Original Article - Retrospective Study

Clinical outcome of surgical treatment of T1-2 N0 squamous cell carcinoma of oral tongue with observation for the neck: Analysis of 176 cases

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ABSTRACT

Objective: To analyze various demographic, clinical, and histopathologic factors in T1-2 N0 squamous cell carcinoma (SCC) of the oral tongue to define a high-risk group for regional recurrence that will benefit from elective neck dissection. **Materials and Methods:** Retrospective outcome analysis of a patient cohort without palpable or ultrasound (USG) detectable nodal metastases undergoing per oral wide glossectomy for T1-2 N0 SCC of oral tongue. Patients were followed up using palpation and serial USG neck and fine-needle aspiration cytology. **Results:** Of the 176 patients, 69 (39%) showed recurrence during follow-up. Fifty-eight cases developed regional neck node metastases, i.e., overall regional node recurrence rate of 33%. Fifty-three (91%) with regional neck node metastases were salvaged successfully with further treatment. In 110 cases with tumor thickness more than 5 mm, 39% cases developed regional neck node metastases. This association was significant with $P = 0.0402$. Among 44 cases with perineural invasion, 54% developed regional neck node metastases. Similarly in 39 cases with lymphovascular invasion, 61% developed regional neck node metastases. Association of both of these parameters with the development of regional neck node metastases was significant. **Conclusion:** We recommend prophylactic selective neck dissection in early stage SCC of oral tongue, especially with depth of invasion more than 5 mm, perineural and lymphovascular invasion.

Keywords: Elective neck dissection, nodal metastases, squamous cell carcinoma, tongue

INTRODUCTION

Development of the regional neck node metastases is not only the main cause of failure but also most significant prognostic indicator of survival for the oral tongue squamous cell carcinoma (SCC).[1] Several studies have demonstrated 13%–33% and 27%–53% of occult nodal metastases in Stage I and II SCC of oral tongue, respectively.[2,3] Identification of the patients without regional node metastases who do not require elective neck treatment is the greatest challenge faced by head and neck surgeons. Electively treating such necks who actually do not have the disease and form a major group means incurring unnecessary surgery and costs. It is also associated with increasing morbidity which otherwise could have been avoided. There is still no final agreement whether the N0 neck should be electively treated. Some studies have shown neither any benefit in overall survival (OS) nor any reduction of recurrence when the clinically negative neck is electively treated

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with surgery.[1,4,5] On the contrary, some authors have reported reduction in the regional nodal metastases and prolonged OS for cases treated with elective neck dissection.[6-9] The identification of factors associated with high risk of lymph node metastases may be useful for the proper selection of patients that will benefit from elective neck dissection. The aim of this study is to evaluate the demographic, clinical, and pathological factors associated with the risk of occult metastases and hence prognosis in patients with clinical T1-2 N0 SCC of the oral tongue.

MATERIALS AND METHODS

A retrospective analysis of early stage SCC of the oral tongue was done from January 2003 to January 2010 in Head and Neck Unit of Prince Aly Khan Hospital, Mumbai, India. This study is limited to the patients with previously untreated, biopsy proven, limited T1-2 N0 cancer of oral tongue that underwent peroral wide excision. All cases had N0 neck on clinical palpation, ultrasound (USG) with color Doppler, and guided fine-needle aspiration (FNA). Intense follow-up rather than neck dissection was used for clinically negative neck. First, USG assessment of the neck was done 4–6 weeks after surgery and thereafter every 2 months for 1 year. All the cases were asked to follow-up immediately if they felt any swelling in the neck between the follow-up time. All the patients presenting with a palpable node were subjected to fine-needle aspiration cytology for confirmation of the disease, and definite modified neck dissection was performed. Modified neck dissection meant removing of lymph node bearing areas from Level I to V and sternocleidomastoid muscle, while preserving nonlymphatic structures such as internal jugular vein and spinal accessory nerve if not directly infiltrated. M0 status was considered when there was no evidence of distant metastases by abdominal ultrasonography, and chest X-ray was normal. Staging was based on the american joint committee on cancer (AJCCs) Manual for Staging of Cancer (2002, 6th Edition). Clinical and histopathologic factors assessed included age (<40 years vs. ≥40 years), gender, clinical T-stage (T1 vs. T2 stage), tumor cell differentiation (well vs. moderate vs. poor), depth of invasion (<5 mm vs. >5 mm), presence or absence of intrinsic muscle involvement, perineural invasion, and lymphovascular invasion. All the cases were treated with peroral wide glossectomy. In all the cases, frozen section was used to see that margins are adequately free, i.e., more than 0.5–1 cm. Same was confirmed on final paraffin histopathology. On final histopathology, tumor thickness was measured from the surface of normal mucosa to the deepest portion of the tumor invasion using an optical micrometer. Perineural and lymphovascular invasion was also determined on final histopathology. Occult node metastases were defined as development of regional neck node metastases during the follow-up without recurrence at the primary site (oral tongue). While as regional neck node metastases in patients with recurrence at the tongue also was not considered occult regional neck node metastases. OS was calculated from the date of first surgical treatment to the date of last follow-up or death from any cause. Disease-free survival (DFS) was the length of time from the date of first surgical treatment to the date of recurrence.

Statistical methods

All statistical analyses were performed using the SPSS software for Windows (version 13.0, SPSS, Chicago, IL, USA). Variables were independently tested for their relation to presence of regional recurrence using the Chi-square and Fisher's exact tests. Univariate analysis was performed to determine prognostic factors of statistical significance. Differences were considered significant for $P < 0.05$ and all P values were two-tailed.

RESULTS

A total of 176 patients with a diagnosis of T1-2 N0 SCC of oral tongue were found eligible for the study. The patients were not evenly distributed by gender (133 males, 43 females). The male-to-female ratio was 3:1 in this study. At the time of diagnosis, the median age was 50 years (range: 21–86 years). The prevalence rate of habitual tobacco/betel nut/alcohol intake was documented in 108 patients, i.e., 61.37%. Premalignant lesions in the form of leukoplakia, erythroplakia, and oral submucous fibrosis were seen in 34 (19.31%) cases. Of the 108 cases with habit of tobacco/betel nut/alcohol intake, premalignancy was seen in 22 cases (20.37%). Of the 68 cases without habits, premalignancy was seen in 12 cases (17.64%) showing no statistically significant association. The median follow-up time was 56 months (standard error, 1.50; 95% confidence interval). Of the 176 patients, 69 (39%) showed recurrence during follow-up. Fifty-eight cases developed regional neck node metastases, i.e., overall regional neck node recurrence rate of 33%. Another five (3%) cases had recurrence both at the primary site and regional neck nodes and remaining six (3%) cases developed recurrent lesion in the primary site only [Table 1]. In 62 of the 69 (90%), recurrences were seen in the 1st year of the follow-up with median time to recurrence of 5 months [Table 2]. Sixty-two (90%) of the 69 recurrences could be salvaged with further treatment. In cases with only regional neck node recurrence, 53 (91%) could be salvaged. All the patients with local recurrence could be salvaged. Of the seven cases which were not amenable to salvage, five cases had unresectable regional neck node recurrence, and two cases had unresectable recurrence both at the primary site and neck. Surgery as single modality was used for ten cases, surgery with adjuvant radiotherapy in forty cases, and surgery with adjuvant chemoradiation was used in rest 12 cases for salvage. Fourteen patients developed second recurrence, of which only one could be salvaged, this patient had both first and second nodal recurrence. Rest of the thirteen could not be salvaged because of unresectable regional nodal metastases in six cases and unresectable recurrence at the primary site and regional neck nodes in seven cases. Four cases of these 13 also had distant metastases. No case of second primary cancer was found in this study group. Three patients in this group developed contralateral neck nodes. As of January 2011, 156 patients (89%) were alive without disease, whereas 15 patients (8%) were dead as a result of malignant disease, two patients (1%) were alive with disease, and three patients (2%) died from unrelated causes [Table 3]. Five-year OS and DFS for the whole cohort of patients were 90% and 61%, respectively [Figures 1 and 2]. Various clinical and pathological factors were analyzed and correlated with the

Table 1: Recurrence as per site

Site of Recurrence	Number (%)
No recurrence	107 (61)
Local recurrence	6 (3)
Regional recurrence	58 (33)
Locoregional recurrence	5 (3)
Total	176 (100)

development of regional node metastases. Histopathological factors such as depth of infiltration, perineural invasion, and lymphovascular invasion of the primary tumor showed statistically significant correlation to the regional neck node recurrence. In the group of 110 cases with tumor thickness more than 5 mm, 39% cases developed regional neck node metastases. On the contrary, when the tumor thickness was ≤5 mm only 23% cases had neck node metastases. This association was statistically significant with $P = 0.0402$ [Table 4]. Among 44 cases with perineural invasion, 54% developed regional neck node metastases. On the contrary, in 132 cases without perineural invasion only 26% developed regional neck node metastases. This association was also significant with $P = 0.0009$ [Table 4]. Similarly, in 39 cases with lymphovascular invasion, 61% developed metastatic regional neck nodes. On the other hand, in 137 cases without lymphovascular invasion, only 25% cases had regional neck node metastases on follow-up. This association was also significant with $P = 0.0001$ [Table 4]. However, regional neck node metastases did not statistically correlate with age, gender, tobacco chewing and alcohol intake, location of primary tumor, T-stage, degree of differentiation, tumor type, and mode of invasion.

Table 2: Recurrence according to the duration from the date of primary resection

Recurrence in months	Frequency (%)
≤3	18 (10)
3-6	23 (13)
6-9	11 (6)
9-12	10 (6)
>12	7 (4)
No recurrence	107 (61)
Total	176 (100)

Table 3: Final control status

Final Control Status	No (%)
Disease free/Alive without disease	156 (89)
Alive with disease	2 (1)
Dead cancer related	15 (8)
Dead due to other causes	3 (2)
Total	176 (100)

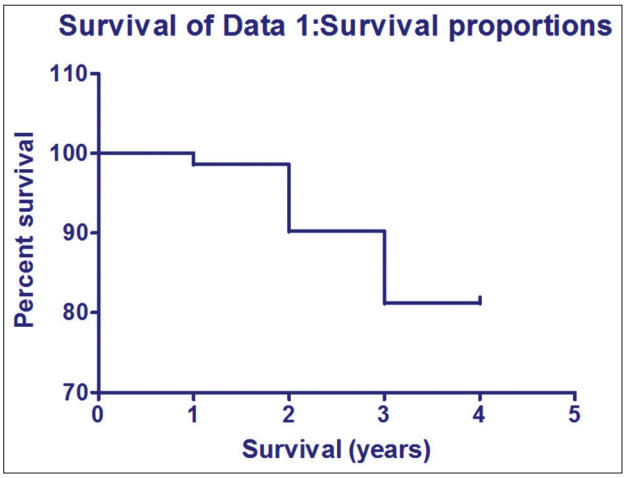

Figure 1: Kaplan–Meier curve showing overall survival at last follow-up excluding other deaths

DISCUSSION

Although elective treatment of the N0 neck may result in better regional neck control of the tumor, this routine policy subjects a significant proportion of patients to an unnecessary surgery and attendant morbidity. However, when an N0 neck with actual occult metastases is not included in the management plan, the implications are poor treatment outcome with increased morbidity and mortality rates. To address this controversial issue, we analyzed the outcomes of T1-2 N0 SCC of the oral tongue with special reference to the potential effect of the observation rather than elective neck treatment. The neck is the most common site of recurrence for early Stage I and Stage

Table 4: Univariate analysis for different clinicopathologic variables with the development of neck nodes

Variable	No. of patients	Univariate analysis	
	Regional recurrence (%)	*P* (%)	
Sex			
Male	133	43 (32)	0.1724
Female	43	15 (35)	
Age (Yr)			
≤40	55	23 (42)	0.1346
>40	121	35 (29)	
Clinical T stage			
T1	99	30 (30)	0.4728
T2	77	28 (36)	
Histological grade			
WDSCC	80	21 (26)	0.8682
MDSCC	88	32 (36)	
PDSCC	8	5 (61)	
Depth of invasion			
≤5 mm	66	15 (23)	0.0402 Significant
>5 mm	110	43 (39)	
Perineural invasion			
Present	44	24 (54)	0.0009 Significant
Absent	132	34 (26)	
Lymphovascular emboli			
Present	39	24 (61)	0.0001 Significant
Absent	137	34 (25)	

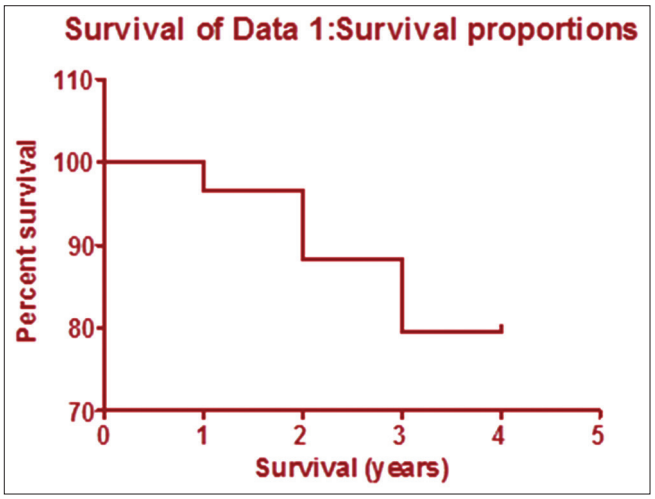

Figure 2: Kaplan–Meier curve showing overall survival at last follow-up including other deaths

II tongue SCC. The incidence of occult disease in the lymph nodes after initial treatment ranges from 13% to 33% and 27%–53% in Stage I and II, respectively.[2,3,10-14] The rate of occult metastases in regional neck nodes in our study is 33%. Therefore, strengthening the fact that clinical palpation is grossly inadequate for evaluation of N0 neck in oral SCC.[15-17] Moreover, USG was not able to pick the metastases in this 33% clinically N0 necks in our study. This is in accordance with the other studies where available radiological investigative tools have shown some improvements in the detection of neck metastases, but sensitivity ranged between 70% and 80%.[18-22] Haberal *et al*. found USG findings correlated more with the pathological findings than palpation, but computed tomography (CT) gave most effective and reliable results when combined with USG in neck staging.[19] Fluorodeoxyglucose-positron emission tomography (FDG-PET) is another useful tool for evaluation of the neck because it accurately detects metastatic lymph nodes >10 mm and has fewer false positive cases than CT scan. The high specificity of FDG-PET for lymph nodes may play an important role in avoiding unnecessary neck dissection.[21] Yonn *et al*. compared the diagnostic value of USG, CT, magnetic resonance imaging (MRI), and PET/CT for preoperative detection of metastases from SCC of head and neck region and showed no statistically significant difference among them. The combination of CT, MR, USG, and PET/CT improved sensitivity (86.5%), without loss of specificity (99.4%) and accuracy (97.0%) although the difference failed to reach the statistical significance.[22] In our study, median time to recurrence was 5 months and 90% recurrences were seen in the first 12 months of the follow-up. Similarly, Yuen *et al*. also reported that 90% of the regional neck node recurrence occurred in the early postoperative period, within 20 months.[1] We analyzed various clinical and pathologic parameters and correlated them with the development of regional neck nodes. Recurrence in the neck was chosen because development of regional neck nodes is not only the most common form of failure but also most important prognostic factor. The first parameter studied was the age at presentation. There are conflicting reports in literature, some studies have shown that SCC of the tongue is aggressive in the younger age group with higher local and regional recurrence. Friedlander *et al*. reported 44% local and regional neck node failure in case of younger patients as compared to only 22% failure in older patients with significant $P < 0.05$ without translation into the survival difference.[23] On the contrary, Davidson *et al*. showed increased disease-specific mortality with increasing age in patients with cancer of oral tongue.[24] In our study, although 42% of the cases with age <40 years developed regional metastatic nodes as compared to only 29% cases with age >40 years, but the association was not statistically significant ($P = 0.13$) [Table 4]. Neither could our data be translated into significant survival difference between the two groups. In accordance with our study, Pitman *et al*. and Lim and Choi could not find any significant difference in the outcomes of treatment for SCC oral tongue in the young (<40 years) and older patients (>40 years).[25,26] Several studies have focused on the correlation of depth of invasion with the occurrence of the regional neck node metastases. Nonetheless, the criteria for elective neck dissection in terms of tumor depth are still inconclusive. Fukano *et al*. suggested a discerning point at 5 mm depth of invasion at which cervical metastasis is probable and recommended elective neck treatment for tumors exceeding 5 mm invasion.[27] O'Brient *et al*. suggested tumor depth as a significant, objectively measurable prognostic factor in early-stage oral cancer.[28] They showed that prognosis changed significantly at a cutoff of 4 mm depth of invasion. Sparano *et al*. also reported that only tumors with >4 mm were associated with occult neck metastases.[29] However, in tumors >4 mm invasion, the rate without neck metastasis was approximately 59%, forming major subgroup. In our study, only 23% of cases with depth of invasion <5 mm developed neck nodes, while 39% cases with >5 mm depth of invasion developed metastatic neck nodes. This association with cutoff of 5 mm was statistically significant with $P = 0.0402$ confirming the finding that depth of invasion is an important prognostic indicator of occult regional neck node metastases [Table 4]. Sparano *et al*. also reported that the presence of perineural invasion and lymphovascular invasion significantly correlated to occult regional neck node metastasis.[29] Our results are in complete agreement with the findings of this study. In our study, 54% cases with perineural invasion developed metastatic neck nodes, while only 25% cases without perineural invasion had a recurrence in regional neck nodes. This correlation was significant with $P = 0.0009$. Moreover, 61% cases with lymphovascular invasion developed regional neck node metastases compared to only 25% cases had regional nodal recurrence where lymphovascular invasion was not present. This correlation was also significant with $P = 0.0001$. Therefore, in addition to the depth of invasion, perineural invasion and lymphovascular invasion are important prognostic indicators of occult regional neck node metastases in our study. No correlation between any other clinical or pathological parameter could be found that was significant. In their study on early SCC of oral tongue, An *et al*. concluded that T-stage, depth of invasion, intrinsic muscle involvement, and histological grade related to neck recurrence.[30] While parameters such as age, gender, perineural invasion, lymphovascular emboli, resection margin, and pathologic nodal stage were not significantly related in their series.

The benefits of elective neck dissection in patients with oral cavity tumors with N0 neck are still not clear because the results of numerous existing studies on the topic have been generally inconclusive. Most studies have failed to show statistically significant differences in survival outcome between the patients with oral cavity cancers in elective neck treatment and observation groups.[6,31-34] However, there have been few studies which showed a significant survival benefit in favor of elective neck dissection in oral carcinoma patients with clinically N0 neck.[2,6,8,35] Meta-analysis done by Fasunla *et al*. concluded that elective neck dissection significantly reduced the risk of death due to the disease.[36] They also pointed to the fact that this observed pooled effect in their meta-analysis between elective neck dissection group, and observation might have been largely influenced by the older studies. Perhaps, if similar studies are conducted now that there are better investigative tools to detect and stage neck node metastasis, this observed difference might be absent. We strongly recommend elective conservative neck dissection in early SCC of the oral tongue with N0 status as 33% cases had a regional recurrence after surgical treatment of the primary cancer despite preoperative USG picking no abnormal nodes, in our study. Ideally, accurate preoperative assessment of the depth of infiltration can solve the problem to some extent, but inspection and palpation cannot reliably

estimate tumor thickness. In addition, limitation of punch biopsy for the evaluation of tumor thickness has been reported.[37] Shintani *et al*. have recently published their experience with intraoral USG and have shown a good correlation with the final histological sections.[38] This may prove to be a useful tool for preoperative assessment of tumor thickness and decision making. If imaging studies (USG, CT, or MRI) are not available, measurement of tumor thickness obtained from a frozen section of the surgical specimen may be used. In our study, 5 years overall and DFS were 90% and 61%, respectively. An *et al*. reported 5-year OS rate of 97.1% in Stage I and 76.2% in Stage II SCC of the oral tongue.[30] O-Charoenrat *et al*. reported 5 years actuarial OS, DSS, and DFS for the whole cohort of early tongue cancer patients of 65.7%, 67.8%, and 58.1%, respectively.[39] Keski-Säntti *et al*. reported 3- and 5-year OS rates for the whole patient series of T1-2 N0 74% and 43% and the DSS rates were 82% and 79%, respectively.[6] In our study, 91% cases could be salvaged after first nodal recurrence. An *et al*. also reported a high overall salvage rate of 70% after regional recurrence in their series on early stage oral tongue SCC.[30] In comparison, other studies have reported a much lower salvage rate of about 30%–40% in case of regional recurrence in oral tongue cancers.[5,6,32,34] Our better salvage rate can be attributed to vigilant follow-up with clinical palpation and USG/guided FNA if indicated every 2 months for the 1st year. Limited follow-up time and an underpowered sample inherently limit our ability to draw more conclusions which are statistically significant. These limitations, however, highlight the benefit of single institution publishing their own clinical experience so that these data can eventually be consolidated and interpreted through meta-analysis.

CONCLUSION

Five years OS rate was comparable with the standard world literature because regional recurrence was successfully salvaged by modified neck dissection with or without postoperative radiotherapy. Despite high success rate of salvage treatment, recurrence of cancer is a fear to patients, and regular close follow-up is difficult for some patients. We recommend conservative elective neck dissection in T1-2 N0 SCC of the oral tongue, especially in cases with the depth of invasion more than 5 mm, presence of perineural and lymphovascular invasion. Clinical palpation and USG are inadequate for evaluation of the N0 neck. CT, MR, or PET can be utilized when available. The high salvage rate (91%) indicates that strict follow-up for the first 2 years aided with radiologic tools will help in early detection of recurrence in the primary site, as well as neck.

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Conflicts of interest
There are no conflicts of interest.

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