RESEARCH ARTICLE

Risk factors associated with disease recurrence in patients with T4 staged Squamous Cell Carcinoma of the Oral Cavity treated with surgery and postoperative radiotherapy

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Abstract

Objective: To determine the association of clinical and pathological parameters on recurrence of treated stage T4squamous cell carcinoma of oral cavity patients managed with surgery followed by concomitant chemo and radiation therapy.

Method: The retrospective, cohort study was conducted at Patel Hospital, Karachi, and comprised data of patients diagnosed with oral squamous cell carcinoma and admitted between January 1, 2014, and January 30, 2019. Patients of either gender aged 20-80 years who had a minimum follow-up of one year were included. Data was collected using the Head and Neck Cancer registry form and the medical record files. The subjects were also contacted by telephone when needed. The study end-points were disease-free survival and overall survival. Data was analysed using SPSS 21.

Results: Out of the 83 patients, 65(78%) were male. The overall median(range) age was 46(20-80) years, and 43(52%) of them were aged 31-50 years. Overall, 15(18%) patients had positive margins and 48(58%) had proven cervical node metastasis on histopathology. Overall survival was 42.2% with the median(range) follow-up time was 14(9-21) months and 5-year disease-free survival was 45.8% with the median (range) follow-up time was 13(7-19). The factor that affected the final outcome was found to be the increasing nodal ratio (p=0.043).

Conclusion: Among T4 oral squamous cell carcinoma patients treated with surgery and adjuvant therapy, the rate of disease recurrence was found to be high. Tumours with a high cervical nodal disease burden and/or margin involved were at substantially higher risk of recurrence.

Keywords: Squamous cell carcinoma, Oral cancer, Recurrence, Survival. (JPMA 72: 2399; 2022)

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Introduction

Squamous cell carcinoma (SCC) of the oral cavity is a globally prevalent disease with 2% incidence and 1.8% mortality reported in 2020[1] and has significantly high recurrence. As such, there is a lot of room for researchers to identify the factors that can improve outcomes.[2] Oral cancer, especially of the cheek, is the most common cancers in Pakistan and among the 10 most common malignant tumours in Asia.[2] In our region, chewable tobacco is widely consumed, resulting in the higher prevalence of oral cancers.[3] The age of most of the patients with oral cavity squamous cell carcinoma (OCSCC) ranges 50-70 years, the mean age being 51-55 years. Clinicopathological parameters have a vital role in prognosis, recurrence and survival, following oral squamous cell carcinoma(OSCC).[4] The tumour, nodes, metastasis (TNM) classification is used clinically to decide the treatment pathway and access its response and prognosis.[5] However, in reality, the prognosis of the disease and the outcome is not described. Tumours of similar stage can have a different behaviour.[6] The best curative treatment for OCSCC is wide local excision when the tumour is regarded resectable, with or without reconstruction and neck dissection. Adjuvant treatment, mostly radiation therapy (RT), is often required, but chemotherapy has a limited role and is most commonly used as a radiosensitiser or in a neo-adjuvant setting.[7] Since the past many years, the survival of locally advanced oral cancers has remained the same despite the different aggressive combined treatments used. At the same time, different studies have reported variable survival rates for stage III and IV oral cancers mainly due to the heterogeneous treatment pathways applied.[8]

The current study was planned to determine the association of clinical and pathological parameters on recurrence of treated stage T4 OCSCC patients managed with surgery followed by concomitant chemo and radiation therapy.

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Materials and Methods

The retrospective, cohort study was conducted at Patel Hospital, Karachi, and comprised data of patients diagnosed with OCSCC and admitted between January 1, 2014,and January 30, 2019, after obtaining exemption from the institutional ethics review committee.

Those included were stage T4 tumour patients of both genders aged 20-80 years who were histopathologically proven cases of OCSSC and had undergone surgical treatment, and had a minimum follow-up of one year. Patients who underwent any treatment modality before the surgical treatment were excluded. Tumour staging was done in accordance with the 8th edition of the American Joint Committee on Cancer (AJCC) staging guidelines.[5]

Patients' demographic data, including age, gender, addiction habits, the primary site of tumour and trismus, and presenting features were noted. Histopathological parameters, including tumour size, tumour grade, tumour margins, depth of invasion, perineural invasion, bone involvement, vascular invasion, extracapsular spread, and nodal stage were also retrieved. Patients after surgical excision of the tumour had been referred to get adjuvant treatment. Head and Neck Cancer registry form was used for data collection, while missing data was retrieved from the medical record files. The patients or their families were contacted by telephone when needed.

The study end-points were disease-free survival (DFS) and overall survival (OS). Disease recurrence included regional, local, and/or distant metastasis as shown by histopathology report. DFS was defined as an interval from surgery to disease recurrence within 5 years of treatment. OS was considered the time interval from surgical tumour resection to death or completed five-year follow-up.

Data was analysed using SPSS 21. Descriptive statistics were used to summarise the data in terms of frequency and percentages of qualitative variables. Local, regional and distant recurrences of the disease were all noted to assess DFS. Kaplan Meier was used to analyse DFS and OS. Univariate analysis (UVA) and multivariate analysis (MVA) were performed using Cox proportional hazards regression to identify patient-, tumour- and treatment-related variables associated with inferior DFS. $P<0.05$ was considered significant.

Table-1: Demographic variables.

Variables	Frequency (%)
Age Group	
<- 30	8(10%)
31 - 50	43(52%)
> 50	32(39%)
Gender of the Patient	
Male	65(78%)
Female	18(22%)
Primary Lesion Site	
Floor of Mouth	1(1%)
Cheek	44(53%)
Lower Alveolar Ridge	20(24%)
Others	18(21%)
Truisms	
Yes	51(61%)
No	32(39%)
Pterigoid Muscle	
Yes	5(6%)
No	78(94%)
Tumour Grade	
Well Differentiated	13(16%)
Moderately Differentiated	59(71%)
Poorly Differentiated	11(13%)
Margins	
Involved	13(16%)
Not Involved	70(84%)
Depth of Invasion	
>10mm	67(82%)
<=10mm	15(18%)
Bone Involvement	
Yes	45(54%)
No	38(46)
Perineural Invasion	
Yes	18(22%)
No	65(78%)
Extracapsularspread	
Yes	12(14%)
No	71(85%)
Nodes	
N0	35(42%)
N1	12(14%)
N2a	3(4%)
N2b	21(25%)
N2c	3(4%)
N3b	9(11%)
Radiotherapy	
Yes	71(85%)
No	12(14%)
Chemotherapy	
Yes	15(18%)
No	68(82%)

Results

Out of the 83 patients, 65(78%) were male. The overall median (range) age was 46 (20-80) years, and 43(52%) of them were aged 31-50 years. Overall, 13(16%) patients had positive margins and 48(58%) had proven cervical node metastasis on histopathology. The two most frequently involved sub-sites were buccal mucosa

Table-2: Univariate & Multivariate Cox regression associated with inferior disease-free survival (DFS).

	N=83	
	P-value	**HR (95% CI)**
Univariate analysis		
Addiction (Yes vs. No)	0.560	1.360
Involvement Of Infratemporal Fossa (Yes vs. No)	0.867	0.049
Tumour Grade (PD vs. MD/ WD)	0.938	0.999
Margins (Involved vs. Not Involved)	0.049*	2.109
Depth Of Invasion (≤ 10mm vs. >10mm)	0.708	0.869
Perineural Invasion (Yes vs. No)	0.523	1.240
Extracapsularspread (Yes vs. No)	0.416	1.399
Size Of Maximum Lymph node (≤ 3 vs. >3)	0.610	1.685
Nodes (N0/ N1 vs. N2/N3)	0.031*	0.527
Adjuvant Radiotherapy (Yes vs. No)	0.368	0.672
Concurrent Chemotherapy (Yes vs. No)	0.918	1.039
Multivariate analysis		
Margins (Involved vs. Not Involved)	0.074	1.969
Nodes (N0/ N1 vs. N2/N3)	0.043	0.547

HR: Hazard ratio, CI: Confidence interval.

44(53%) and lower alveolus 20(24%). Furthermore, 51(61%) patients had restricted mouth opening either due to submucosal fibrosis or direct invasion of the disease. However, involvement of pterygoid muscle was evident in only 5(6%) patients. All patients were advised post-op adjuvant radiotherapy (RT), but 12(14%) were not compliant. Besides, 15(18%) patients also received concurrent cisplatin-based chemotherapy (Table-1).

Overall survival was 42.2% with the median (range) follow-up time was 14 (9-21) months, and 5-year disease-free survival was 45.8% with the median (range) follow-up time was 13 (7-19) months (Figure-1). Using MVA, the factor that affected the final outcome was found to be the increasing nodal ratio (p=0.043) (Table-2).

Five-year DFS for patients with increasing nodal stage (p=0.024) and positive margin (p=0.038) had worst outcome compared to those without these risk factors (Figure-2).

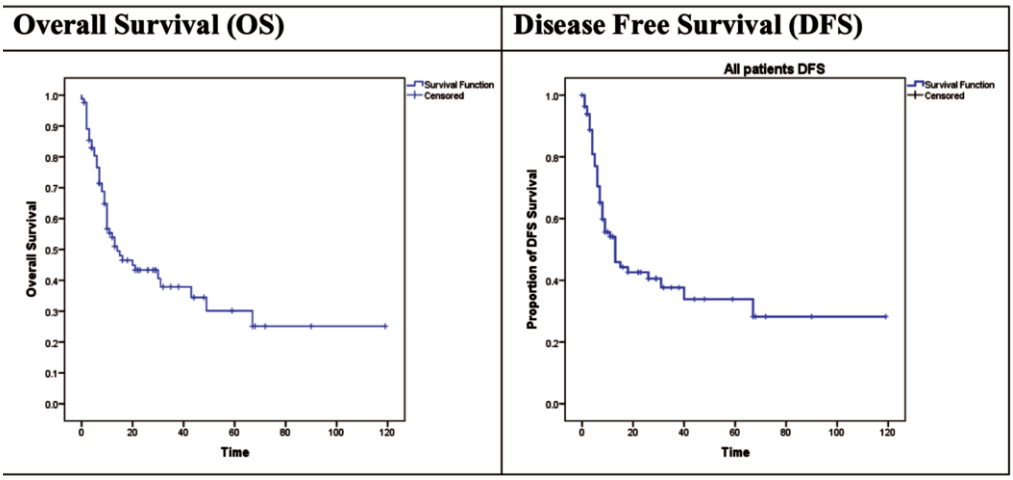
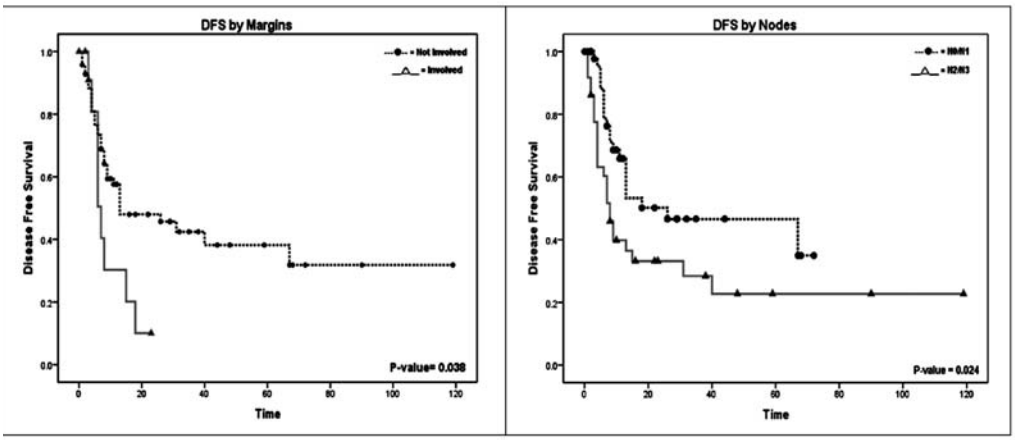


Figure-1: Kaplan Meier survival curves.



Figures-2: Disease-free survival (DFS) by positive margin and cervical nodal metastasis.

Discussion

Positive resection margin and extensive cervical nodal metastasis and recurrence of tumours are poor prognostic factors and the outcome is guarded in patients having these factors as was the case in the current study (47% and 55% respectively) compared to international literature.[5] Extensive cervical nodal metastasis has been known as a poor prognostic factor in OCSCC, but the burden of cervical nodal disease in OCSCC has not previously been evaluated[9-11] as it is difficult to examine this particular factor. A randomised study evaluating adjuvant chemoradiotherapy (CRT) versus upfront CRT in oropharyngeal cancer (OPC) using nodal staging in addition to positive margins and/or extracapsular extension (ECE) to identify patients at high risk[12] was closed as it was unable to achieve accrual objectives.

However, the current data emphasises the use of cervical nodal metastasis as an important tool for risk stratification in OCSCC. Literature has explained tumour histological appearance as a potential factor that can alter the prognosis, and have found grade III tumours to be significantly associated with poor survival.[13,14] Others have identified tumour differentiation, invasion pattern, immune response, and degree of keratinisation as the tools to stratify the risk of recurrence.[15] Incorporating these tools in practice showed that an infiltrative tumour and limited immune response is significantly related to poor survival and high recurrence in patients with OCSCC.[16,17] However, current results did not show poor outcome associated with poorly differentiated tumours which might be due to the small sample size.

Patients with positive margins and/or extra nodal disease are likely to have bad outcome and should be offered adjuvant concomitant CRT (CCRT).[9] Positive margins were closely correlated in the current study, but extra nodal disease was not a predictor of bad overall performance.

In the early 20th century, studies mentioned that poor prognosis was associated with positive margins and extra nodal disease along with invasion around the nerves, addiction to tobacco, and N2 disease.[9,18,19] A study comprised 201 advanced OCSCC patients managed with surgery and adjuvant RT only, confirming the correlation between massive cervical nodal metastasis, extra nodal disease and dedifferentiation of tumours with worse DFS.[20] Later on, advanced stage (T4) and absence of chemotherapy were also found to be related to poor outcome.[21] Cervical nodal metastasis in more than 4 lymph nodes (LNs) was reported to be significantly associated with failure in a few studies.[22] Liao et al. suggested a larger number of factors, including dedifferentiated tumours, positive lymphovascular invasion (LVI), depth of invasion (DOI) $\geq$11mm, N2 disease, and extra nodal disease as high-risk factors for recurrence.[22,23] Extra nodal disease extension was studied in detail by a team of oncologists and concluded that tumour invasion>1.7mm of the capsule of a LN should be labelled as a poor prognostic factor.[24] It can be seen that in literature the factor affecting the overall outcome of advanced-stage OCSCC is variable due to which it is impossible to design a uniform treatment policy which is most likely the most important reason for a suboptimal outcome in this cohort of patients. Hence, the clinical aspects of the disease have a limited role in defining the outcome and prognosis.

Genomic profiling opens a new era in the management of advanced OCSCC patients with an attempt to identify significant molecular biomarkers. Cetuximab which is an epidermal growth factor receptor (EGFR) inhibitor was approved for investigation on therapeutic grounds as initial reports proposed over-expression of EGFR in 90% OCSCCs.[25] Further studies have shown 4 distinct tumour subtypes depending upon different gene expression, and these different types were associated with variable DFS.[25] Some authors have attempted to determine various patterns of gene expression within different malignant cells which are associated with poor prognosis.[15] This is a relatively new area in the field of OCSCC, but to know the molecular profile of neoplastic cells appears to have a promising impact on treatment modalities.

In terms of limitations, being a retrospective study, an obvious bias related to physician and selection does exist in addition to many others. Besides, in the last decade, major changes have been made from staging to treatment protocols, and the study was conducted during an era of treatment evolution. Like in the initial phase of the study, CCRT was advised to all patients, but later, as the guidelines changed, the treatment patterns also changed. It is difficult to evaluate every histological aspect of the tumour biology, the extent of extra nodal disease, and different patterns of tumour invasion and response of lymphocytes to tumour cells; all of these may have prognostic value.

Conclusions

For patients with stage T4 OCSCC treated with surgery and postoperative CRT, the rate of disease recurrence was high. Tumours with a high cervical nodal disease burden and/or margin involved were at substantially higher risk of recurrence.

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Conflict of Interest: None.

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