Original Article

Correlation of Local Recurrence in Oral Squamous Cell Carcinoma with Tumour Size, Resection Margins and Delay in Post-Operative Adjuvant Radiation

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ABSTRACT

Objective: To correlate local recurrence in oral squamous cell carcinoma with tumour size, safe margin resection and delay in post-operative adjuvant radiotherapy.

Study Design: Cohort study.

Place and Duration of Study: This study was conducted at the ENT Department, Jinnah Medical College Hospital, Karachi between November 2017 and December 2021.

Materials and Methods: All patients presented with resectable squamous cell carcinoma of oral cavity were included in the study. These were followed-up with minimum period of two years for disease recurrence at the primary site.

Results: Total 116 patients were included in the study, out of which 29(25%) were females and 87(75%) were males with mean age of 48.8 ± 8.2 years. Most common site was buccal mucosa 64(55.1%) and moderately differentiated carcinoma on histopathology 96(82.8%). Local recurrence rate was 0% in T1, 8.6% in T2, 19.1% in T3 and 40.0% in T4 lesions (p-value = 0.001), 1.6% where safe margin is > 10 mm, 34.7% where margins are between 1 to 5 mm and 100% where < 1 mm (p-value = 0.002). Similarly recurrence rate was 5.5% when adjuvant radiation started within 1 month, 4.8% when started between 1 to 3 months, 30.4% when between 3 to 6 months and 78.5% when started > 6months after primary surgery (p-value = 0.001).

Conclusion: There are higher local recurrence rate in patient presenting with advanced T-stage disease, less distance of tumour from the resected margins and delay in initiation of post-operative adjuvant radiation therapy.

Key Words: Oral carcinoma, Tumour recurrence, Adjuvant Radiotherapy, Oral tumours, Local recurrence.

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INTRODUCTION

Squamous cell carcinoma of the oral cavity is the commonest malignancy in head and neck region.[1,2] As estimated in 2018, global deaths per year due to oral carcinoma are around 177,000.[3] This condition is much more prevalent in sub-continent specially in Karachi due to addictions such as pan, chaliya and gutka. According to the Karachi cancer registry, it is the second commonest malignancy in both genders.[4] Surgery is the preferred modality of treatment with adjuvant chemo-radiation in advance disease. Despite many advancement in its management, overall survival rate has not changed significantly over last 20 years.[5] Loco-regional recurrence is common despite of the new treatment modalities. Loco-regional recurrence is a significant fate-deciding feature for patients of oral carcinoma and we face this challenge every day. Tumour stage, size, histopathological feature, delays in adjuvant chemo-radiation and safe margin resection plays important part in deciding patient's fate.

The histopathological grading and tumour free margins of the resection are other prognostic factors.[6] Numerous histopathological schemes are available for grading of carcinoma, but none is satisfactory to predict prognosis in these tumours.[7] Tumour free surgical margins is also considered imperative to predict overall long term prognosis and recurrence rate.[8,9] A safe margin of 5 mm or more is associated with enhanced local recurrence control and disease free survival.[10] Safe margin is not only significant for recurrence and survival, rather it is

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also very pertinent for making decision regarding post-operative adjuvant radiotherapy and chemotherapy. It is very important for decreasing both local as well as regional recurrence of the disease.

This is a cohort study where we had followed up patients of oral carcinoma for local recurrence and to correlate it with primary tumour size, safety margin on resection in final histopathology and delay in initiation of post-operative adjuvant radiation therapy due to any reason.

MATERIALS AND METHODS

This was a cohort study conducted at the department of Otorhinolaryngology, Jinnah Medical College Hospital (JMCH), Korangi, Karachi. This study was started in November 2017 and patients were followed up till December 2021. Prior ethical review committee (ERC) approval from JMCH was taken before the start of this study. Written consent was also taken from all the patients included in the study. Inclusion criterion was all patients of oral squamous cell carcinoma operated at JMCH and underwent surgery as the primary treatment with or without adjuvant radiotherapy and followed up regularly for local recurrence. Exclusion criterion were patients who lost for follow-up, who had not given written consent for inclusion in this study, where data like safety margin resection was not available on final histopathology and where there was nodal recurrence after surgery. All the demographic and relevant data was entered on a pre-designed proforma. These patients were followed up regularly in OPDs and on phone calls for local recurrence for a minimum period of 2 years (till January 2022). Patients underwent primary surgery with neck dissection and post-operative adjuvant radiation therapy when required. Patients at clinical stage I-II were treated with surgery, if there were adverse features on final histopathology then adjuvant radiation therapy was given. Patients with stages III-IV underwent surgery first followed by postoperative radiotherapy. Primary resection of the tumour was done with taking care to have at least 10 mm tumour free margins where possible. Larger defects were repaired with different local, regional or free flaps. For clinical N_0 cases, ipsilateral selective neck dissection was done from level I to III. In cases where nodal metastasis was present (cN+), ipsilateral or bilateral radical/modified radical neck dissection was performed. SPSS 20.0 was used for statistical analysis. Chi-square or Fisher's exact test were used for different categorical parameters and p-value of <0.05 was considered significant.

RESULTS

There were a total of 116 patients included in this study having minimum age of 24 years to maximum age of 84 years, with a median age of 48.8 ± 8.2 years (table 1). There were 87 males and 29 females with a ratio of 3:1. Buccal carcinoma was the most common site (55.1%), followed by tongue carcinoma (27.5%). Other site of carcinoma are shown in table 2. Of the 116 cases, 12 were well differentiated, 96 cases were moderately differentiated and 8 patients were poorly differentiated squamous cell carcinoma. Wide local excision of tumour with unilateral neck dissection was done in 107 cases and bilateral neck dissection was done in 9 cases.

Table No.1: Basic demography

Total number of patients N =		116
Gender	Male	87 (75%)
	Female	29 (25%)
	Male to Female ratio	3:1
Age	Minimum age (in years)	24
	Maximum age (in years)	84
	Mean Age (in years)	48.8 ± 8.2
Local Recurrence	Positive	25 (21.5%)
	Negative	91 (78.5%)
Neck Dissection	Unilateral	107 (92.2%)
	Bilateral	9 (7.8%)
Cell differentiation on Histopathology	Well Differentiated	12 (10.3%)
	Moderately Differentiated	96 (82.8%)
	Poorly Differentiated	8 (6.9%)

Fig 1 shows the correlation between the primary tumour size (T stage) with the recurrence. In early T1 lesions out of total 11 cases, no recurrence occurred in any patient (0%), in T2 lesion out of 23 cases, recurrence was present in 2 (8.6%), in T3 out of 47 cases, recurrence occurred in 9 (19.1%) while in T4 lesion out of total 35 cases, recurrence was positive in 14 patients (40%),. So there was a definite increase in recurrence rate with the increase in primary T stage (p-value = 0.001). Fig 2 depicts the correlation between the safety margin on resection with the recurrence rate. In those patients where the tumour was reaching upto the resected margin (< 1 mm.), out of total 8 cases, recurrence occurred in all patients (100%), in cases where the tumour margins were close to resected margin (> 1 mm to < 5mm.), out of total 46 cases, recurrence occurred in 16 (34.7%) while in cases where tumour margins are distinct/far from resected margin (> 10 mm) out of total 62 patients, recurrence was positive in only 1 case (1.6%). So There was again positive correlation of recurrence with the safety margin resection (p-value = 0.002).

Post-operative radiation therapy was given in 82 cases out of total 116 cases. Out of these 82 cases, 18 patients received radiotherapy within 1 month after surgery, 27 received between 1 to 3 months, 23 received between 3 to 6 months and 14 received after 6 months of surgery.

Table No.2: Site of lesions, T staging and tumour margins

Site	Total No. of cases N (%)	T staging				Tumour margin on histopathology		
		T1	T2	T3	T4	Involved (< 1 mm)	Close (1 - < 5 mm)	Distinct (> 5 mm)
Buccal mucosa alone	64 (55.1%)	4	12	28	20	1	19	44
Tongue	32 (27.5%)	6	7	9	10	2	14	16
Buccal mucosa + Upper alveolar margin	1 (0.86%)	1	0	0	1	0	1	0
Buccal mucosa + Lower alveolar margin	10 (8.6%)	0	0	6	4	4	6	0
Hard Palate	4 (3.4%)	0	3	1	0	0	3	1
Buccal mucosa + Retromolar trigone	3 (2.5%)	0	0	2	1	1	2	0
Lip	2 (1.7%)	1	1	0	0	0	1	1
Total	116(100%)	11	23	47	35	8	46	62

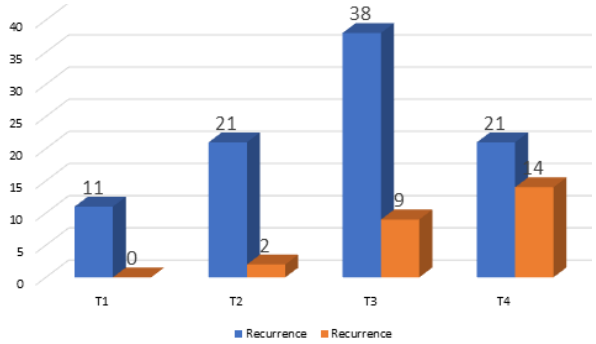

Figure No.1: Correlation of Tumour size (T staging) with recurrence

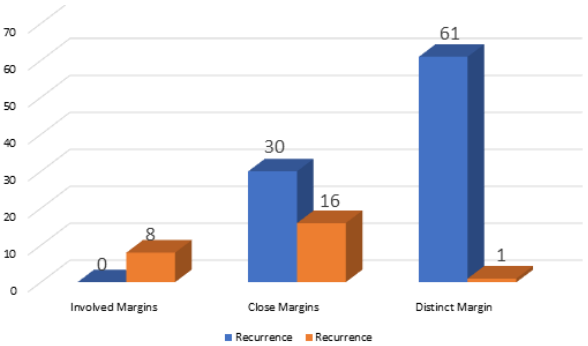

Figure No. 2: Correlation of Tumour margin on histopathology with Recurrence

Fig 3 represents the correlation of delay in post-operative radiation therapy with the recurrence rate. In patients who received radiotherapy within 1 month, out of 18 only 1 patients had recurrence (5.5%), those who received between 1 to 3 months, out of 27, 4 had recurrence (14.8%), those who had radiotherapy between 3 to 6 months, out 23, 7 had recurrence (30.4%) and those who had radiotherapy after 6 months, out of 14, 11 had recurrence (78.5%). Again there is a definite positive correlation of recurrence with delay in post-operative radiotherapy (p-value = 0.001). The recurrence time varied from 2 months to 60 months with median survival time of 12.09 ± 1.2 months and most of the recurrences were noted within first 12 months.

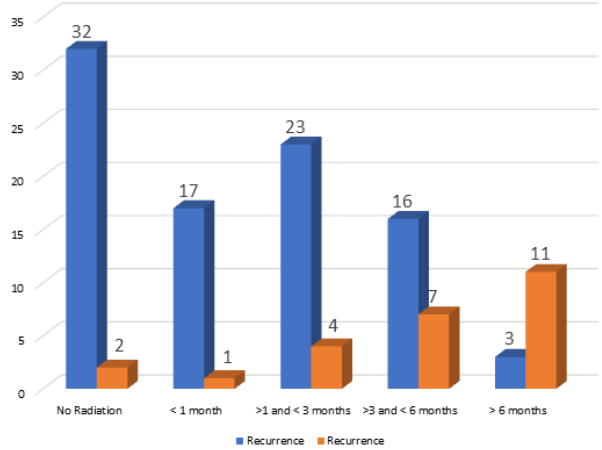

Figure No. 3: Correlation of Delay in post-operative Radiotherapy with Recurrence

DISCUSSION

Carcinoma of the oral cavity has a very high global burden, having approximately 275,000 new patients every year.[11] It ranks second among all malignancies in countries like Pakistan and India.[12] Different variables are used to calculate loco-regional recurrence and thus overall prognosis in oral carcinoma. It usually comprises of TNM staging, histological differentiation of cells and sometimes different sub-sites in the oral cavity. The final outcome in oral carcinoma is mainly affected by the clinical staging at time of presentation. More tumour mass is related with high metastasis in the nodes, greater loco-regional recurrence and thus overall bad prognosis.[13] The currently used 'TNM' staging narrates very well in oral carcinoma regarding overall prognosis and patient's survival. Less is the clinical T-stage, better is the prognosis and thus treatment is less complicated and more succesful.[14] Our study also supports the similar finding where recurrence rate increased from 0% to 40% in T1 to T4 lesions.

Another significant factor for prognosis and recurrence in oral squamous cell carcinoma, is the distance of tumour from the resected margin. It is considered as the utmost significant prognostic factor even if it is measured independently with other factors.[15,16] The decision for safe margin is made by the surgeons during operation by considering the site and extent of the primary tumour and bearing in mind how to reconstruct the defect after excision.[17] A negative margin is defined as the resected tissue does not contain any tumour cells within a zone of 10 mm all around the tumour while the close margin is defined as the resected tissue is free of tumour cells for at least 5 mm zone.[18] If the tumour cells are present in any of the excised margin, it is called as positive. The excised margins are also considered as positive even if the margins has only dysplastic changes or carcinoma in-situ.[19] Many other studies have also shown distance of the tumour from the resected margin has no importance as far as the margins are tumour free. They consider that close margin (< 5mm) is comparable to clear margin (> 10 mm) and it has same value for recurrence.[20] Thus according to these studies, presence of close margin is not used for decision making regarding post-operative adjuvant radiotherapy or chemotherapy.

Different studies had mentioned different cut-off values for close margins in oral carcinoma ranging from 1 mm to 7 mm. A study by Tasche et al showed that only significant margin involvement for recurrence is important if it is less than 1 mm.[21] While a study by Zanoni et al showed that recurrence rate is higher only if the resected margins for tumour is < 2.2 mm.[22] In our study, there was a definitive difference in the recurrence rate between the group having positive margins (< 1 mm.), close margins (1 to < 5 mm.) and distinct margins (> 10 mm.).

In our region, there is one problem of delay in timely post-operative adjuvant radiation therapy because of so many reasons. It could be financial as patient is not able to afford high cost, lack of education in patients/their attendant considering radiotherapy as hazardous, poor post-operative wound healing and poor nutritional status of the patient so not fit to receive radiotherapy and over-burden on radiotherapy departments especially in public sector institutions having long waiting list. Delay in initiation of adjuvant radiotherapy is defined as start of radiotherapy more than 6 weeks after the primary surgery. This delay in adjuvant radiotherapy is one of the important reason for higher recurrence rate both at the primary site and in cervical nodes.[23] Our study also shows the similar results with much higher recurrence of 78.5% when there is delay for more than 6 months versus only 5.5% when radiotherapy was initiated within one month after surgery. The most important cause for delay in our study was found to long waiting list in radiotherapy departments.

To conclude, oral carcinoma is one of the most common malignancy in Pakistan. We have studied the correlation of local recurrence with the primary tumour size (T-stage), safe margin on resection and delay in post-operative adjuvant radiotherapy. The limitation of this study is that it was conducted in only one center with limited number of patients. More studies with multicenter involvement and higher number of patients are required further to investigate these prognostic factors for the recurrence of oral carcinoma in our region.

CONCLUSION

Local recurrence after primary surgery is a dilemma for surgeon, patient and family. There are increased chances of recurrence in patient presenting with advanced T-stage disease, less distance of tumour from the resected margins and delay in initiation of post-operative adjuvant radiation therapy.

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Conflict of Interest: The study has no conflict of interest to declare by any author.

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