Affect on Survival Per Increase in Each Millimeter of Tumor Depth in Tongue Cancer

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Abstract The critical tumor depth at which the risk of occult metastasis increases in tongue cancer has been demonstrated as ≥ 4 –5 mm. Conventional T staging might not be an accurate predictor for survival in situations wherein infiltrative growth pattern is easily overlooked. Thus risk of death associated with increase in tumor depth per millimeter might be useful to understand patient's disease status during follow up. Historical cohorts of patients with pT1N0 and pT2N0 primary squamous cell carcinoma of tongue treated between January 2010 and December 2011 were selected and analyzed in univariate and multivariate cox-regression model to indicate the risk of death associated with an increase in each millimeter of tumor depth. The median period of follow up was 34 months. Total 67 patients fulfilled the above mentioned criteria, among them 11 patients died by the end of study period. The mean (SD) age of the patients studied was 49.7 (12.7) years and their age ranged from 21 to 74 years. Among these 66 % ($n = 44$) were males. In the univariate log-rank test, margin status

($p = 0.016$), t-stage ($p = 0.018$) and increased tumor depth ($p < 0.0001$) were risk factors for occurrence of death. When adjusted for other risk factors in the multivariate cox-regression model, per one unit increase of tumor depth (mm) there was 1.07 (95 % CI 0.95, 1.21) units increased risk of death. Depth of tumor with increase in each millimeter in tongue cancer appears to be associated with risk of death irrespective of regional lymphatic spread.

Keywords Tumor depth · Tongue cancer · Survival

Introduction

Oral cancer is one of the leading cause of cancer associated deaths in developing countries, among the various subsets in oral cancer; carcinoma of tongue is associated with higher risk of occult metastasis in early stages; possibly due to greater density of lymphatic channels [1].

Critical tumor depth at which risk of occult metastasis increases has been demonstrated as ≥ 4 to 5 mm. Fukano et al. [2] demonstrated an occult metastatic rate of approximately 65 % for tongue cancers of >5 mm depth, whereas it was 6 % in thinner tumors.

Association of increased depth of invasion to occult metastasis in tongue cancer led to consideration of elective neck dissection in early tongue cancers with critical depth [2]. Conventional T staging might not be an accurate predictor for survival in situations wherein; infiltrative growth pattern is easily overlooked. Thus, the risk of death associated with increase in tumor depth for each millimeter in stage I and stage II oral tongue cancers might be useful to understand patient's disease status during follow up.

Present paper describes the risk associated with depth of tumor in stage I and stage II oral tongue cancers, stage III

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and stage IV tumors are complicated with regional disease impacting survival to greater extent than primary tumor related prognostic factors; hence those patients are not included in this study.

Patients and Methods

A retrospective data of patients treated surgically for oral cancer from January 2010 to December 2011 were screened for this study. Approval from IRB and registration—IEC/2014/42. Patients with primary pT1 and pT2 squamous cell carcinoma of tongue with N0 neck were filtered (according to UICC TNM staging). Patients with primary squamous cell carcinoma of anterior one third of tongue were only included.

The selected population was analyzed in univariate and multivariate cox-regression model to indicate the risk of death associated with an increase in each millimeter of tumor depth. Depth of tumor is measured from the surface of adjacent epithelium to the depth of infiltration.

The median period of follow up was 34 months.

Statistical Analysis

The descriptive statistics were presented with mean and standard deviation for a continuous data. Kaplan–Meier survival analysis was used to draw the curves and log-rank test was utilized. Univariate and multivariate Cox-proportional hazard models were used to determine the risk factors and produced the adjusted hazards ratios for failure after controlling for the effect of the potentially confounding variables in the multivariate Cox-proportional hazards model. A two sided *p* value of <0.05 was considered to be statistically significant.

Results

Total of 563 patients of oral cancer patients were treated from January 2010 to December 2011 of which the filtered group comprised of 67 patients who fulfilled the above mentioned criteria, among them 11 patients died (8 patients died of locoregional recurrence, one patient died of development of second primary and two patients died of distant metastasis). Univariate analysis of the patients is illustrated in Table 1.

The mean (SD) age of the patients studied was 49.7 (12.7) years and their age ranged from 21 to 74 years. Of these 66 % (*n* = 44) were males. The mean age was not significantly different between the alive and dead patients [50.43 (12.70) vs 45.91 (13.02)].

Age and gender were not risk factors for the risk of death in this studied population, on applying log-rank test, males were more likely to die when compared to female population, however, it was not significant; 20.5 versus 8.7 % (*p* = 0.211). Grade of the tumor [moderate or well differentiated (*p* value: 0.763)] did not make difference in the risk of death. Tumor volume (*p* = 0.148) and the area of tumor (*p* = 0.189) were not significantly different between patients who are alive and dead. None of the patients showed lymphovascular emboli.

In the univariate log-rank test margin status (*p* = 0.016), T-stage (*p* = 0.018) and increased tumor depth (*p* < 0.0001) were risk factors for occurrence of death (tumor depth was analyzed as a continuous variable). In the multivariate cox-regression model that adjusted for margin status; perineural invasion; T-stage and tumor depth; higher risk of death was noticed in patients with involved margin status, adjusted hazard ratio (HR): 12.93 (95 % CI 1.40, 119.06) (*p* = 0.024). Patients with stage II disease had higher risk of death according to multivariate Cox-regression model, HR: 3.87 (95 % CI 0.78, 19.38) (*p* = 0.099), however, it was borderline significantly associated. In the univariate log-rank test; increased tumor depth was significantly associated with increased risk of death (*p* < 0.0001). When adjusted for other risk factors in the multivariate cox-regression model, for every unit of increase in tumor depth (mm) there were 1.07 (95 % CI 0.95, 1.21) units increase in risk of death. It was, however, not significantly associated (*p* = 0.250). It can be speculated that the insignificant result in this instance (tumor depth and survival) can be due to small sample analyzed in this study (Table 2).

Figure 1 Illustrating survival of patients in the current study.

Discussion

Staging in cancer is based on overall prognosis; however, conventional staging system does not accommodate influence of many prognostic factors that might impact the outcome of disease.

The prognostic factors which not accommodated in conventional staging of cancer associated with primary tumor are margin status, perineural spread and lymphovascular emboli along with depth of tumor. Whereas; those associated with neck disease is perinodal spread.

However; multi variable studies done in these aspects give overall information to the clinician to assess the risk associated with all of them. Judgments on further therapy such as post operative adjuvant radiotherapy (PORT) are made depending on extant of associated risk through all these prognostic factors.

Table 1 Univariate analysis of prognostic indicators in the sample

Factors	Total sample N	Died n (%)	p value ^a
Margin status			
Involved (<1 mm)	8	4 (50.0)	–
Close (1–5 mm)	36	6 (16.7)	0.016
Clear (>5 mm)	23	1 (4.3)	–
Perineural invasion			
Absent	63	10 (15.9)	0.701
Present	4	1 (25.0)	–
T stage			
T1	35	2 (5.7)	0.018
T2	32	9 (28.1)	–

^a Based on log-rank test**Table 2** Multivariate cox-proportional hazards model predicting the overall survival status in the studied patients

Factors	Total sample N	Death n (%)	Adjusted HR (95 % CI)	p value
Margin status				
Involved	8	4 (50.0)	12.93 (1.40, 119.06)	0.024
Close	36	6 (16.7)	3.29 (0.39, 27.65)	0.274
Clear	23	1 (4.3)	1.00	–
Perineural invasion				
Absent	63	10 (15.9)	1.00	0.773
Present	4	1 (25.0)	0.73 (0.09, 6.25)	–
T Stage				
T1	35	2 (5.7)	1.00	0.099
T2	32	9 (28.1)	3.87 (0.78, 19.38)	–
Tumor depth (mm)	67	11 (16.4)	1.07 (0.95, 1.21)	0.250

Fig. 1 Kaplan meier survival curve the entire population

Clark JR et al. [3] showed risk of 46 % for occult nodal metastasis in tumors greater than 5 mm to that of 10 % for tumors less than or equal to 5 mm in depth in oral cancer.

Many authors have demonstrated the influence of tumor thickness in tongue cancer on occult cervical nodal metastasis [4–11]. Fakihi et al. [12] showed greater than 30 % metastasis and neck relapse in early staged tongue cancers with ≥ 4 mm in thickness of the tumor.

Irrespective of the potential for metastasis in deep tumors an association with locoregional disease failure has been observed; 72.7 % ($n = 8$) of the total patients who died were reported with locoregional disease failure (rest died of either second primary or metastasis without locoregional recurrence) and 81.8 % ($n = 9$) of deaths in sample of current study had depth of tumor greater than or equal to 4 mm and 18.1 % ($n = 2$) patients had tumor depth less than 4 mm, although involved status of margin would have some influence in this regard the risk of tumor depth cannot be overlooked.

Margin status, T stage and depth of tumor were the significant factors in univariate analysis for survival, the risk associated with depth did not appear to be significant

in the multivariate model. Factors such as the use of tobacco is associated with development of second primary through field cancerization, microscopic involved margin is another factor of concern. Small sample size in current study might be responsible for diminished significance of tumor depth in multivariate cox regression model. However, exclusion of stage III and Stage IV cancers in whom other major prognostic factors are influencing the mortality is eliminated.

Ganly et al. [13] showed that in pT1N0 and pT2N0 cancers, the regional recurrence rate was 5.7 % for tumors <4 mm and 24 % for tumors $\geq$ 4 mm. The multivariate analysis indicated that tumor thickness was the only independent predictor of neck failure (regional recurrence-free survival, 94 versus 72 % ($p = 0.02$) for tumors <4 mm versus $\geq$ 4 mm, respectively). Patients who developed recurrence in the neck had a significantly poorer disease-specific survival to the patients who did not (33 vs 97 %; $p < 0.0001$).

In our study, locoregional recurrence was 14 % in cases with $\geq$ 4 mm of tumor depth, Disease free survival (DFS) among them was 80.7 %. None of the patients with <4 mm depth reported with locoregional recurrence, but two patients died of disease associated factors (one patient developed second primary and another metastasis to lung without evidence of locoregional disease). DFS for patients with less than 4 mm tumor depth was 70 %. This might be another factor responsible for diminished significance of tumor depth in multivariate analysis.

Two thirds ($n = 6$) of the patients developing neck recurrences had depth of tumor $\geq$ 4 mm.

Ganly et al. [13] has suggested that the reason of neck failure in such instances might be failure of clearance of subcentimeter nodes during neck dissection or failure of detection of micrometastasis in pathological examination. However; on further investigation into this aspect through immunohistochemistry of neck dissection specimens, they observed that there was no association between micrometastasis and neck recurrence in their patients, authors further expressed that this phenomenon might be due to absence of perinodal spread in those patients, but cautioned that, the patients with tongue cancer appear to have higher than expected risk regarding neck recurrence which increased with tumor depth.

Considering the sample size and retrospective nature of the study absolute determination of all prognostic factors might not be sufficient in current study. Since number of patients fitting into this narrow group is very less in

number, multicentre collaborations might be necessary to obtain sufficient data to validate this finding.

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Conflict of Interest None.

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