and oral lichen planus^[7].

A poor 5-year overall survival rate of less than 50% has been identified due to late diagnosis and uncontrolled cervical metastatic spread, which represents a mortality of 85%. Especially if we consider the fact that its clinical evaluation, even with the support of imaging techniques, allows only 68% of cases to be detected. Some studies consider age at diagnosis as a possible prognostic factor, estimating a disease-free survival of 48% for patients under 45 years of age and 54% in patients over 46 years of age^[1]. Some common carcinogenic factors were thought to be related to tongue cancer, including heat, chronic lesions and ultraviolet rays. This tumor was characterized by high lymphatic metastasis, along with recurrence and drug resistance, which were the three leading causes of death in patients with tongue cancer^[35].

In addition to clinical examination, other studies are necessary to adequately diagnose, characterize and stage the disease. In the case of the tongue, lesions are usually easily accessible and therefore amenable to incisional biopsy or needle biopsy under local anesthesia in a clinical setting. For lesions at the base of the tongue, if not accessible transorally, tissue diagnosis can be obtained by flexible laryngoscopy or under direct visualization with general anesthesia. For patients with macroscopic neck lymphadenopathy, ultrasound-guided fine needle aspiration biopsy (FNA) is also an option. Computed tomography of the neck with intravenous contrast is also part of the diagnostic workup. This will provide information on tumor size, location, extent and radiological appearance of the draining neck lymph nodes^[23]. In general, the clinical features and treatment strategies for SCCT are similar to those of other HNSCC, with surgical resection being the primary treatment option. However, due to the late diagnosis of locally advanced malignant tumors, in many cases of SCCT, surgery is no longer an option or should be avoided to maintain the patient's quality of life. Despite advances in treatment options, the prognosis of patients with advanced SCCT remains poor^[6]. The diagnosis of oral cancer is one of the most psychologically traumatic events to live through. Among other disturbing (or distressing) aspects, social isolation and altered perception of future prospects are of utmost importance^[36].

OTSCC is the most frequently diagnosed type of cancer. For its correct diagnosis it is necessary to perform a clinical examination together with biopsy studies, by incision or puncture. Other studies will be done transorally, by flexible laryngoscopy or under direct visualization with general anesthesia, fine needle aspiration biopsy and CT of the neck with intravenous contrast are also part of the diagnostic study.

3.5 Treatment

Currently, surgery combined with postoperative radiotherapy and chemotherapy is the treatment of choice for tongue cancer. Due to short-term recurrence and poor therapeutic efficacy, the neoplasm has a dismal prognosis and severely affects the quality of life of affected patients. The 5-year survival rate of oral cancer is reported to be 50%^[10].

The treatment of choice is endoral surgical resection, the most commonly used radiotherapy is that of opposite lateral fields, including the upper neck. As for chemotherapy, its role is not fully defined; patients with extensive local involvement or distant metastatic disease may be candidates for chemotherapy.

Cisplatin and 5-fluorouracil are the most commonly used

agents in squamous cell cancer of the head and neck, with responses ranging from 30% to 35% and survival for metastatic disease averaging 6 months^[1]. Advanced tongue cancer requires wide excision and reconstructive surgery. In patients with locally advanced tongue lesion, preservation of the larynx in total glossectomy can also preserve swallowing function and maintain long-term airway protection compared to concurrent total laryngectomy^[7]. In terms of treatment, although internal radiation therapy is performed for superficial T1-2 or T3 cancers or concurrent chemoradiotherapy for advanced cancer, surgical resection of tumors is the best established definitive approach for oral cancer^[37, 38, 39]. In general, early stage (T1 or T2) carcinoma of the tongue can be successfully treated with single modality therapy, namely surgery or radiation. However, when considering the long-term morbidity of treatment, cost and other factors, surgery is recommended in advance^[23].

Resistance to chemotherapy has been a major challenge in the successful treatment of cancers. As cancer cells rapidly gained tolerance to first-line chemotherapies, such as 5-fluorouracil (5-FU), cisplatin and docetaxel, and target drugs in most patients, clinical outcomes remained unsatisfactory, although the reason was unknown. Despite the fact that researchers have been continuously exploring alternative treatments, it was not enough to improve the current status of tongue cancer^[40, 41, 42, 43, 44].

One of the first line options of treatment considered is surgery combined with postoperative radiotherapy and chemotherapy. The most popular treatment is endoral surgical resection, while the most commonly used radiotherapy is opposite lateral fields, including the upper neck. Advanced tongue cancer requires wide excision and reconstructive surgery but, if detected at an early stage (T1 or T2), it can be successfully treated with either surgery or radiation. However, when the morbidity rate is high, surgery is recommended in advance.

4. Conclusions

The incidence of tongue cancer occurs in the posterolateral portion with 66% of tongue carcinomas, while the ventral and anterior aspect is affected in approximately 20%. Its etiology as a fundamental factor for the occurrence of tongue cancer are heavy smoking and alcohol consumption, which have a synergistic effect. The American Joint Committee on Cancer AJCC and the International Union for Cancer Control UICC classification provides the TNM staging system as a resource for physicians to stage different types of cancer according to certain standards. Diagnostic studies should include a clinical examination along with biopsy studies, surgery and CT of the neck. The most popular treatment is surgery combined with postoperative radiation therapy and chemotherapy.

5. References

- 1 Ramírez CD, Ramírez CA. Epidermoid cancer of the tongue. *Rev Med Cos Cen*. 2016;73(620):601-609.
- 2 Paderno A, Morello R, Piazza C. Tongue carcinoma in young adults: a review of the literature. *Acta Otorhinolaryngol Ital*. 2018;38(3):175-180.
- 3 Patel SC, Carpenter WR, Tyree S, Couch ME, Weissler M, Hackman T, *et al*. Increasing incidence of oral tongue squamous cell carcinoma in young white women, age 18 to 44 years. *J Clin Oncol*. 2011;29(11):1488-94.
- 4 Ng JH, Iyer NG, Tan MH, Edgren G. Changing epidemiology of oral squamous cell carcinoma of the tongue: A global study. *Head Neck*. 2017;39(2):297-304.
- 5 Bello IO, Soini Y, Salo T. Prognostic evaluation of oral

- tongue cancer: means, markers and perspectives (I). *Oral Oncol*. 2010;46(9):630-5.
- 6 Zhou RS, Zhang EX, Sun QF, Ye ZJ, Liu JW, Zhou DH, *et al*. Integrated analysis of lncRNA-miRNA-mRNA ceRNA network in squamous cell carcinoma of tongue. *BMC Cancer*. 2019;19(1):779.
- 7 Okubo M, Iwai T, Nakashima H, Koizumi T, Oguri S, Hirota M, *et al*. Squamous Cell Carcinoma of the Tongue Dorsum: Incidence and Treatment Considerations. *Indian J Otolaryngol Head Neck Surg*. 2017;69(1):6-10.
- 8 Campbell BR, Netterville JL, Sinard RJ, Mannion K, Rohde SL, Langerman A, *et al*. Early onset oral tongue cancer in the United States: A literature review. *Oral Oncol*. 2018;87:1-7
- 9 Gan RH, Wei H, Xie J, Zheng DP, Luo EL, Huang XY, *et al*. Notch1 regulates tongue cancer cells proliferation, apoptosis and invasion. *Cell Cycle*. 2018;17(2):216-224.
- 10 Tang M, Dai W, Wu H, Xu X, Jiang B, Wei Y, *et al*. Transcriptome analysis of tongue cancer based on high-throughput sequencing. *Oncol Rep*. 2020;43(6):2004-2016.
- 11 Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. *J Clin Oncol*. 2008;26(4):612-9.
- 12 Jamal A, King BA, Neff LJ, Whitmill J, Babb SD, Graffunder CM. Current Cigarette Smoking Among Adults - United States, 2005-2015. *MMWR Morb Mortal Wkly Rep*. 2016;65(44):1205-1211.
- 13 Tota JE, Anderson WF, Coffey C, Califano J, Cozen W, Ferris RL, *et al*. Rising incidence of oral tongue cancer among white men and women in the United States, 1973-2012. *Oral Oncol*. 2017;67:146-152.
- 14 Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C. Epidemiology of Human Papillomavirus-Positive Head and Neck Squamous Cell Carcinoma. *J Clin Oncol*. 2015;33(29):3235-42.
- 15 Bosetti C, Negri E, Franceschi S, Conti E, Levi F, Tomei F, *et al*. Risk factors for oral and pharyngeal cancer in women: a study from Italy and Switzerland. *Br J Cancer*. 2000;82(1):204-7.
- 16 Huang WY, Winn DM, Brown LM, Gridley G, Bravo-Otero E, Diehl SR, *et al*. Alcohol concentration and risk of oral cancer in Puerto Rico. *Am J Epidemiol*. 2003;157(10):881-7.
- 17 Varela-Lema L, Ruano-Ravina A, Juiz Crespo MA, Barros-Dios JM. Tobacco consumption and oral and pharyngeal cancer in a Spanish male population. *Cancer Lett*. 2010;288(1):28-35.
- 18 Radoi L, Menvielle G, Cyr D, Lapôtre-Ledoux B, Stücker I, Luce D; ICARE Study Group. Population attributable risks of oral cavity cancer to behavioral and medical risk factors in France: results of a large population-based case-control study, the ICARE study. *BMC Cancer*. 2015;15(1):827.
- 19 Farhood Z, Simpson M, Ward GM, Walker RJ, Osazuwa-Peters N. Does anatomic subsite influence oral cavity cancer mortality? A SEER database analysis. *Laryngoscope*. 2019;129(6):1400-1406.
- 20 Pelucchi C, Gallus S, Garavello W, Bosetti C, La Vecchia C. Cancer risk associated with alcohol and tobacco use: focus on upper aero-digestive tract and liver. *Alcohol Res Health*. 2006;29(3):193-8.
- 21 Marttila E, Uittamo J, Rusanen P, Lindqvist C, Salaspuro M, Rautemaa R. Acetaldehyde production and microbial

- colonization in oral squamous cell carcinoma and oral lichenoid disease. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2013;116(1):61-8.
- 22 Feller L, Chandran R, Khammissa RA, Meyerov R, Lemmer J. Alcohol and oral squamous cell carcinoma. *SADJ.* 2013;68(4):176-80.
- 23 Gonzalez M, Riera March A. *Tongue Cancer.* In: *StatPearls.* Treasure Island (FL): StatPearls Publishing; c2022.
- 24 Mehanna H, Paleri V, West CM, Nutting C. Head and neck cancer-part 1: epidemiology, presentation, and preservation. *Clin Otolaryngol.* 2011;36(1):65-8.
- 25 Perry BJ, Zammit AP, Lewandowski AW, Bashford JJ, Dragovic AS, Perry EJ, *et al.* Sites of origin of oral cavity cancer in nonsmokers vs smokers: possible evidence of dental trauma carcinogenesis and its importance compared with human papillomavirus. *JAMA Otolaryngol Head Neck Surg.* 2015;141(1):5-11.
- 26 Almangush A, Bello IO, Coletta RD, Mäkitie AA, Mäkinen LK, Kauppila JH, *et al.* For early-stage oral tongue cancer, depth of invasion and worst pattern of invasion are the strongest pathological predictors for locoregional recurrence and mortality. *Virchows Arch.* 2015;467(1):39-46.
- 27 Piazza C, Montalto N, Paderno A, Taglietti V, Nicolai P. Is it time to incorporate 'depth of infiltration' in the T staging of oral tongue and floor of mouth cancer? *Curr Opin Otolaryngol Head Neck Surg.* 2014;22(2):81-9.
- 28 Amin MB, Edge S, Greene F, *et al.* *AJCC Cancer Staging Manual*, 8th edición. Nueva York: Springer, 2017.
- 29 Mascitti M, Rubini C, De Michele F, *et al.* American Joint Committee on Cancer staging system, 7th edition vs. 8th edition: ¿any improvement for patients with squamous cell carcinoma of the tongue? *Oral Surgery Oral Med Oral Patol Oral Radiol.* 2018;126:415-23.
- 30 Almangush A, Bello IO, Heikkinen I, Hagström J, Haglund C, Kowalski LP, *et al.* Improving Risk Stratification of Early Oral Tongue Cancer with TNM-Immune (TNM-I) Staging System. *Cancers (Basel).* 2021;13(13):3235.
- 31 Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. *American Joint Committee on Cancer Staging Manual.* 7th ed. New York, NY: Springer; 2010.
- 32 National Cancer Institute. *Cancer Staging.* 2015. Accessed at www.cancer.gov/cancertopics/factsheet/detection/staging on March 20, 2015.
- 33 Yarbro CH, Frogge MH, Goodman M, Groenwald SL, eds. *Cancer Nursing Principles and Practice.* 5th ed. Sudbury, MA: Jones and Bartlett Publishers, Inc. 2000.
- 34 Almangush A, Bello IO, Heikkinen I, Hagström J, Haglund C, Kowalski LP, *et al.* Stromal categorization in early oral tongue cancer. *Virchows Arch.* 2021;478(5):925-932.
- 35 Han G, Xu C, Yu D. Mechanisms correlated with chemotherapy resistance in tongue cancers. *J Cancer Res Ther.* 2018;14(1):1-5.
- 36 De Berardinis R, Guidi P, Ugolini S, Chu F, Pietrobon G, Pravettoni G, *et al.* Coping With Oral Tongue Cancer and COVID-19 Infection. *Front Psychiatry.* 2021; 12:562502.
- 37 Shah JP, Gil Z. Current concepts in management of oral cancer--surgery. *Oral Oncol.* 2009;45(4-5):394-401.
- 38 Nibu KI, Hayashi R, Asakage T, Ojiri H, Kimata Y, Kodaira T, *et al.* Japanese Clinical Practice Guideline for Head and Neck Cancer. *Auris Nasus Larynx.* 2017;44(4):375-380.
- 39 Colevas AD, Yom SS, Pfister DG, Spencer S, Adelstein D, Adkins D, *et al.* NCCN Guidelines Insights: Head and Neck Cancers, Version 1.2018. *J Natl Compr Canc Netw.* 2018;16(5):479-490.
- 40 Gao X, Dai M, Li Q, Wang Z, Lu Y, Song Z. HMGA2 regulates lung cancer proliferation and metastasis. *Thorax Cancer.* 2017;8(5):501-510.
- 41 Karatzanis AD, Psychogios G, Mantsopoulos K, Zenk J, Velegarakis GA, Waldfahrer F, Iro H. Management of advanced carcinoma of the base of tongue. *J Surg Oncol.* 2012;106(6):713-8.
- 42 Yanamoto S, Yamada S, Takahashi H, Kawasaki G, Ikeda H, Shiraishi T, *et al.* Predictors of locoregional recurrence in T1-2N0 tongue cancer patients. *Pathol Oncol Res.* 2013;19(4):795-803.
- 43 Abdalmear MM, Tomita M, Shibuya H. Long-term results of brachytherapy in early mobile tongue cancer with 10-year minimal follow-up. *Anticancer Res.* 2013;33(1):317-24.
- 44 Bicalho LS, Longo JP, Cavalcanti CE, Simioni AR, Bocca AL, Santos Mde F, *et al.* Photodynamic therapy leads to complete remission of tongue tumors and inhibits metastases to regional lymph nodes. *J Biomed Nanotechnol.* 2013;9(5):811-8.