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ORIGINAL RESEARCH

Clinicopathological Parameters and Locoregional Recurrence in Oral Squamous Cell Carcinoma Patients

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ABSTRACT

Objectives: To study the clinicopathological parameters associated with recurrence of oral squamous carcinoma and analyze the survival of patients managed in ENT and Head and Neck Surgery Department between January 2008 and December 2013.

Materials and methods: Records of 178 cases were reviewed for clinical details, histopathological data, and follow-up status. Age, gender, addiction, subsite, T–N pathological staging, tumor thickness, margin status, grade of differentiation, lymphovascular permeation, perineural spread, and adjuvant therapy were analyzed.

Results: The recurrence rate was 13.5%. The median follow-up for the entire cohort was 20 months. Twenty-four patients had locoregional recurrence: 9 (37.5%) local recurrence alone, 11 (45%) regional recurrence alone, and 4 (17.5%) had both local and regional recurrence. The average time to recur in case of negative margin was 12.1 months, for close margin was 11.9 months, and with positive margin was 4.1 months. Looking at all patterns of recurrence, 4/98 (4%) of cases with negative margins, 15/65 (23%) cases with close margins, and 5/15 (33.3%) of those with positive margins recurred. Out of 24 cases of recurrence, 22 were sent for salvage surgery and others for salvage chemoradiation therapy. The Kaplan–Meier method and log-rank tests showed that the 2- and 5-years survival rates were significantly lower in the recurrence group compared with nonrecurrence group (78 *vs* 94%, 37 *vs* 66%, $p < 0.001$). Locoregional recurrence is strongly correlated with margin status according to univariate and multivariate analysis.

Conclusion: Among all clinicopathological parameters, the status of the surgical margin is the most important prognosticator. Good local control is mandatory to ensure patient's survival. Adequate margins at initial resection for complete clearance without the need of revision should be pursued by every surgeon. Although it is in surgeon's control, the achievement can be limited by the aggressiveness of the disease.

Keywords: Clinicopathological parameters, Oral squamous cell carcinoma, Recurrence.

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INTRODUCTION

The incidence of head and neck squamous cell carcinoma remains high. It is ranked to be the 6th most common malignancy worldwide, responsible for approximately half a million new cases every year. Approximately 60% of patients present with locally advanced, but no distant metastatic disease (stage-III or IVA/B) at diagnosis.[1]

Oral squamous cell carcinoma (OSCC) has been one of the top 10 causes of death from cancer since 1991 in Taiwan and the death toll for oral cancer in males has been rising at a surprising rate. Surgery is the preferred treatment in multidisciplinary setting along with chemotherapy, radiotherapy, and targeted therapy. However, OSCC is still a challenging disease to treat in the field of head and neck oncology, due to aggressiveness of its local invasion, metastases, and second primary, leading to recurrence. Recurrence is solely an important prognosticator in patients with OSCC. Most of locally advanced tumors relapse usually within the first 2 years after treatment; 20 to 30% with distant metastases give limited offer for salvage surgery and radiation.

In this retrospective analysis, the clinicopathological parameters of OSCC were studied and correlated with recurrence.

MATERIALS AND METHODS

Patient Characteristics

We carried out a retrospective database of 178 patients with previously untreated squamous oral cancer in the period from January 2008 through December 2013, in the Department of ENT and Head and Neck Surgery at Shin Kong Wu Ho-Su Memorial Hospital, Taipei. Local recurrence, regional recurrence, or both were all defined as recurrence. Local recurrence was defined as lesions arising in oral cavity relative to primary tumor beyond 6 weeks after the first definitive treatment. Time to recurrence was determined by the duration from the first surgery to pathologically confirmed recurrence.

Clinicopathological Characteristics

The patients' data were entered onto proformas. The fields included a range of gender, age, any addiction, tumor subsite, clinical staging, histology differentiation, and histopathology variables related to the surgical margin. Margins were documented in histopathology report as per the protocol followed at our institute – a resection margin of 5 mm or greater was taken as negative, a margin between 1 and 5 mm was close, while a margin of equal to or less than 1 mm was placed in the category of positive margin. Thickness of the lesions were divided into less than and more than 5 mm thickness. Data collected also included pathological staging (T and N stage), adjuvant therapy, any salvage therapy, disease-free survival, date of death, cause of death, and last clinic review. Causes of death were collated in two categories: (1) Tumor related (i.e., locoregional or distant metastases) and (2) nontumor related (e.g., pneumonia or any other cause that led ultimately to cardiorespiratory failure).

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 17 was used for statistical analysis. The correlation between all clinicopathological factors for OSCC was analyzed using chi-square tests or Fisher's exact test. The Kaplan–Meier estimate and log rank were obtained for survival analysis.

RESULTS

The patient population comprised 153 males (85.9%) and 25 females (14.1%). Their mean age at the first diagnosis of OSCC was 50.7 years old (26–68). Primary sites were mainly identified in the tongue (50), followed by buccal mucosa (37) and gum (36). Clinical characteristic and stage distribution according to American Joint Committee on Cancer (AJCC) clinical staging system are summarized in Table 1. Most of the identified OSCC were of low risk (stage TI–T2) and no distant metastases were reported.

Table 1: Analysis of patient characteristics and appearance of recurrence

Variable	*Total (n)*	*Local recurrence n(%)*	*Regional recurrence n(%)*	*Locoregional recurrence n(%)*	*No recurrence n(%)*
Gender					
Male	153	4 (2.6)	0 (0)	0 (0)	149 (97.4)
Female	25	5 (20)	11 (44)	4 (16)	5 (20)
Age					
<60 years	100	5 (5)	5 (5)	0 (0)	90 (90)
≥60 years	78	4 (5)	6 (8)	4 (5)	64 (82)
Addiction					
Areca nut/Betel chewer	51	5 (10)	0 (0)	0 (0)	46 (90)
Smoker	74	4 (5)	2 (3)	0 (0)	68 (92)
Both	26	0 (0)	0 (0)	0 (0)	26 (100)
None	27	0 (0)	9 (33)	4 (16)	14 (52)
Tumor subsite					
Lips	29	0 (0)	0 (0)	0 (0)	29 (100)
Tongue	50	7 (14)	2 (4)	2 (4)	39 (78)
Cheek	37	1 (3)	2 (5.1)	0 (0)	34 (91.9)
Gum	36	1 (2.7)	4 (11.3)	1 (2.7)	30 (83.3)
RMT	14	0 (0)	1 (7.1)	0 (0)	13 (92.9)
FOM	5	0 (0)	1 (20)	1 (20)	3 (60)
Palate	5	0 (0)	1 (20)	0 (0)	4 (80)
Clinical T stage					
T1	91	2 (2)	1 (1)	1 (1)	87 (96)
T2	20	2 (10)	3 (15)	1 (5)	14 (70)
T3	57	4 (7)	5 (8.7)	2 (3.5)	46 (80.8)
T4	10	1 (10)	2 (20)	0 (0)	7 (70)
Differentiation					
Well differentiated	19	2 (10.5)	1 (5.3)	0 (0)	16 (84.2)
Moderate	150	4 (2.6)	8 (5.3)	4 (2.6)	134 (89.5)
Poor	9	3 (33.3)	2 (22.2)	0 (0)	4 (44.5)
Thickness					
≤ 5 mm	71	2 (2.8)	1 (1.4)	0 (0)	68 (95.8)
> 5 mm	107	7 (6.5)	10 (9.3)	4 (3.7)	86 (80.5)

(Contd…)

(Contd…)

Variable	*Total (n)*	*Local recurrence n(%)*	*Regional recurrence n(%)*	*Locoregional recurrence n(%)*	*No recurrence n(%)*
AJCC stage					
Stage I–II	116	4 (3.4)	4 (3.4)	2 (1.7)	96 (91.5)
Stage III–IV	62	5 (8)	7 (11.3)	2 (3.2)	48 (77.5)
Pathological T stage					
T1	92	2 (2)	1 (1)	1 (1)	88 (96)
T2	24	2 (8)	3 (12.5)	1 (4)	18 (75.5)
T3	49	2 (4)	4 (8)	1 (2)	42 (86)
T4	13	3 (23)	3 (23)	1 (7)	6 (47)
Pathological N stage					
N0	148	3 (2)	6 (4)	2 (1)	137 (93)
N plus	22	6 (27)	3 (14)	2 (9)	11 (50)
Unknown	8	0 (0)	2 (25)	0 (0)	6 (75)
Margin resection					
Free	98	0 (0)	3 (3)	1 (1)	94 (96)
Close	65	7 (10.7)	8 (12.3)	0 (0)	50 (77)
Positive	15	2 (13.3)	0 (0)	3 (20)	10 (66.7)
PNI					
Not present	175	8 (4.5)	11 (6.3)	4 (2.2)	153 (87)
Present	3	1 (33.3)	0 (0)	0 (0)	2 (66.7)
LVE					
Not present	167	2 (1.2)	11 (6.5)	4 (2.3)	150 (90)
Present	11	7 (63.6)	0 (0)	0 (0)	4 (36.4)
Adjuvant therapy					
Yes	74	6 (8.1)	6 (8.1)	3 (4)	59 (80.8)
No	104	3 (2.8)	5 (4.8)	1 (0.9)	95 (91.5)
Neck dissection					
SOHD	148	3 (2)	6 (4)	2 (1)	137 (93)
MRND	22	6 (27)	3 (14)	2 (9)	11 (50)
None	8	0 (0)	2 (25)	0 (0)	6 (75)

Of all the patients, 51 (28.6%) were betel nut chewers, 74 (41.5%) were smokers, and 26 (14.6%) had both addiction.

All patients were submitted to primary resection as an initial treatment, and 170 cases were submitted for neck dissection, out of which 148 were supraomohyoid neck dissection and 22 modified radical neck dissection. In 104 patients, surgery was the sole treatment modality, while postoperative radiotherapy and/or chemotherapy to primary tumor and neck region were carried out in 74 patients.

Pathological analysis revealed that more than half of the cases (84.2%) were moderately differentiated, 19 (10.6%) cases well differentiated, and only 9 (5.2%) cases were poorly differentiated. According to pathological staging for OSCC, 92 cases were pathologically at stage T1, 24 at stage T2, 49 at stage T3, and 13 at stage T4; 148 patients (83%) were pathologically N0, while 22 patients (12%) were N plus, and in 8 cases (5%) nodal surgery was not done, therefore in those cases, pathological N staging was not available. Pathological tumor-node metastasis differed somewhat from the clinical tumor-node metastasis. Mean depth of tumor invasion was 7 mm (1–50 mm). Thick tumor (thickness ≥ 5 mm) was evident in most of the specimen (n = 107, 60.1%). Lymphovascular permeation (LVE) was identified in 11 patients, while only three cases presented with perineural invasion (PNI). From the final histopathology report, it was found that there were 15 cases (8.4%) with positive margins and 65 cases (36.5%) with close margins. The rest 98 (55.1%) cases had negative or free margins.

The average follow-up was 20 months for the entire cohort. Ninety-six (53.9%) patients had a follow-up of more than 36 months. Patients with advanced cancers had been followed up for an average of 30.5 months (5–65) and those with early stage followed up for an average of 36.5 months (12–58.5 months).

Tumor clearance was achieved in 153 patients; unfortunately, tumor recurred in 24 patients. Out of 24 cases of locoregional recurrences, 22 were treated with salvaged surgery and/or chemoradiation.

Recurrence was identified in 4 males and 20 females. Most common oral sites included tongue (11) and gum (6). At the end of study period, 9 patients evolved with local recurrence only, 11 had regional recurrence only, and 4 had both local and regional recurrence. Looking

at the pathological T stage, 22.5% of advanced cases and 8.5% of early stage recurred.

A total of 5% of N0 (8/148) and 23% of N plus (5/22) patients had regional recurrence. All these patients were initially treated with neck dissection. Frozen section was not routinely practiced for assessment of lymph node metastasis intraoperatively. All the resected specimens were sent for final histopathology analysis.

Univariate and Multivariate Logistic Analysis for Overall Recurrence

Overall recurrence was associated with gender in 82.6% ($p < 0.001$), pathological N stage disease in 27% ($p < 0.001$), thickness in 23.7% ($p < 0.001$), and margin status in 60.3% ($p < 0.001$) of the patients. Multivariate analysis revealed margin status as an independent factor for recurrence ($p < 0.001$), as shown in Tables 2 and 3.

The histological section of this group was evaluated and we found 4/98 (4%) cases with negative margins recurred, 15/65 (23%) cases with close margins, and 5/15 (33.3%) of those with positive margins recurred (Table 1). Mean depth of tumor invasion was 14 mm (4–45 mm).

The average time to recur in case of negative margin was 12.1 months, while for close margin was 11.9 months, and with positive margin was 4.1 months. For local recurrence alone, only 7/65 (10.7%) cases with close margins and 2/15 (13.3%) cases with positive margins recurred. Looking at the impact of adjuvant therapy on margin as shown in Table 4, 25% (n = 8) of close margin and 28.5% (n = 4) of positive margin with adjuvant therapy recurred.

Table 2: Univariate logistic analysis for the factors influencing recurrence

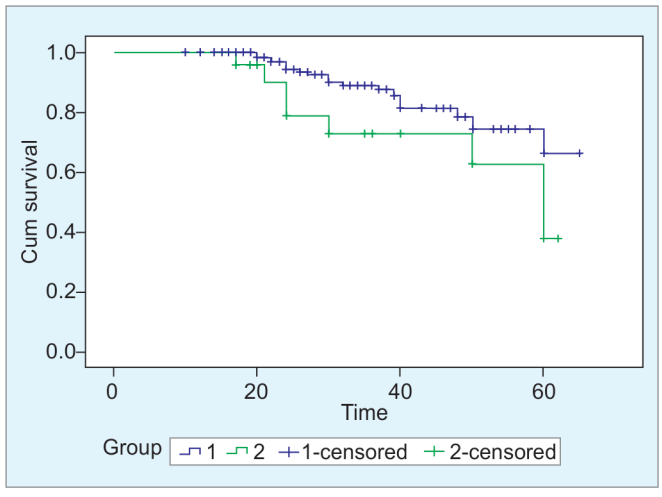
Factors	*Odds ratio*	*95% CI*	*p-value*
Gender			
(Male *vs* Female)	4.23	1.87–9.6	<0.001
Age			
(<60 *vs* >60 years old)	0.8	0.36–1.76	0.474
Addiction			
(Yes *vs* No)	1.45	0.65–3.30	0.572
Differentiation			
(Well-diff *vs* Moderately + Poorly diff)	1.37	0.42–3.10	0.887
Thickness			
(< 5 mm *vs* > 5 mm)	5.88	1.76–9.77	<0.001
T stage			
(T1–T2 *vs* T3–T4)	1.69	0.59–5.24	0.475
N stage			
(No *vs* N+)	7.20	3.0–16.41	<0.001
LVE			
(Yes *vs* No)	1.22	0.84–3.28	0.967
Margin			
(Free *vs* Close + Positive)	7.79	6.16–43.83	<0.001
Postoperative adjuvant radiotherapy			
(Yes *vs* No)	1.26	0.75–4.26	0.357

Table 3: Multivariate logistic analysis for the factors influencing recurrence

Factors	*Odds ratio*	*95% CI*	*p-value*
Margin (free *vs* close + positive)	8.12	2.28–23.45	p < 0.001

Table 4: Recurrence *vs* adjuvant therapy *vs* margin

Margin + Adj therapy	*Recurrence n(%)*	*No recurrence n(%)*	*Total*
Free with adjuvant	3 (10)	25 (90)	28
Free without adjuvant	1 (1)	69 (99)	70
Close with adjuvant	8 (25)	24 (75)	32
Close without adjuvant	7 (21.2)	26 (78.8)	33
Positive with adjuvant	4 (28.5)	10 (71.5)	14
Positive without adjuvant	1 (100)	0 (0)	1



Graph 1: Survival curve recurrence *vs* nonrecurrence group

Eight patients died in the recurrence group and six patients died due to tumor-related disease. The Kaplan–Meier method and log-rank test showed that the 2 and 5 years survival rates were lower in recurrence group compared with nonrecurrence group (78% *vs* 94%, 37% *vs* 66%, $p < 0.001$) (Graph 1).

DISCUSSION

Recurrence has been known to have great impact on survival of OSCC patients. Camisasca et al[2] have reported the 5-years survival rate as 92% in patient without recurrence and 30% with OSCC recurrence.

The present study showed 24 patients had recurrence (13.5%). Univariate analysis revealed that gender, addiction, thickness, N stage, and margin status were important factors for overall recurrence. The 2- and 5-years survival rates were lower in those patients with

recurrence than in those without, as determined by Kaplan–Meier curve and log-rank test.

Most studies corroborated that the median time to recur is 7.5 months after treatment and 86% of the recurrence occur within 24 months.[3,4] The average interval for recurrence in our study was 12 months in case of negative or close margins, while it was 4 months for positive margins. Sadeghi et al[5] and Priya et al[6] also found that positive margin patients tend to have earlier recurrence (8 months *vs* 11 months, 34 months *vs* 10 months).

Factors that related to the recurrence of OSCC have been explored for years. Ebrahimi et al[7] have reported that T stage and N stage were important factors affecting regional recurrence in OSCC. Some studies about depth of invasion[8,9] and local recurrence have been reported, but we did not investigate it because the primary regions varied in our patients and the evaluation may have been difficult due to differences in anatomical characteristics.

Gender and race have also been reported to relate with cancer at certain sites. Franco et al[10] in their study strongly pointed out that female patients found to have 17% lower risk of recurrence. In contrast, we identified that women are at greatest risk of recurrence. Women tend to seek medical treatment earlier and more often than men, therefore this result may be biased. In our analysis also we did not discriminate between young, premenopause, and postmenopause women, which correlated with high-circulating estrogen level. Robbins,[11] more than 20 years ago, had addressed the laryngeal prognosis in relation with gender and menopausal status. The prognosis of female patients has been described as similar (tongue),[12] better (all site),[13] or worse (oropharynx)[14] compared to males. In the latter case, the adverse influence of female gender has been attributed to low prevalence of human papilloma virus (HPV) infection. Although Kourelis et al[15] investigated and also showed women were at high risk for tongue cancer recurrence and treatment failure, but their study failed to show estrogen receptor to be involved in the biology of the tumor. They postulated that other sex hormone and variation in HPV infection may play a role, but this hypothesis requires further investigation.

Tumor site might play critical role for local control. As reported previously, floor of mouth and buccal mucosa tumors may have worse local control compared to other sites within oral cavity. However, we did not find this difference, which probably due to lack of number of tumors at that particular subsites.

There was a trend of increasing local recurrence with LVE and PNI, but the number of patients was too small to find significant relation.

In the present study, we have demonstrated that margin status was significant independent predictive factor for locoregional recurrence. Margin status has been controversial throughout the literature. Currently, maximum uniformity is "1 cm three-dimensional (3D) margin." This should be reflected in > 5 mm pathological margin.[16] A surgeon was able to obtain free margins on the first instance in 67% cases according to Byers et al.[17] Although surgeons always aim at a resection with clear margin, close margins are still inevitable.

Loree et al[18] found that the local recurrence rate for the close margin category (≥ 5 mm) was significantly different from the negative margin rate. Priya et al[6] demonstrated that close and positive margins significantly influenced local and overall recurrence, which was also shown in our study. The incidence of local recurrence in our patients with positive surgical margins was greater than those with close margins (13.3% *vs* 10.7%). Regional recurrence was seen in 12.3% of our cases with close margin and 20% with positive margin, which might be explained that frozen section during re-excision of margin might improve the prospect of clearance but not the outcome of patients with close and positive margins.

In a study Looser et al[19] found an overall local recurrence rate of 17% in patients with T1-2 N0 lesions and 20% in patients with T3-4 N0 lesions treated with surgery alone with margins greater than 5 mm. The presence of negative margins does not predict cure, and the presence of positive margins does not predict recurrence either.[9] According to Sutton et al,[20] close and positive surgical margins in OSCC reflect tumor biology; therefore patients with positive margin usually presented with aggressive tumor behavior which has an impact on overall survival.

Binahmed et al[21] did not find beneficial effect of adjuvant treatment on survival when margins were inadequate. Loree and Strong[18] found that local recurrence rates in patients with positive margins who underwent radiotherapy was greater than that in patients with negative margins not receiving radiotherapy. We also have similar result on this issue. The recurrence rate with close and positive margins who received adjuvant therapy was relatively greater than those with negative margins without adjuvant.

A few patients with a locoregional recurrence can be salvaged by surgery or re-irradiation. Most patients with recurrent disease only qualify for palliative treatment. However, only small group of patients are candidate for salvage surgery. Although most of recurrence cases in our study were operable and treated with surgery with or without adjuvant therapy, but longer follow-up period is required for these patients to confirm survival rate post salvage.

Chewing areca/betel nut has been an important public health problem in Taiwan and in other South-East Asian countries. Unlike tobacco, areca nut is portrayed as a safe mouth freshener; therefore, it is freely available and

widely consumed. Although from the present study we did not find significant correlation between this habitual chewing and recurrence, but areca nut has been known as major risk factor for OSCC. Based on our findings that most of the patients have at least one addiction, widespread health education programs are necessary to reach both urban- and rural-based populations in education and motivation against the habit of chewing areca nuts and smoking. The sale and production of areca nut should also be discouraged.

Tumor recurrence implies poor prognosis for patients with OSCC. The present study showed 5 years survival rate of 37% for patients with recurrence. Other researchers have reported 5 years survival between 24.5 and 50% or 3 years survival of 52.6% for those patients with recurrence.[22,23]

Current study is a retrospective study. The weaknesses of this study were not all the prognostic factors evaluated, lack of advanced cases, and short follow-up period. We acknowledge that statistics in such a limited number of advanced cases are not solid, and merely provide suggestions for larger-scale, multi-institutional studies. This retrospective review of OSCC patients treated at single institute in this study could not represent the overall recurrence rate in Taiwan, but it confirms the importance of adequate resection of the primary tumor and early cancer detection to ensure survival of OSCC patients. Patients with initial negative margins had lower recurrence rates and longer interval to recurrence than those with close or positive margins.

CONCLUSION

The survival rate of patient with recurrence was significantly lower than those without recurrence. Some clinicopathological parameters have been described to identify those at greater risk of developing locoregional recurrence after definite treatment, and among them, the status of the surgical margin is the important predictor of disease control and patient's survival even for early stage OSCC. In contrast to the other prognostic indicators, it is under the direct control of the surgeon; therefore, the objective of surgical management of squamous cell carcinoma of the oral cavity is adequate resection with a clear margin. The aggressiveness of tumor's behavior can limit our approach to ensure good local control.

REFERENCES

1. Bagan JV, Scully C. Recent advances in oral oncology 2007: Epidemiology, aetiopathogenesis, diagnosis and prognostication. Oral Oncol 2008 Feb;44(2):103-108.
2. Camisasca DR, Silami MA, Honorato J, Dias FL, de Faria PA, Lourenço Sde Q. Oral squamous cell carcinoma clinicopathological features in patients with and without recurrence. ORL J Otorhinolaryngol Relat Spec 2011;73(3):170-176.
3. Kowalski LP, Magrin J, Saboia M, Santos JC, Torloni H. Squamous cell carcinoma of the tongue: a review of 629 patients treated at a single institute. South Am J Cancer 2011;107:697-702.
4. Fan S, Tang QL, Lin YJ, Chen WL, Li JS, Huang ZQ, Yang ZH, Wang YY, Zhang DM, Wang HJ, et al. A review of clinical and histological parameters associated with contralateral neck metastases in OSCC. Int J Oral Sci 2011 Oct;3(4):180-191.
5. Sadeghi A, Kuisk H, Tran LM, Mackintosh R, Mclaren JR, Parker RG. The role of radiation therapy in squamous cell carcinoma of the upper aerodigestive tract with positive surgical margins. Am J Clin Oncol 1986 Dec;9(6):500-503.
6. Priya SR, D'cruz AK, Pai PS. Cut margin and disease control in oral cancers. J Can Res Ther 2012 Jan-Mar;8(1):74-79.
7. Ebrahimi A, Clark JR, Zhang WJ, Elliott MS, Gao K, Milross CG, Shannon KF. Lymph node ratio as an independent prognostic factor in oral squamous cell carcinoma. Head Neck 2011 Sep;33(9):1245-1251.
8. Brandwein-Gensler M, Teixeira MS, Lewis CM, Bryant L, Rolnitzky L, Johannes J. Oral squamous cell carcinoma: Histologic risk assessment, but not margin status is strongly predictive of local disease free and overall survival. Am J Surg Pathol 2005 Feb;29(2):167-178.
9. Liao CT, Chang JTC, Wang H, Ng SH, Hsueh C, Lee LY, Lin CH, Chen IH, Huang SF, Chen AJ, et al. Analysis of risk factors of predictive local tumor control in oral cavity cancer. Am J Surg Oncol 2008 Mar;15(3):915-922.
10. Franco EL, Dib LL, Pinto DS, Lombardo V, Contesini H. Race and gender influences on the survival of patients with mouth cancer. J Clin Epidemiol 1993 Jan;46(1):37-46.
11. Robbins KT. Prognostic and therapeutic implications of gender and menopausal status in laryngeal cancer. J Otolaryngol 1988 Apr;17(2):81-85.
12. Garavello W, Spreafico R, Somigliana E, Gaini L, Pignataro L, Gaini RM. Prognostic influence of gender in patients with oral tongue cancer. Otolaryngol Head Neck Surg 2008 Jun;138(6):768-771.
13. Guntinas-Lichius O, Wendt T, Buentzel J, Esser D, Lochner P, Mueller A, Schultze-Mosgau S, Altendorf-Hofmann A. Head and neck cancer in Germany: a site-specific analysis of survival of the Thuringian cancer registration database. J Cancer Res Clin Oncol 2010 Jan;136(1):55-63.
14. Kumar B, Cordell KG, Lee JS, Worden FP, Prince ME, Tran HH, Wolf GT, Urba SG, Chepeha DB, Teknos TN, et al. EGFR, p16, HPV Titer, Bcl-xL and p53, sex, and smoking as indicators of response to therapy and survival in oropharyngeal cancer. J Clin Oncol 2008 Jul;26(19):3128-3137.
15. Kourelis K, Tsue T, Girod D, Tawfik O, Sykes K, Shnayder Y. Negative prognostic factors for head and neck cancer in the young. J BUON 2013 Apr-Jun;18(2):459-464.
16. McMahon J, O'Brien CJ, Pathak I, Hamill R, McNeil E, Hammersley N, Gardiner S, Junor E. Influence of condition of surgical margins on local recurrence and disease-specific survival in oral and oropharyngeal cancer. Br J Oral Maxillofac Surg 2003 Aug;41(4):224-231.
17. Byers RM, Bland KI, Borlase B, Luna M. The prognostic and therapeutic value of frozen section determination in the surgical treatment of squamous carcinoma of the head and neck. Am J Surg 1978 Oct;136(4):525-528.
18. Loree TR, Strong EW. Significance of positive margins in oral cavity squamous carcinoma. Am J Surg 1990 Oct;160(4):410-414.

19. Looser KG, Shah JP, Strong EW. The significance of positive margins in surgically resected epidermoid carcinomas. Head Neck Surg 1978 Nov-Dec;1(2):107-111.
20. Sutton, Brown JS. The prognostic implications of the surgical margin in oral squamous cell carcinoma. Int J Oral Maxillofac Surg 2003 Feb;32(1):30-34.
21. Binahmed A, Nason RW, Abdoh AA. The clinical significance of positive surgical margin in oral cancer. Oral Oncol 2007 Sep;43(8):780-784.
22. Kernohan MD, Clark JR, Gao K, Ebrahimi A, Milross CG. Predicting the prognosis of oral squamous cell carcinoma after first recurrence. Arch Otolaryngol Head Neck Surg 2010 Dec;136(12):1235-1239.
23. Gonzales Garcia R, Naval Gias L, Romero-Romero L, Sastre Perez J, Rodriguez-Campo FJ. Local recurrence and second primary tumor from squamous cell carcinoma of the oral cavity; a retrospective analysis study of 500 patients. Head Neck 2009 Sep;31(9):1168-1180.