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Five-year Survival and Prognostic Factors Among Oral Cavity Squamous Cell Carcinoma Patients: Analyses of Data from the Cancer Institute of Iran

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ABSTRACT

Background: We conducted a historical cohort study and studied the survival rate and prognostic factors of oral cavity squamous cell carcinoma among patients admitted at the Cancer Institute of Iran.

Methods: We recruited 352 patients who were referred to the Cancer Institute hospital in 2004-2011. Patients were newly diagnosed and pathologically confirmed as oral cavity squamous cell carcinoma. We abstracted data from the archived medical records and followed up with the patients until their death or end of follow-up in January 2015.

Results: A total number of 347 patients (212 males and 135 females) were analyzed in this study. Surgery, alone or in combination with other modalities, was performed in 308 (88.8%) patients. The median time of follow-up was 18.7 months. The 1, 3, and 5-year survival were 84%, 53%, and 41%, respectively. The risk of death was significantly higher in patients older than 70 years of age (HR: 2.0, 95% CI: 1.1-3.7), moderately differentiated tumors (HR: 3.6, 95% CI: 1.3-9.7), "surgery with adjuvant treatment" group (HR: 2.6, 95% CI: 1.6-4.2), and the "surgery with neoadjuvant treatment" group (HR: 3.1, 95% CI: 1.4-7.0). Patients diagnosed with a higher TNM staging also experienced a higher probability of death. An increase in the number of involved lymph nodes was another independent indicator of outcome.

Conclusion: the 5-year survival rate of oral cancer was 41% among patients admitted to the Cancer Institute of Iran. A higher survival rate in early-stage oral cancer patients indicates the importance of early detection among these patients.

Keywords: Oral Cavity; Squamous Cell Carcinoma; Survival; Prognostic Indicators

INTRODUCTION:

Oral squamous cell carcinoma (OCSCC) is the most common type of head and neck cancer, and approximately 350,000 patients were diagnosed in 2018 worldwide (1). It is estimated that the incidence of head and neck squamous cell carcinoma to rise by 30% by 2030, with approximately 1.08 million new cases per year. (2) Head and neck cancers are two to five times more frequent among men than women (2,3). The incidence increases with aging, and the median age at the time of diagnosis is between 60 and 70 years (4). Up to 75% of patients are diagnosed with locally advanced tumors (stage III and IV M0) (5).

The primary site of involvement, potential lymph node involvement, distant metastasis and patient-related characteristics such as age, functional status, and previous comorbidities should be taken into consideration before treatment of the patients (6). Although treatment plan may vary according to the patient's characteristics, surgical resection is the principal method of treatment for most early-stage tumors (stage I and II) (7), while for the majority of locally advanced head and neck squamous cell carcinomas, surgical resection followed by adjuvant treatments, if indicated, or concurrent chemo-radiotherapy reserving salvage surgery for non-responsive tumors are the standard treatment procedures (11).

Despite improvements in early detection of the disease, surgery methods, radiotherapy, chemotherapy regimens, and the application of multi-modality treatments, curing patients with advanced tumors is still challenging (8). It is a significant health issue in many aspects all around the world (9).

In general, 5-year survival of head and neck cancers is low (10). It has a considerable adverse effect on the quality of life because of eating and speaking disabilities and cosmetic issues following treatment(11). The fundamental reasons for a low survival rate are the invasive behavior of the disease and resistance to the treatment strategies leading to the high rate of treatment failure (12,13), locoregional recurrences (14), associated comorbidities, second malignancies arising in the aerodigestive tract, and socioeconomic factors impacting the success of treatment, including poor compliance, limited access to health care facilities, and inadequate patient resources (15). Locoregional failure is the most prevalent mode of recurrence. It varies between 10% and 34% among these patients (16–19).

Regarding the analysis within the Surveillance, Epidemiology, and End Results (SEER) registry of the USA, for all subsites of head and neck cancer, the 5-year overall survival had increased significantly over the past twenty years due to improvement of the treatment modalities, from 54.7% over 1992-1996 to 65.9% during 2002-2006 (20). In explanation, improved staging of the tumors and better treatments can be mentioned. However, attempts to decrease tobacco use in recent decades may also play a role (15).

In developing countries, a low level of education, low socioeconomic status, and lack of knowledge about head and neck cancer are statistically associated with a delayed presentation affecting outcomes (21). Therefore, sufficient treatment would be hard to achieve (22).

The age-standardized incidence rate (ASR) of the OCSCC in Iran among males and females was 0.9 and 0.7 per 100000, respectively (1). In a study conducted in Iran in 2008, the 5-year overall survival rates were 30% and 60% for oral cavity and lip tumors (23). Several improvements in infrastructure and human resources occurred during the last decade in Iran. Cancer Institute of Iran established a comprehensive department for the management of head and neck cancer (24).

Most of the patients, especially the complicated ones, receive treatment after discussion in a multidisciplinary tumor board for head and neck cancers at the Cancer Institute of Iran. We aimed to study the survival and prognostic factors of oral cancer patients diagnosed and treated in this center.

Method and material:

We recruited 352 OCSCC patients admitted for treatment at the Cancer Institute of Iran between 2004-2011. We reviewed the hospital records and included the patients who met our inclusion criteria consisting of a) patients who received at least the first course of cancer-specific treatment with curative intent in the Cancer Institute, b) at least the patient's name or birth date was available in archived medical documents, c) SCC histology confirmed through surgical or biopsy pathology report, d) patient had primary OCSCC, e) tumor primary site was an oral cavity. We excluded five patients because of exclusion criteria consisted of a) the patient's name and birth date were not available in archived medical documents, b)

other histologies except SCC, c) the primary tumor site was not in the oral cavity, d) patients who have received the initial curative cancer-specific treatment before referring to the Cancer Institute, e) patient had recurrent or second primary tumors and f) patient left the Cancer Institute before receiving any kinds of treatment.

We used two different checklists to extract information from the archived materials. The first checklist consisted of demographic, clinicopathological, and treatment information, and the second one was about follow-up visits, recurrence, and death-related questions. The first checklist was completed based on the archived medical records for those who attended the follow-up visits at the surgery-oncology clinic until 2015. To complete the second questionnaire, we called patients or their first-degree relatives.

The 8th edition of the American Joint Committee on Cancer TNM staging system (AJCC) was applied to describe the extent of the disease progression (28). The clinical TNM stage is defined based on clinical and paraclinical information. For patients with metastatic disease at the time of diagnosis, TNM stage IV was reported even if other information (T and N stage) was unavailable. 3rd edition of the International Classification of Disease for Oncology (ICD-O-3) was applied to specify oral cavity tumors through pathology reports (25).

Tumor histopathological differentiation was determined based on the World Health Organization (WHO) histological grading system. In 52 pathology reports, differentiation grade was not mentioned, grouped as the "not reported" category. In 7 cases, it could not be assessed and grouped as the "cannot be assessed" category.

Recurrences are categorized into three groups, locoregional, distant metastasis, and unknown. Information on the cause of death was gathered through archived medical histories or follow-up contacts and classified into three subgroups: primary cancer, cancer recurrence, and unknown etiologies. Treatments were grouped as only surgery, radiotherapy, chemotherapy, or chemo-radiotherapy and combined methods which consisted of patients who received radiotherapy or chemo-radiotherapy or chemotherapy before (as neo-adjuvant treatment) or after (as adjuvant treatment) surgery. Overall survival (OS) is defined as the time interval between the date of cancer diagnosis and the date of death due to cancer or the date of the last follow-up. Disease-free survival (DFS) is calculated from the date of completion of treatment to the date of locoregional or distant metastasis recurrence or death.

Statistical analysis

Statistical analysis was performed using STATA version 11 (State Corp., College Station, TX), and all p-values were two-sided. Cox regression hazard models were applied to obtain hazard ratios (HR) with 95% confidence intervals (CI) to assess the association between oral cavity cancer survival and potential risk factors. Fully adjusted models included variables that showed a p-value of more than 0.2 in the univariate analysis. To choose the best model, we fitted the multivariate analysis based on the likelihood ratio test and estimated the area under the curve that was between 0.70-0.80. We reported the HR and 95% CI for each variable utilizing two models. Both models included age, sex, education, primary tumor histopathological differentiation, type of treatments, surgical margins status, and the number of pathologically involved lymph nodes. In the main model, we introduced the TNM staging of the tumor while for the second one, we used the tumor size (T), nodal, and distant metastases status instead of TNM staging. Overall survival (OS) curves were created using the Kaplan-Meier method.

Results:

Patient demographic and clinicopathological features

Table 1 shows the demographic and clinicopathological characteristics of a total number of 347 cases of OCSCC that met the inclusion criteria. There were 135 (34.90%) females and 212 (61.10%) males. 160 (46.11%) patients were more than 70 years old at the time of diagnosis, while 99 (19.90%) aged less than 60 years. 186 (53.60%) patients were illiterate, while 34 (9.8%) patients had diplomas or upper educational degrees.

In this cohort, 174 (50.14%) patients presented with early-stage diseases (stage I and II), and 152 were diagnosed at the advanced stages. Recurrence was observed in 20.17% of patients, from which 80.5% had a locoregional recurrence, while distant metastases were reported in 8.5% of them. Death occurred in 120 patients until the end of the follow-up, while 51 (14.70%) and 45 (13.00%) of deaths were due to primary cancer and cancer recurrence, respectively.

We found that 152 (43.80%) patients underwent surgery alone, 134 (38.60%) and 22 (6.3%) were treated with surgery in combination with adjuvant and neoadjuvant radiotherapy or chemo-radiotherapy, respectively. While 39 (11.2%) underwent radiotherapy, chemo-radiotherapy,

Table 1. Demographic and clinic-pathological features of patients with oral squamous cell carcinoma admitted at the Cancer Institute of Iran during 2004-2011

Variable	Number (%)
Sex	
Female	135 (34.9)
Male	212 (61.1)
Age group	
<60	99 (28.5)
60-70	69 (19.9)
>70	160 (46.1)
Unknown	19 (5.6)
Education	
Illiterate	107 (30.8)
High School	78 (22.5)
Diploma & Upper Diploma	34 (9.8)
Unknown	128 (36.9)
Stage	
I	109 (31.4)
II	65 (18.7)
III	75 (21.6)
IV	77 (22.2)
Unknown	21 (6.1)
Grade of histology	
well differentiated	177 (51.0)
moderately differentiated	102 (29.4)
poorly &undifferentiated	9 (2.6)
Can not	7 (2.0)
Not reported	52 (15.0)
Recurrence occurrence	
No	277 (79.8)
Yes	70 (20.2)
Type of recurrence	
Locoregional	66 (80.5)
Metastasis	7 (8.5)
Unknown	9 (10.9)
Cause of death	
Primary cancer	51 (14.7)
Cancer recurrence	45 (13.0)
Other causes	24(6.9)
Censored	227 (65.4)
Type of treatment	
Only surgery	152 (43.8)
Only radiotherapy	25 (7.2)
Only chemotherapy	6 (1.7)
Only Chemoradiotherapy	8 (2.3)
Surgery + adjuvant radiotherapy or chemoradiotherapy	134 (38.6)
Surgery + neo adjuvant radiotherapy or chemoradiotherapy	22 (6.3)

or chemotherapy alone at the Cancer Institute.

The median time of follow-up was 18.7 months. The 1, 3, and 5-year overall survival rates were 84%, 53%, and 41%, respectively. The DFS rate decreased from 70% in the 1st year to 47% and 34% in the 3rd and 5th years, respectively. The median time of overall and disease-free survival was 30.11 (±0.03) and 22.33 (±1.52) months, respectively.

Figure 2 shows the OS rate based on TNM staging. Patients with a higher stage had consistently lower survival rates. The median survival time also dropped from 9.6 months for stage I to 1.3 months for stage IV.

Concerning the treatment outcome, a higher proportion of patients who underwent surgery alone were alive compared with those treated with other modalities. For the "surgery alone" group, 5-year OS was approximately two and three times more than the "surgery combined with adjuvant treatment" and "radiotherapy, chemoradiotherapy and chemotherapy" group. Moreover, the OS rate for the "surgery alone" group was five times higher than the "chemo-radiotherapy alone" group. Their survival rate dropped from 88% at the end of the first year to 62% at the end of the fifth year. The most dramatic reduction in OS rate was observed for the group that received radiotherapy or chemo-radiotherapy before surgery as 80% of them were alive at the end of the 1st year while only 14% were alive at the end of the 3rd year. We could not estimate their 5-year survival rate due to small power. r.

Patients with lip tumors experienced a survival advantage over other sites of the oral cavity. At the end of the first year, a nearly similar percentage of patients of both groups were alive (89% of lip tumors and 82% of other sites), but at the end of the fifth year, 64% of patients with lip tumors were alive that is approximately two times more than other sites (34%) as it is shown in Figure 1.

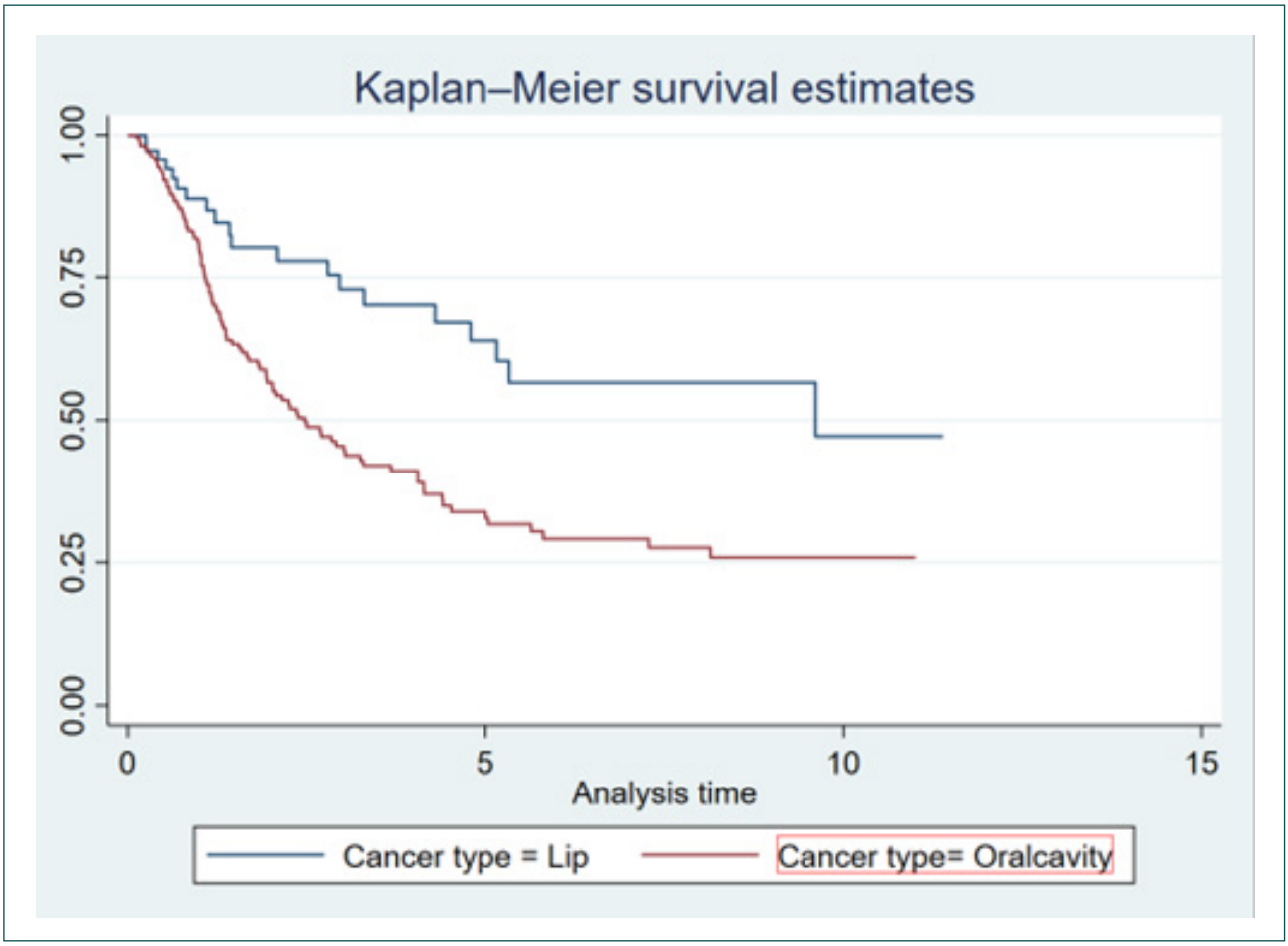

Figure 1: Kaplan–Meier plots analysis by sub site group for patients with OCSCC referred primarily to the Cancer Institute of Iran during 2004-2011

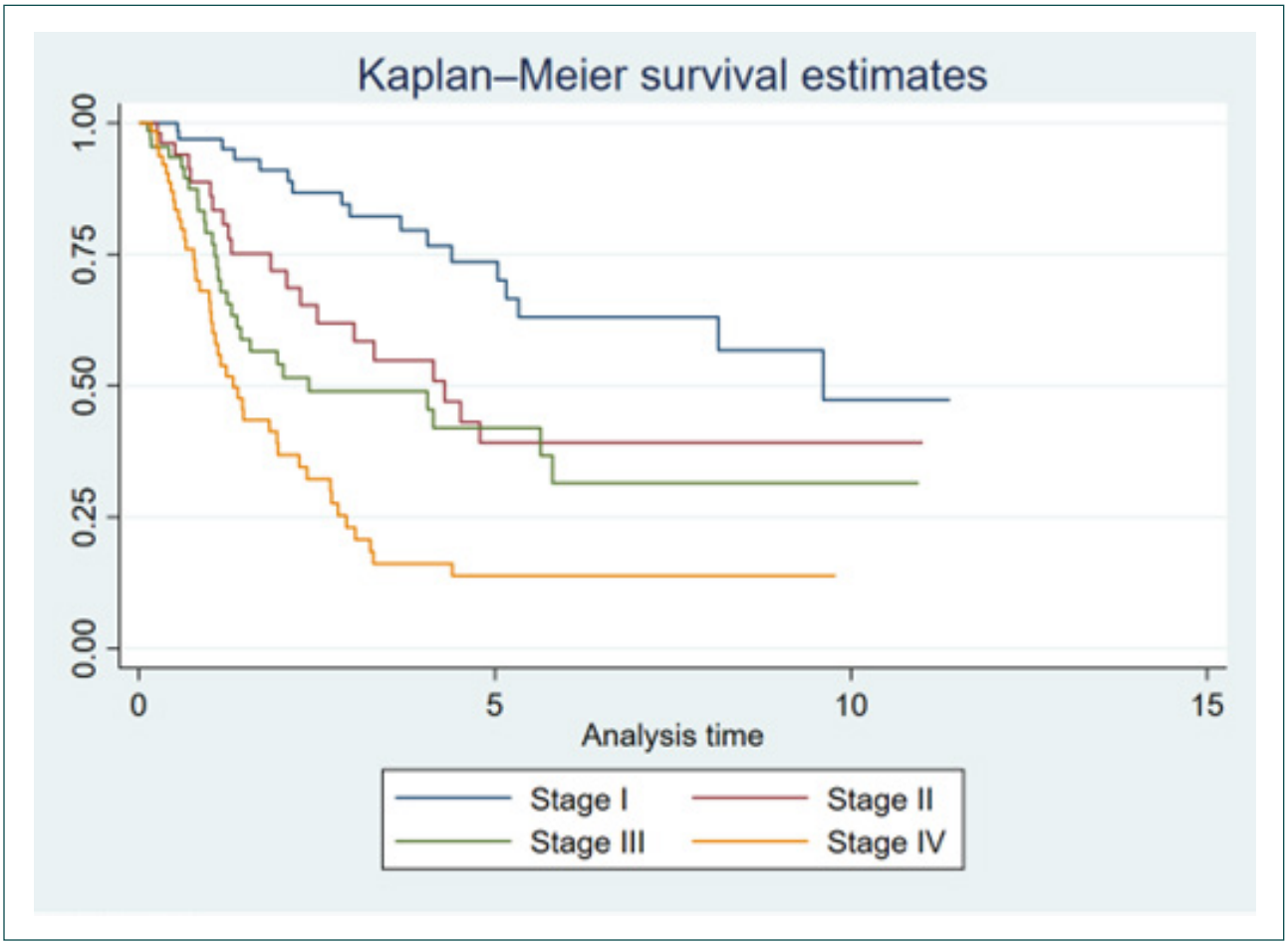

Figure 2: Kaplan–Meier plots analysis by stage group for patients with OCSCC referred primarily to the Cancer Institute of Iran during 2004-2011

Patients without pathologically involved lymph nodes and with free surgical margins had persistently higher OS rates (Table 3). However, the involvement of lymph nodes affected the survival rate more significantly. The 5-year OS rate for patients without nodal involvement was 45% in contrast with 14% for those with involved lymph nodes. While, for patients with clear surgical margins this rate was 49% in comparison with 36% for those with involved surgical margins. The involvement of lymph nodes and surgical margins reduced the median survival from 4.3 (±0.3) and 4.4 (± 0.9) months to 1.1 (± 0.2) and 1.4 (± 0.5) months, respectively.

In the univariate Cox hazard regression analysis, the patient's characteristics were not significant statistically. However, male sex, age above 60, and higher educational level were associated with a statistically insignificant better prognosis. Those with a diploma and college degree had a 50% less risk of death, while the "under diploma" group had only a 10% improvement in their risk of death compared with the illiterate group. We could not observe any difference between the risk of death for those who were diagnosed between 2009-2011 (HR: 1, 95% CI: 0.7-1.5) after establishing the Cancer Institute and those who were diagnosed before that.

Regarding the tumor characteristics, histopathology of the tumor, TNM staging, T stage, lymph node involvement, and surgical margin status showed an impact on survival. Although we observed that less differentiated tumors increased the risk of death, only moderate differentiation of tumor was a significant predictor of survival (HR: 1.7, 95% CI: 1.1-2.6).

Treatment-wise, those who received all treatment modalities rather than surgery alone, experienced a higher probability of death, and this variable could affect the outcome significantly. The "surgery+neoadjuvant treatment" group risk was the highest at 4.4 times more

Table 2. OS rate according to stage, treatment, and sub-site of disease for patients with OCSCC referred primarily to the Cancer Institute of Iran during 2004-2011

Survival	1-year	3-year	5-year	Median Survival (± SE)
Stage				
I	96%	82%	73%	9.6 (± 0.2)
II	88%	62%	39%	4.3 (±0.8)
III	79%	49%	42%	2.4 (±1.2)
IV	68%	23%	14%	1.3 (± 0.2)
Type of treatment				
Only surgery	88%	72%	62%	....
Only radiotherapy	79%	40%	26%	2.4 (± 0.5)
Only chemotherapy	NA	NA	NA	0.4 (± 0.1)
Only Chemo-Radiotherapy	75%	36%	12%	1.2 (± 0.7)
Surgery + adjuvant treatment *	83%	43%	30%	2.0 (± 0.6)
Surgery + neoadjuvant treatment*	81%	14%	NA	1.4 (± 0.1)
Type of Cancer				
Lip	89%	75%	64%	9.6 (± ...)
Oral Cavity	82%	45%	34%	2.4 (±0.4)

* Radiotherapy or Chemo-Radiotherapy

Table 3. 1, 3, and 5 OS rate according to the lymph node involvement and surgical margin status for patients who underwent surgery or lymph node dissection for patients with OCSCC referred primarily to the Cancer Institute of Iran during 2004-2011.

LND status	1-year	3-year	5-year	Median Survival (± SE)
LN Involvement				
No LN involved	93%	67%	45%	4.3 (±0.3)
LN involved	63%	14%	14%	1.1 (± 0.2)
Margin status				
Free	89%	60%	49%	4.4 (± 0.9)
Involved	75%	42%	36%	1.4 (± 0.5)

Table 4. Multivariate analysis for OCSCC according to variables for patients with OCSCC referred primarily to the Cancer Institute of Iran during 2004-2011

Variables	Number (Censored/death)	Lip Oral Cavity	
		Crude HR*	Adjusted HR
Sex			
Female	78/57	Reference	Reference
Male	149/63	0.8 (0.6, 1.2)	1.0 (0.6, 1.5)
Age Group			
<60	74/25	Reference	Reference
60-70	48/21	1.5 (0.8, 2.7)	1.9 (1.0, 3.8)
>70	97/63	1.6 (1.0, 2.6)	2.0 (1.1, 3.7)
Unknown	8/11	.....	.....
Education			
Illiterate	57/50	Reference	Reference
Under Diploma	51/27	0.8 (0.4, 1.3)	0.9 (0.5, 1.7)
Upper Diploma and College	26/8	0.60 (0.2, 1.4)	0.5 (0.2, 1.2)
Unknown	93/35	....	...
Grade			
Well-differentiated	124/53	Reference	Reference
Moderate	57/45	1.8 (1.2, 2.8)	1.5 (1.0, 2.3)
Poor & Undifferentiated	4/5	2.1 (0.8, 5.7)	3.6 (1.3, 9.7)
Cannot assess	6/1	0.8 (0.1, 1.8)	0.3 (0.0, 2.6)
Not reported	36/16	1.0 (0.7, 1.8)	1.1 (0.6, 2.1)
Time of diagnosis (Year)			
2004-2008	113/69	Reference	Reference
2009-2011	114/51	1.5 (1.0, 2.2)	1.1 (0.7, 1.7)
Surgical margin status			
Free	163/67	Reference	Reference
Involved	49/33	1.6 (1.0, 2.6)	1.1 (0.7, 1.7)
Unknown	15/20	NA	NA
Type of treatment			
Only surgery	118/34	Reference	Reference
Surgery + adjuvant**	78/56	2.6 (1.7, 4.0)	2.6 (1.6, 4.2)
Radiotherapy/ Chemotherapy / Chemoradiotherapy	19/ 20	3.5 (2.0, 6.1)	2.2 (0.7, 6.6)
Surgery + neo adjuvant **	12/10	4.5 (2.2, 9.3)	3.1 (1.4, 7.0)
Stage			
I	91/18	Reference	Reference
II	45/20	1.90 (1.0, 3.8)	2.2 (1.1, 4.3)
III	47/28	2.5 (1.3, 4.8)	2.4 (1.3, 4.5)
IV	34/43	5.9 (3.2, 10.6)	3.1 (1.4, 7.0)
Unknown	10/11	....	...
Number of involved lymph nodes £			
Not Involved	82/33	Reference	Reference
1-4	26/29	3.5 (2.0, 6.1)	3.0 (1.7, 5.3)
>5	5/13	5.5 (2.6, 11.7)	3.6 (1.8, 7.5)
Unknown ***	114/ 45	NA	NA
T£			
0	9/ 6	Reference	Reference
1	101/ 33	0.3 (0.1, 0.7)	0.7 (0.2, 2.1)
2	63/ 41	0.5 (0.2, 1.3)	1.1 (0.4, 3.4)
3	40/ 24	0.4 (0.1, 1.1)	1.1 (0.3, 3.4)
4	14/ 16	0.6 (0.2, 1.9)	1.7 (0.5, 5.4)

than the "surgery alone" group. Patients with an involved surgical margin also were at an increased risk of death (HR:1.8, 95% CI: 1.2-2.8).

Even though having metastases at the time of diagnosis was associated with a 60% increase in the risk of death in patients (HR: 1.6, 95% CI: 0.4-6.4), such a difference was not meaningful.

In the multivariate analyses, age above 60 years, poor and undifferentiated histopathology (HR:3.6, 95% CI: 1.2-10.9), TNM staging of the tumor, T stage 2 and 4, treatment modalities, and the number of pathologically confirmed involved lymph nodes were significant prognostic factors for lower survival.

Discussion:

We studied epidemiological and clinicopathological characteristics of patients with OCSCC retrospectively who were treated primarily at the Cancer Institute of Iran, Tehran, Iran, during 2007-2011. In this study, the 5-year OS rate was 41% which was similar to the rates reported from less developed countries, including Brazil (43%), and India (30.5%), but lower than rates reported from developed countries, including the USA (64.0%), and UK (64.0%) (4,26–31). the present data showed that the survival rate in this study was considerably higher than the rates reported previously from Iran (32).

We found that 20.2% of cases had a recurrence. Among this group, 80.5% and 8.5% had a locoregional recurrence and distant metastasis, respectively. The recurrence rate is compatible with previous reports from Germany and Brazil (33,34). The locoregional recurrence rate is higher than reports from developed countries, including the USA (35), which might be due to the more failure in the local control of cancer in Iran, which could be related to the less advanced treatment methods and facilities and the interval time between surgery and adjuvant treatments (41,42).

Patients with lip tumors lived longer than those with tumors originating from other sites of the oral cavity; this result was reported in other publications (32,36,37). However, the 5-year OS rate for lip and other sites of oral cavity tumors is significantly lower than that in Western countries (4,38,39)

The 5-year OS rate for all sites of oral cavity tumors was 41% in Iran, which was higher than in Malaysia (18%) (40) and India (30.5%) (31), but lower than the rates reported in Taiwan (61%)(41) and most of the developed countries (42,43).

Surgery alone is considered a treatment modality of choice for less advanced tumors. Therefore, as expected, patients who underwent surgery alone had a better prognosis than those who underwent neoadjuvant or adjuvant therapy. In patients with advanced-stage tumors, for whom other modalities were combined with surgery, and those who received treatments other than surgery, the 5-year OS rate was lower, and the type of treatment was significantly associated with a lower survival rate (32). Many studies have demonstrated that radiotherapy or chemo-radiotherapy after surgery increases the survival rate significantly (44–46) compared with patients who underwent surgery alone at the same stage. We did not have sufficient power to study the effect of treatment modalities in each stage exclusively which can describe the observed difference. Patients who were not appropriate candidates for surgery might had other comorbidities, which can subsequently attribute to a lower chance of survival.

Radiotherapy or chemo-radiotherapy after surgery increased the 3-year and 5-year OS rate rather than before surgery. In other words, adjuvant treatment, which results in better locoregional control and less locoregional failure, plays a great role in improving survival (2,47,48). This difference was also demonstrated in univariate and multivariate analysis as the "surgery with adjuvant therapy" experienced a 90% reduction in risk of death compared with the "surgery with neoadjuvant therapy" group.

Considering the surgical margin status, although the involvement of margins could influence survival meaningfully (HR 1.8, 95% CI: 1.2-2.8) in univariate analysis, it was not a meaningful predictor of survival independently.

As in other studies (49–52), the 5-year OS rate had an inverse association with the tumor stage. The 5-year OS rate has dropped from 73% for stage I to 14% for stage IV. In both univariate and multivariate hazard analysis, this was proved significant. The risk of death was 7.5 times (HR: 7.5, 95% CI: 3.9-14.2), and for stage III tumors it was 3.8 times (HR: 3.8, 95% CI: 1.9-7.4) higher than the risk for stage I.

As the T stage (size) of the tumors increased, the probability of survival reduced significantly. This finding is in line with previous studies (53,54). Pathological involvement of lymph nodes was also another indicator of outcome and its influence was accentuated consistently with an increase in the number of affected nodes which is comparable to other studies (55,56). Patients with more than 5 involved lymph nodes had 3.7 and those with 1-4

involved lymph nodes experienced 3.1 times the risk of death compared with those without involved lymph nodes. As essential components of TNM staging, both tumor size and involvement of lymph nodes change the stage which as a result can influence the treatment plan, risk of locoregional failure, and ultimately, survival.

Our study had several strengths, including a reasonable power and a large sample size. In addition, it was the first attempt to assess the role of different treatment modalities in oral cavity cancer survival in Iran. Despite the several strengths of our study, we faced some limitations, including retrospective design and data loss to follow-up. Another limitation was the incomplete archived medical documents. On the other hand, patients referred to the Cancer Institute from different areas of Iran could be at more advanced stages than those treated in other centers which further complicates the situation, and further data from other centers is needed to study the prognosis and quality of oral cancer care in Iran.

In conclusion, our hospital-based survival study revealed that TNM stage, number of involved lymph nodes, histopathological differentiation, site of origin (lip vs. other parts of the oral cavity), and type of treatment are important prognostic factors among Iranian oral cancer patients. More data at the national level and analysis of patients' outcomes over time is required

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