Original Article

Oral cavity cancers: A single-center study

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ABSTRACT

Objectives: This study aims to evaluate demographic characteristics, tumor characteristics, and survival outcomes of surgically treated patients with oral cavity cancer (OCC).

Patients and Methods: A total of 459 OCC patients (269 males, 190 females; mean age 61.4±15.0 years; range, 18 to 90 years) who were treated with surgery between January 2000 and December 2015 were retrospectively analyzed. Demographic data, diagnosis, histopathological type, tumor origin, tumor stage, neck status, type of surgery, reconstruction technique, complications, follow-up duration, recurrence, and survival status were recorded.

Results: The tumor originated from the lip in 134 (29.2%) of the patients. The histopathological diagnosis was a squamous cell carcinoma in 403 patients (87.8%). The five-year overall survival and disease-free survival rates were 69.5% and 60.8%, respectively. The five-year overall survival rate was significantly lower in patients with neck metastasis ($p<0.05$).

Conclusion: Our study results suggest that regional lymph node metastasis, age, and surgical margin are the main factors affecting survival and prognosis in OCC.

Keywords: Oral cavity cancer, oral cavity tumor, survival.

Oral cavity cancers (OCC) are the 11th most common cancer worldwide in men, the 17th most common in women, and the 18th most common including both genders with a mortality rate reaching 50%.[1] The global incidence of OCC is 1.5 times higher in men than in women.[2] Oral cancer is a predominantly disease of the middle age, with only 6% of cases reported in patients under 45 years of age.[3] On the other hand, there are reports of an increasing incidence rates of oral tongue squamous cell carcinoma (SCC) in young males aged 20 to 44 years.[4] Oral cavity cancer is usually synonymously used for SCC of the oral cavity, as this histopathological type constitutes nearly 95% of all OCC cases.[5] The next common malignant histopathological type is tumors of the salivary gland.[5] Osteosarcoma, rhabdomyosarcoma, fibrosarcoma, liposarcoma, lymphoma, mucosal melanoma, and nerve sheath tumors may be also present in the oral cavity.[6,7]

Tobacco and alcohol consumption are the well-known risk factors for developing OCC. Tobacco use is not only linked to the development of head and neck SCCs, but it is also associated with more aggressive disease.[8] Patients with a history of tobacco use are more likely to have

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regional metastases and extracapsular spread, compared to those without such a history.[9] Oral cavity has seven subsites including lips, oral tongue (anterior two-thirds), floor of the mouth, buccal mucosa, gingiva (upper and lower alveolar ridges), retromolar trigon, and hard palate. Lip is the most common site for cancer of the oral cavity, followed by tongue and floor of the mouth. Early stage (Stage I-II) OCC are managed with radiotherapy (RT) or surgery, whereas a treatment combination of chemotherapy (CT) and RT, or surgery and postoperative RT is required for advanced-stage tumors (Stage III-IV) to improve locoregional control and overall survival (OS) rate.

In the present study, we aimed to evaluate demographic characteristics, tumor characteristics, and survival outcomes of surgically treated patients with OCC.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at a tertiary academic center between January 2000 and December 2015. Medical records of a total of 459 OCC patients (269 males, 190 females; mean age 61.4±15.0 years; range, 18 to 90 years) who were treated with surgery were retrospectively analyzed. No exclusion criteria were used. A written informed consent was obtained from each patient. The study protocol was approved by the Ege University Institutional Review Board. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data were collected from the pre- and postoperative follow-up records of the patients at the Departments of Otorhinolaryngology, Radiology, Oncology, Radiation Oncology, and Pathology. Demographic data, diagnosis, histopathological type, tumor origin, tumor stage, neck status, type of surgery, reconstruction technique, complications, follow-up duration, recurrence, surgical margin, and survival status were recorded. Tumor stage was classified according to the 7th Edition of Tumor, Node, Metastasis (TNM) classification designated by the American Joint Committee on Cancer.[10] Other than medical records, the data regarding the survival status were checked using the Turkish National Death Database to confirm the data obtained and to clarify the cause of death.

Outcome measures

Demographic data, age, and gender were recorded. To analyze the survival function in young adults, a separate survival analysis was made for patients less than 45 years old. The characteristic features of the primary tumor were noted such as the tumor origin, tumor (T) size, neck lymph node (N), and distant metastasis (M). Among the treatment options, the surgical reconstruction method (primary closure, local or free flaps), neck dissection and adjuvant therapies (RT and CT) were assessed. The histopathological data, status of the margins (positive versus negative), and lymph node status of the neck (positive versus negative) were recorded. Regarding the follow-up data, recurrence of the disease and survival were calculated.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Data were expressed in mean ± standard deviation (SD), range (min-max) values, median (IQR) or number and frequency with odds ratio (ORs) and 95% confidence interval (CI). The chi-square (χ^2) exact test was used for the comparison of categorical data, while independent and paired samples t-tests were used for the analysis of parametric variables. The Wilcoxon and Mann-Whitney U tests were used for the analysis of non-parametric variables based on the distribution pattern of the data. Correlation analysis was performed using the Spearman or Pearson correlation analysis depending on the type of the variable. The receiver operating characteristic (ROC) analysis was applied for scale variables which might be a factor for selected criteria. Survival analysis was made using the Kaplan-Meier method and the effects of multiple independent factors were evaluated with the Cox regression analysis. A p value of <0.05 was considered statistically significant.

RESULTS

Of all patients, 58 (12.6%) were <45 years old and 401 (87.4%) were ≥45 years old.

The tumor originated from the lip in 134 (29.2%) of the patients, followed by oral tongue in 128 (27.9%), buccal mucosa in 48 (10.5%), floor of mouth in 47 (10.2%), hard palate in 43 (9.4%), alveolar ridge in 37 (8.1%), and retromolar trigone in 22 (4.8%). Regional lymph node metastasis was present in 126 patients (27.5%). The histopathological diagnosis was SCC in 403 patients (87.8%), basal cell carcinoma in 17 (3.7%), adenocarcinoma in nine (2.0%), mucoepidermoid carcinoma in eight (1.7%), and the following histopathological diagnosis were verrucous carcinoma in six (1.3%), adenoid cystic carcinoma in six (1.3%), osteosarcoma in three (0.7%), malignant melanoma in one (0.2%), spindle cell sarcoma in one (0.2%), and malignant mesenchymal tumor in one (0.2%). Primary tumor stage was T_1 in 216 (47.1%), T_2 in 150 (32.7%), T_3 in 42 (9.2%), and T_4 in 51 patients (11.1%). A total of 191 patients (41.6%) had Stage I, 94 (20.5%) had Stage II, 59 (12.9%) had Stage III, and 115 (25.1%) had Stage IV disease. Demographic and clinical data are presented in Table 1.

The median follow-up duration was 61 (range, 6 to 186) months. Eighty-six patients (18.7%) had recurrence. Primary local recurrence was observed in 41 patients (47.6%) and the other recurrence sites were regional recurrence in 22 (25.5%), locoregional recurrence in 18 (20.9%), and secondary primary in five patients (5.8%). The median time interval for recurrence was 12 (range, 2 to 120) months.

The five-year OS and disease-free survival (DFS) rates were 69.5% and 60.8%, respectively. The five-year survival rate in lymph node-positive and negative patients were 50.1% and 76.1%, respectively. The difference between these groups was statistically significant ($p<0.05$). The five-year survival rate was found to be 76.6%, 57.8%, 58.9%, and 35.8% in Stage I, II, III, and IV patients, respectively. The five-year DFS rates according to the tumor subsites were 73.3% in lip, 55.5% in oral tongue, 32.0% in alveolar ridge, 62.5% in hard palate, 62.5% in retromolar trigone, 60.6% in the floor of mouth, and 62.7% in buccal mucosa. The five-year OS rate was 81.8% and the five-year DFS rate was 74.6% for the patients younger than 45 years. The five-year OS rate was 67.9% and the five-year DFS rate was 59.0% for the patients older than

Table 1. Demographic data and tumor characteristics

	n	%
Age (year)		
<45	58	12.6
≥45	401	87.4
Gender		
Male	269	58.6
Female	190	41.4
Sub-sites		
Lip	134	29.2
Oral tongue	128	27.9
Buccal mucosa	48	10.5
Floor of mouth	47	10.2
Hard palate	43	9.4
Alveolar ridge	37	8.1
Retromolar trigone	22	4.8
Histopathology		
Squamous cell carcinoma	403	87.8
Basal cell carcinoma	17	3.7
Adenocarcinoma	9	2.0
Mucoepidermoid carcinoma	8	1.7
Others	22	4.8
T stage		
T_1	216	47.1
T_2	150	32.7
T_3	42	9.2
T_4	51	11.1
Overall stage		
No recurrence	373	81.3
Primary recurrence	41	8.9
Neck recurrence	22	4.8
Primary and neck recurrence	18	3.9
Secondary primary recurrence	5	1.1
Treatment		
Surgery only	216	47.1
Surgery + radiotherapy	185	40.3
Surgery + radiotherapy and chemotherapy	50	10.9
Surgery + chemotherapy	8	1.7
Neck dissection		
None	157	34.2
Done	302	65.8
Reconstruction		
Primary closure	313	68.2
Local flaps	38	8.3
Regional flaps	97	21.1
Free flaps	11	2.4
Complications		
None	367	80.0
Wound infection	31	6.8
Flap dehiscence	28	6.1
Orocutaneous fistula	12	2.6
Chylous fistula	4	0.9
Flap necrosis	3	0.7
Others	18	3.9
Total	459	100

Table 2. Five-year overall and disease-free survival rates

	Disease-free survival	Overall survival	
	%	%	*p*
Age (year)			<0.05
<45	74.6	81.8	
≥45	59.0	67.9	
Lymph node metastasis			<0.05
Negative		76.1	
Positive		50.1	
Sub-sites			
Lip	73.3	80.6	
Oral tongue	55.5	69.7	
Alveolar ridge	32.0	40.4	
Hard palate	62.5	67.6	
Retromolar trigone	62.5	67.1	
Floor of mouth	60.6	70.5	
Buccal mucosa	62.7	75.5	
Surgical margin			<0.05
Negative	64.0	72.7	
Positive	29.7	38.2	
Total	60.8	69.5	

45 years. There was a statistically significant difference in the five-year OS and DFS rates between younger and older patients (p<0.05).

A total of 302 patients (65.8%) underwent neck dissection. Primary closure was performed in 313 patients (68.2%). In total, 146 patients (31.8%) required reconstruction with flaps after tumor excision. Regional flaps were performed in 97 (21.1%), local flaps in 38 (8.3%), and free tissue transfer flaps in 11 patients (2.4%). A total of 243 patients (52.9%) were given adjuvant therapy after surgery. A total of 185 patients (40.3%) received RT, 50 (10.9%) had RT and CT, and eight (1.7%) had CT after surgery. Forty-four patients had positive surgical margins (9.6%) and the rest of the patients (n=415; 90.4%) had negative surgical margins. The five-year OS rates in surgical margin-negative and positive patients were 72.7% and 38.2%, respectively. Also, the five-year DFS rates in surgical margin-negative and positive patients were 64.0% and 29.7%, respectively. Both differences between the patient groups were statistically significant (p<0.05).

Postoperative complications, within 30 days of the operation, were present in 92 patients (20%). Despite perioperative antibiotherapy given to all patients, the most frequent complication was wound infection which was observed in 31 patients (6.8%) within 30 days of the operation. The other complications were flap dehiscence in 28 (6.1%), an orocutaneous fistula in 12 (2.6%), a chylous fistula in four (0.9%), marginal mandibular branch injury in four (0.9%), flap necrosis in three (0.7%), hematoma at the donor site in three (0.7%), pneumonia in three (0.7%), spinal accessory nerve injury in two (0.4%), and osteoradionecrosis in two patients (0.4%). Eighteen of 28 patients with flap dehiscence were reconstructed with regional flaps. Additionally, nine patients of 12 with orocutaneous fistulas were reconstructed with regional flaps and six of them were diagnosed with floor of mouth cancer. Three patients complicated with flap necrosis had free tissue transfer flaps, such as an anterolateral thigh free flap or radial forearm free flap. Five-year OS and DFS rates are shown in Table 2.

DISCUSSION

There is an increase in the incidence of OCC over the last few decades.[11] Well-known risk factors include smoking, tobacco chewing, alcohol consumption, and human papilloma virus (HPV).[12] Intra-oral cancers are strongly associated with cigarette smoking and excessive alcohol consumption, which shows a synergistic effect with tobacco consumption.[13] The incidence of OCC in men is still more than women, although there is an increase in the rate of OCC in women within the last decades. In a review by Boyle et al.,[14] male-to-female ratio of OCC was 2.5. On the other hand, van Dijk et al.[15] reported that the incidence rate of OCC increased throughout the years between 1991 and 2010 and this increase was stronger in women (+1.8% increase per year) than in men (+0.8% per year). Consistent with the previous data, in a study of Kruse et al.,[16] male-to-female ratio was found to be 1.3. Similarly, in the current study, the male-to-female ratio was 1.4 and, consistent with previous authors, we believe that this ratio has been in decline for the last few decades.

In a study by Schwam et al.,[17] the most common primary sites were the oral tongue (40.7%), floor of mouth (21.8%), and buccal mucosa (7.1%) among a total of 408 OCC cases. In this study, it is found that lip cancers were the most common subsite which constituted 29.2% of the cases. Oral tongue was the second common (27.9%) subsite, followed by the buccal mucosa (10.5%). There is a well-known main cause of lip cancer: ultraviolet radiation (UVR) exposure.[18] The Aegean region of Turkey, where this study was conducted, is sunny during most of the year. In addition, agriculture and tourism are the main sources of livelihood. Thus, the UVR exposure is highly expected in this region, through both occupational and recreational exposure. Therefore, higher incidence of lip cancer associated with UVR exposure is an expected consequence in this region of Turkey.

In recent years, there has been an increase in the incidence of OCC among young adults. Although the median age for head and neck cancer diagnosis is around 60 years, it should be noted that an increase in the incidence of these tumors has been described in younger patients, usually less than the age of 45 years. Falaki et al.[19] reported a series of 158 OCC cases with 21 patients (13.2%) being under 40 years old. Similarly, 58 patients (12.6%) were under 45 years old in this study. Some studies have reported that age is a strong independent prognostic factor for survival and survival time is longer in patients under the age of 45 years.[19,20] Warnakulasuriya et al.[20] compared 483 patients under the age of 45 and 4,836 patients over the age of 45 and they found that five-year relative survival was higher among younger patients, compared to the older patients, suggesting that age was a strong independent predictor of crude survival. Lassig et al.[21] also studied on 87 head and neck SCC patients aged <45 years and controls aged ≥45 years and showed that younger patients had a slightly improved OS, but statistically significantly improved DFS rates, particularly in OCC patients. Similarly, patients younger than 45 years had a significantly higher OS and DFS rates, compared to older patients in this study ($p<0.05$). This can be attributed to several factors including comorbidities and performance status. It is also well-known that tumor biology plays an important role in survival and further investigation on this issue are needed. In contrast, Blanchard et al.[22] compared 50 oral tongue SCC patients younger than 40 years and 50 control cases over the age of 40 years and they reported that younger patients had a non-significant trend toward improved OS with a hazard ratio (HR) of 0.53; however, in the multivariate analysis, only the performance of surgery remained statistically associated with improved survival. There was no difference in the use of RT or CT between cases and controls in their cohort study. They also suggested that treatment guidelines developed for older patients should be used for the young adult population. In this study, there was no significant difference in the management strategy between younger and older patient groups.

The significance of lymph node metastasis in staging, prognosis, and decisions regarding the need for adjuvant therapy in head and neck cancers has been well-established. Beside the time of diagnosis and the consequent size of the tumor, the presence of lymph node metastasis in the neck is the most important prognostic

indicator. In this study, the five-year OS rate was significantly lower (76.1% vs 50.1%) in patients with neck metastasis ($p<0.05$). Obviously, this significant difference was not unexpected. Consistent with the results of several reports, negative neck dissection was a strong predictor of regional control and OS. However, contrary to many other reports, lymphovascular invasion was an independent predictor of distant control and OS.

Surgical margin is one of the most important factors which affects the survival and locoregional recurrence in the OCC. Positive surgical margin is associated with poor outcome in terms of disease-free survival and mortality. In many studies, close margin is defined as <5 mm and margins containing carcinoma *in situ*, but not dysplasia, are considered positive by most authors. Sutton et al.[23] defined a clear margin as >5 mm, close as <5 mm, but clear and positive margin, with a series of 200 OCC patients. They reported that the five-year OS rates were 78% and 11% for clear and involved margins, respectively and there was an explicit correlation between the margin status and survival. Kurita et al.[24] reported their series of 148 patients with oral SCC and defined the clear margin as >5 mm. They found the five-year local control rate was 91.0% for a clear margin and 43.8% for involved margins. The authors also reported that the status of the surgical margins had a significant impact on local recurrence. According to the aforementioned and similar studies, it is clear that the positive surgical margins may lead to a high incidence of locoregional recurrence and decreased survival. In this study, the patients were stratified into two groups according to the surgical margin status: positive and negative. Local recurrence was also higher in the patients with positive margins, although only 44 patients (9.6%) had positive margins in this study. In addition, the five-year OS rates in surgical margin-negative and positive patients were 72.7% and 38.2%, respectively, consistent with previous studies in the literature.[25,26]

Auluck et al.[27] analyzed five-year disease-specific survival rates in OCC patients according to disease stage and gender. Among 557 men, the five-year survival rate was 73.3% and 42% in early stage disease (I-II) and late stage disease (III-IV), respectively. Among 380 women, the five-year survival rate was 70% and 50.4% in early stage disease (I-II) and late stage disease (III-IV), respectively. In a study conducted by van Dijk et al.,[15] five-year relative survival estimates for OCC patients were found to be 83%, 73%, 59%, 38%, and 5% in Stage I, II, III, IV-M0, and IV-M1 patients, respectively. For OCC, survival trends were as expected (with increasing T and N stage, there was poorer survival) for both studies. Interestingly, in this study, even Stage IV patients had the lowest five-year OS rates (45.2%), while Stage III patients (71.6%) performed better than Stage II patients (67.4%). This unexpected difference can be due to the lower patient number of Stage III patients, compared to other stages in this study.

According to the literature, surgical site infections (SSIs) following head and neck cancer surgery may occur in up to 10 to 45% of cases, despite antibiotic prophylaxis.[28] Yao et al.[29] reported that 84 patients (23%) of 365 patients developed SSI within 30 days of the operation and the most common SSI formed were neck abscesses (11.5%). In the present study, we observed SSI in 31 patients (6.8%), which is much lower than similar studies. On the other hand, 53 of 92 patients who developed postoperative complications were scheduled to receive adjuvant RT and/or CT and 20 of 92 patients had local/regional recurrence (21.7%). In this context, we consider that the prolonged hospitalization duration and, thus, delayed adjuvant treatment might have been effective in the recurrence development. Therefore, postoperative complications may be associated with locoregional recurrence as dependent risk factors.

In recent years, the expression of certain genes and biomarkers have been reported to be closely related with recurrence, therapeutic effect and prognosis of OCC including serum placental growth factor[30] and overexpression of vascular endothelial growth factor.[31] Also, it has been shown that HPV-positive head and neck SCCs (HNSCCs) occur more frequently in younger patients (<50 years of age), which differs from the typical age of HNSCC.[32] On the other hand, there are several studies suggesting that HPV infection is not significantly related with the development of OCC.[33]

In conclusion, this study includes mostly clinical and epidemiological data from a high-volume academic center. According to our results, positive lymph node metastasis, age, and surgical margin status are the strongest and most consistent predictors of survival outcome in patients with OCC treated with primary surgery and appropriate adjuvant therapy, if necessary. Therefore, management of cervical metastatic lymph nodes and positive surgical margins are vital components in the treatment plan for patients with OCC. Nonetheless, further studies combining data from multiple centers and investigating the molecular background of OCC are needed to elucidate the prognosis and recurrence characteristics.

Declaration of conflicting interests

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