

ORIGINAL

Evaluation of the neck lymph node involvement in outcome of Iranian patients with maxillofacial squamous cell carcinoma

Evaluación de la afectación de los ganglios linfáticos del cuello en los pacientes iraníes con carcinoma maxilofacial de células escamosas

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Abstract

Background: Oral squamous cell carcinoma (OSCC) is the predominant malignancy of oral cavity (about 90% of oral malignant lesions). This study aimed to evaluate the long-term extent of lymph node involvement of the neck among patients with maxillofacial SCC after the surgery.

Methods: In this cross-sectional study, 32 patients with maxillofacial SCC who underwent surgery were evaluated for any type of lymph node involvement (necrotic, reactive, or metastatic) at 3, 6, 12, and 24 months. Data was acquired through clinical and paraclinical examinations such as CT scan, ultrasound of the neck area, pathology and histology.

Results: The SCC of posterior mandible had more lymph node involvement ($P=0.02$). Compared to moderately/poorly differentiated cases, patients with well-differentiated histopathological grade had lower lymph node involvement ($P=0.01$). TNM stage had no influence on lymph node involvement ($P>0.05$). Patients with neck dissection and reconstruction ($P=0.003$) as well as those who received postoperative radiotherapy or chemotherapy/radiotherapy together ($P=0.001$ and 0.005 respectively) had lower degree of lymph node involvement. Post-operative lymph node involvement was significantly more in patients with the positive CT scan status of bilateral metastatic lymphadenopathy in zones 1, 2 and 3 before the operation in comparison to other statuses like bilateral benign lymph nodes ($p=0.001$) or lymphadenopathy in just one or two zones (1and/or 2) ($P>0.05$).

Conclusion: We determined the effect of different parameters on lymph node involvement and determined some positive and negative correlations. Furthermore, some parameters like age, gender, and TNM staging had no influence on the mentioned outcome.

Keywords: OSCC; lymph node involvement; TNM staging.

Resumen

Antecedentes: El carcinoma oral de células escamosas (CCE) es la neoplasia maligna predominante de la cavidad oral (alrededor del 90% de las lesiones malignas orales). El objetivo de este estudio es evaluar la extensión a largo plazo de la afectación de los ganglios linfáticos del cuello entre los pacientes con CCE maxilofacial después de la cirugía.

Métodos: En este estudio transversal, 32 pacientes con CCE maxilofacial sometidos a cirugía fueron evaluados para cualquier tipo de afectación ganglionar (necrótica, reactiva o metastásica) a los 3, 6, 12 y 24 meses. Los datos se absolieron mediante exámenes clínicos y paraclínicos como la tomografía computarizada, la ecografía de la zona del cuello, la patología y la histología.

Resultados: El CCE de la mandíbula posterior tenía más afectación de los ganglios linfáticos ($P=0,02$). En comparación con los casos moderadamente/pobremente diferenciados, los pacientes con grado histopatológico bien diferenciado tenían menor afectación ganglionar ($P=0,01$). El estadio TNM no influyó en la afectación de los ganglios linfáticos ($P>0,05$). Los pacientes con disección y reconstrucción del cuello ($P=0,003$), así como los que recibieron radioterapia postoperatoria o quimioterapia/radioterapia conjuntamente ($P=0,001$ y $0,005$ respectivamente) tuvieron menor grado de afectación ganglionar. La afectación ganglionar postoperatoria fue significativamente mayor en los pacientes con el estado positivo en la TC de linfadenopatía metastásica bilateral en las zonas 1, 2 y 3 antes de la operación en comparación con otros estados como los ganglios linfáticos benignos bilaterales ($p=0,001$) o la linfadenopatía en sólo una o dos zonas (1y/o 2) ($P>0,05$).

Conclusión: Determinamos el efecto de diferentes parámetros sobre la afectación ganglionar y determinamos algunas correlaciones positivas y negativas. Además, algunos parámetros como la edad, el sexo y el estadiaje TNM no influyeron en el resultado mencionado.

Palabras clave: CCE; afectación de los ganglios linfáticos; estadiaje TNM.

Introduction

Oral squamous cell carcinoma (OSCC) as the most common malignant epithelial neoplasm of the oral cavity comprises 2%-4% of all cancer cases¹. A group of neoplasms affecting any region of the oral cavity, pharynx and salivary glands are called oral cancer. However, this term and OSCC tend to be used interchangeably, as the latter comprises more than 90% of all oral neoplasms. Despite the new therapeutic approaches, morbidity and mortality from OSCC have not changed significantly during the last 30 years. It seems that its incidence, however, has been increasing among young white individuals (especially women) aged 18 to 44 years. The five-year survival of patients with OSCC is between 40-50%; its clinical manifestations in advanced stages are so characteristic that misdiagnosis rarely happens. In contrast, incorrect diagnosis is quite possible in the early stages, which may explain why OSCC is usually diagnosed in the advanced stages regardless of easy access to the oral cavity for clinical examination².

Tobacco and alcohol are the greatest risk factors for OSCC in the western world³ and seem to have synergic effect⁴. The use of areca nuts (also called betel quid)⁵ and narcotics are other risk factors⁶. OSCC mostly occurs in older men and people with low socioeconomic status⁷. Immune deficiency, body inability to repair damaged DNA and reduce carcinogens, and vitamin deficiency are represent important risk factors⁸.

The most common symptoms in patients with oral cancer are discomfort and pain which can vary from mild discomfort to severe pain⁹. Some other symptoms are dysphagia, difficulty in breathing and speech, teeth mobility, trismus and paresthesia¹⁰. The tongue and mouth floor are the most common sites for OSCC accounting for more than 50% of cases in the West¹¹. Biopsy and histopathological evaluation are always necessary for diagnosis¹². Evaluating the histological characteristics of the tumor and its adjacent tissues, are essential for devising the treatment plan and predicting the outcome¹³. The factors that mainly affect the prognosis of OSCC include size and site, tumor thickness histopathologic grade, perineural invasion, lympho vascular invasion, tumor suppressor gene impairment (e.g., p53) and the quality of treatment¹⁴. It is crucial to determine the status of lymph nodes after the diagnosis of OSCC. Before requesting paraclinical assessments, a thorough clinical investigation should be done. However this may not be accurate because the tumor cells spread into the adjacent tissues before any clinical symptoms develop¹⁵. The clinical method for detecting regional cervical lymph node involvement is palpation¹⁶, though computed tomography (CT)¹⁷, ultrasonography (US)¹⁸ and biopsy are paraclinical investigations that may be essential in the detection of cervical lymph node involvement. Head and neck cancers usually spread through lymph nodes rather than hematogenously. The size and site of the primary tumor

play an important role in lymph node involvement¹⁹. Proper treatment for early-stage (T1/T2) squamous cell carcinoma (SCC) of the oral cavity is a controversial issue. Surgery and radiotherapy are often used to control the primary tumor, but failure often occurs because of recurrence in cervical lymph nodes²⁰. In this study, we aimed to investigate the long-term extent of lymph node involvement of the neck after surgery among patients with maxillofacial SCC.

Materials and Methods

Study procedure

In this cross-sectional study, 32 patients with maxillofacial SCC who were referred to Rajaei Trauma Hospital affiliated to Shiraz University of Medical Sciences, Shiraz, Iran from 2014-2018 were studied. The protocol of this study was approved by the local Ethics Committee of Shiraz University of Medical Sciences (approval ID: IR.SUMS.DENTAL.REC.1399.117).

The patients underwent surgery and were evaluated for lymph nodes involvement of any type (necrotic, reactive, or metastatic) at 3 months, 6 months, 1 year, and 2 years after the operation. Data was acquitted through the clinical examination as well as the neck CT scan with contrast, ultrasound of the neck area and pathology and histology sheets. In the ultrasound and CT scan, changes in the form, size and the number of lymph nodes were noted. The diagnosis of metastasis was made based on the pathology and radiology reports as well as observations made during the operation. Inclusion criteria were patients below the age of 75 years with primary SCC in the maxillofacial zone. Exclusion criteria were patients with recurrent SCC, end-stage disease, facial involvement, distant metastasis (including the lung and brain), or systemic conditions. According to the data obtained through ultrasound, radiology and clinical examinations, we determined the TNM stage, which indicates the number and size of involved lymph nodes and presence or absence of metastasis (**Table I**).

Table I: The TNM staging system for patients with maxillofacial squamous cell carcinoma.

TNM Stage	Tumor	Node involvement	Metastasis
Stage 0	T is	N0	M0
Stage I	T 1	N0	M0
Stage II	T.2	N0	M0
Stage III	T.3	N0	M0
	T.1	N1	M0
	T.2	N1	M0
	T.3	N1	M0
Stage IVA	T.4a	N0	M0
	T.4a	N1	M0
	T.1	N2	M0
	T.2	N2	M0
	T.3	N2	M0
	T 4a	N2	M0
Stage IVB	Any T	N3	M0
	T 4b	Any N	M0
Stage IVC	Any T	Any N	----

Statistical analysis

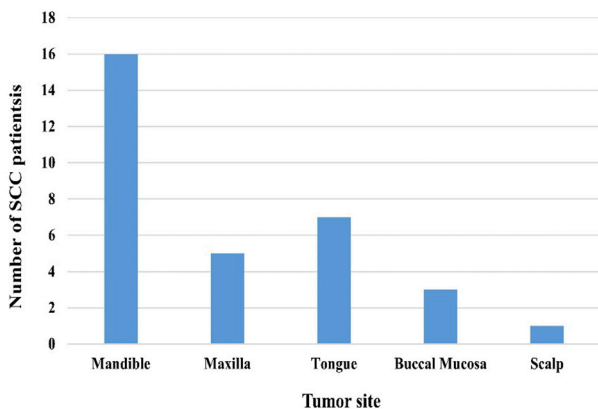
All statistical analyses were carried out using the SPSS software package (SPSS Inc., Chicago, USA). Continuous and normally distributed data were expressed as mean \pm standard deviation (SD). One-way analysis of variance (ANOVA) and the post-hoc Tukey tests were used to compare the differences among experimental groups. A p-value of less than 0.05 was considered statistically significant.

Results

Overall, 32 proven cases of maxillofacial SCC were eligible for the analysis. The patient group consisted of 20 males (62.5%) and 12 females (37.5%). For more insight to the data, the patients were divided into four age groups: below 50 years (n=7), 51-60 years (n=9), 61-70 years (n=13), and older than 70 years (n=3). There was no statistically significant difference in the SCC prevalence between different age groups (P=0.9) and genders (P=0.15). The lymph node involvement did not differ with respect to age (P=0.25) and sex (P=0.18).

As shown in **figure 1**, the mandible (n=16, 50%) was the most common site affected by the OSCC in both males and females.

Figure 1: Sites affected by the OSCC in both males and females' groups.



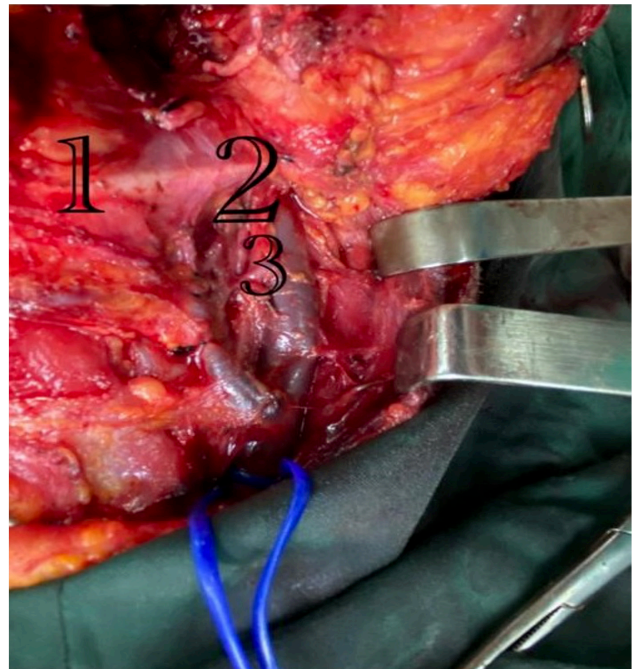
The SCC of the posterior mandible had significantly more lymph node involvement compared with other sites (P=0.02). Most patients had well-differentiated tumors (n=23, 71.9%) while the remaining (n=9, 28.1%) were moderately or poorly differentiated. Lymph node involvement in patients with well-differentiated histopathological grade was significantly lower than moderately and poorly differentiated cases (P=0.01), but the difference between moderately and poorly differentiated tumors was not statistically significant. Mandibular SCC is presented in **figure 2**.

Figure 2: Mandibular squamous cell carcinoma.



In accordance with the TNM classification system, 4 (12.5%), 11 (34.4%), 12 (37.5%), and 5 (15.6%) cases were diagnosed at stage I, II, III, and IV, respectively. Most of the studied patients were diagnosed in stage II and III. Different TNM stage had no remarkable influence on long-term lymph node involvement after surgery (P>0.05), though patients with neck dissection (zones 1, 2 and 3) and reconstruction (**Figure 3**) had less lymph node involvement in comparison with cases without neck dissection and reconstruction (P=0.003).

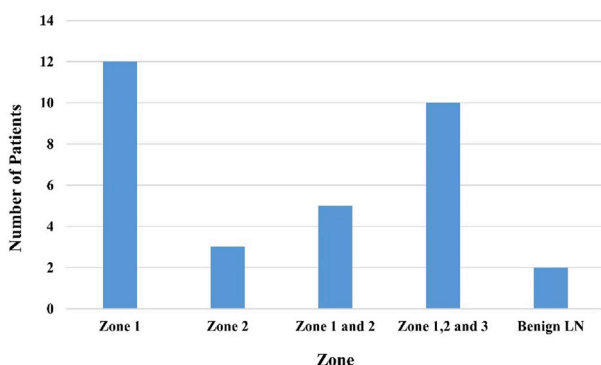
Figure 3: Patient with neck dissection (zones 1, 2 and 3).



There was a significantly lower degree of lymph node involvement among patients visited by an oncologist and those who regularly attended follow-up sessions in comparison with the patients who ignored their follow

up sessions at 1 year and 2 years' evaluation ($P < 0.05$). Patients who received postoperative radiotherapy alone or chemotherapy and radiotherapy together had a significantly lower degree of lymph node involvement ($P = 0.001$ and 0.005 , respectively) than those who didn't receive any adjunctive therapy or who received chemotherapy alone. In fact, postoperative chemotherapy was associated with no significant changes in the mentioned variable. Zone 1 involvement was most seen in CT scan followed by zone 1, 2 and 3 and zone 1 and 2 involvement in the two-year follow-up (**Figure 4**).

Figure 4: Zone involvement of patients with maxillofacial squamous cell carcinoma in CT scans.



Post-operative lymph node involvement was significantly more observed in patients with the positive CT scan status of bilateral metastatic lymphadenopathy in zones 1, 2 and 3 before the operation in comparison to other statuses like bilateral benign lymph nodes ($P = 0.001$), lymphadenopathy in just one or two zones (1 and/or 2) ($P > 0.05$), bilateral reactive lymph nodes of zones 1, 2, and 3 ($P = 0.001$), or unilateral reactive lymph nodes of zones 1, 2, and 3 ($P = 0.003$) and bilateral and unilateral necrotic lymph nodes of zones 1, 2 and 3 ($P = 0.002$ and 0.003 , respectively). Patients with positive sonography for reactive lymph nodes before surgery had statistically more lymph node involvement in two year follow up period in comparison with the benign lymph node situation. However, there was no significant difference in the outcome of patients with unilateral or bilateral lymphadenopathy of any type (reactive, necrotic or metastatic) found in sonography before the operation ($P > 0.05$). Different zones of lymph node involvement found in preoperative sonography had no significant influence on the outcome of patients ($P > 0.05$). Pathological findings of lymph node involvement after surgery coincided with preoperative CT scan findings, but not sonographic details.

Discussion

Originating from oral epithelial cells, OSCC represents the predominant malignancy of the oral cavity, accounting for about 90% of all malignant oral lesions. In primary OSCC

invasion of the deeper layers below the epithelium and drainage to regional lymph nodes may occur²¹. To establish the diagnostic and prognostic parameters of OSCC, we must determine the histological differentiation degree, tumor size, invasion to nearby tissues and metastasis²². The most important prognostic factor is the lymph node status of the neck²³. Although CT and magnetic resonance image (MRI) are used to localize and characterize head and neck tumors, they do not perform well in the evaluation of lymph node metastasis²⁴. Given the immense effect of achieving an accurate pre-operative estimation of invasiveness and nodal metastasis on OSCC patient management and prognosis, novel clinical indicators and advanced radiological techniques are required.

In this study, no relation was found between SCC occurrence, age and gender, but some previous studies have shown different prevalence of SCC among different age groups²⁵ and genders²⁶. Although some studies suggested that sex and age may be prognostic in SCCs²⁷, our findings showed no significant difference in lymph node involvement with respect to age and sex which is in line to some reports²⁸. In the current study, the mandible was the most common site affected by oral SCC in both males and females which is in contrast with the results of previous studies who found the tongue to be the predominant site²⁹. These differences could be due to the different study populations and different sample sizes. We also found that patients with posterior mandibular SCC had more post-operative lymph node involvement in the two-year follow-up compared with SCCs of other regions. Though Sharma et al.³⁰ found SCCs of the posterior maxillary and mandibular areas to have more lymph node involvement both before and after surgery. Uchiyama et al.³¹ and Tajmiriahi et al.³² also found the posterior areas to be more prone to metastasis, which emphasizes the importance of tumor location in lymph node involvement.

Histopathological assessment of the surgical resection specimen always provides useful information which is essential for identifying the post-operative treatment needs and prognosis for individuals with oral/oropharyngeal SCC¹³. In line with our study, Tzu et al.³³ and Amaral et al.³⁴ reported that moderately and poorly differentiated tumors caused more lymph node involvement than well-differentiated tumors, which can be related to the more aggressive nature of cancerous cells in less differentiated ones. The clinical stage is another prognostic factor in the survival rate for SCC patients. However, our study revealed no significant prognostic difference on long-term lymph node involvement between stage II and III OSCC. This limited prognostic value of TNM staging was also shown in the study of Bankfalvi et al.³⁵, though this finding contrasts with that of Amaral et al.³⁴.

In terms of management, there has been conflicting ideas regarding radical neck dissection vs. wait and

watch over the last decades³⁶. It is currently believed that extensive neck dissections cause higher morbidity without offering a better long-term outcome³⁶. We found that patients with neck dissection (zone 1, 2 and 3) and reconstruction had significantly less lymph node involvement in the two-year follow-up relative to the cases without neck dissection, which is in line with some previous studies³⁷ and in contrast with others³⁸. Patients who cared for their regular follow-up sessions had less lymph node involvement in the follow up period which can be due to the prompt detection of any changes by their physicians. The same finding was reported in the study of Kumaran et al.³⁹. Patients with the history of OSCC must visit their doctors every 1-3 months in the first two years and every 3-6 months thereafter. They can be visited yearly if no recurrence occurs after the first five years. Arun et al.⁴⁰ found that patients who visited their oncologist and received adjunctive treatments after surgery had less lymphadenopathy in the follow up period, which coincides with our findings regarding patients who received radiotherapy, (but not chemotherapy) as an adjunctive treatment. It seems that radiotherapy of any type (e.g. teletherapy or brachytherapy) can eradicate the remnant cancerous cells⁴¹. In the current study, there was an accurate relationship between the radiologic findings in the (CT scan, but not sonography) with lymph node involvement. It was shown that compared the efficacy and accuracy of different methods of radiology in detecting lymph node involvement, sonography alone is insufficient³⁰. Sismanis et al.⁴² were probably the first who report the usefulness of ultrasonography in the assessment of neck node metastasis and reported that ultrasonography changed the stage in 28% of their patients and was beneficial even in patients with palpable metastasis. Hajec et al.⁴³ reported similar findings and

concluded that sonography of the neck changed the treatment plan in more than half of their patients. In contrast to these studies and in line with our study, John et al.⁴⁴ reported that sonography provided no additional data in patients with palpable metastasis and declared its inaccuracy in the detection of lymph node involvement. Zone 1 involvement was the most commonly reported zone in CT scan status followed by zone 1, 2 and 3 and zone 1 and 2 involvement in the two-year follow-up. It seems that zone 2 involvement alone can rarely happen, as an interesting finding.

This study has some important limitations due to methodological flaws such as no prior sample size estimation; therefore, we used as many cases as possible. However, due to the relatively small number of participants in our study and limited reports in the Iranian population, further studies with larger sample size and post-operative follow-ups are highly warranted.

Discussion

This study successfully evaluated the lymph node involvement of the neck in the two-year follow-up period for patients who had undergone surgery for maxillofacial SCC. We determined the effect of different parameters on lymph node involvement and some positive and negative correlations and found that parameters like age, gender and TNM staging had no influence on the outcome of patients.

Interests conflict

The researchers declare that they have no conflict of interest.

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