Depth of invasion, size and number of metastatic nodes predicts extracapsular spread in early oral cancers with occult metastases

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ARTICLE INFO

ABSTRACT

Objective: Presence of extracapsular spread (ECS) significantly decreases survival in oral cancer patients. Considering its prognostic impact, we have studied the incidence and factors predicting ECS in clinically node negative early oral cancers.
Materials and Methods: We performed a retrospective chart review of 354 treatment naïve clinically node negative early oral cancer patients operated between 2012 and 2014. Chi-square test and logistic regression were used for identifying predictors of ECS, while cox-regression test was used for survival analysis.
Results: The incidence of occult nodal metastasis was 28.5% (101/354). Among them, ECS was seen in 15.3%(54/354) patients. The incidence of ECS in T1 and T2 lesion was 13.4% (21/157) and 16.8% (33/197), respectively. The overall incidence of ECS was 48% and 29% in lymph nodes smaller than 10 mm and 5 mm respectively. We found that tumor depth of invasion (> 5 mm; p-0.027) and node (metastatic) size > 15 mm (p-0.018) were significant predictors of ECS. p N2b disease was seen in 41/354 (11.6%) of which 31/354 (8.7%) had ECS, i.e. 75.6% of pN2b patients been ECS positive (p-0.000). The 3-year OS of patients without nodal metastasis, nodal metastasis without ECS and nodal metastasis with ECS was 88.4%, 66.9% and 59.2% (p-0.000) respectively.
Conclusion: A significant number of patients with metastatic nodal size less than 1 cm have ECS which suggests aggressive behavior of the primary tumor. Thus, elective neck dissection is the only way of detecting ECS in these patients which may warrant treatment intensification.

Introduction

Oral cancer is a major health problem worldwide with 300,373 new cases detected in the year 2012 [1]. It is the most common cancer in Indian men and fifth most common cancer amongst females [2]. The presence of nodal metastasis in oral cancers is one of the most important prognostic factors that may decrease survival by 50% [3]. It is important to note that clinically node negative (c N0) oral cancer patients harbor occult nodal metastasis to the range of 13–53% [4]. This occult nodal metastasis may also have Extracapsular spread (ECS) that adversely affects survival [5]. Pooled analysis of two randomized control trial demonstrated that ECS and positive margins are high-risk features that warrant adjuvant concurrent chemoradiation (CCRT) [5]. Elective neck dissection is the preferred modality of treatment for

clinically negative neck in patients with early stage disease [6]. It helps in detection of occult metastasis as well as ECS which mandates intensification of adjuvant treatment. Even though ECS is a known poor prognostic factor, little is known about the predictors of ECS in cN0 early oral cancers. This study was undertaken to evaluate the predictors of ECS and its impact on survival in this subgroup of patients.

Materials and Methods

We performed a retrospective chart review of 354 treatment naïve early oral cancer patients. All patients were clinically node negative and biopsy-proven squamous cell carcinoma operated at our hospital (a tertiary cancer center) from January 2012 to January 2014. Patients with advanced T stage, clinically or radiologically detected nodal

metastasis or with any form of previous treatment were excluded from the study. However, it is important to note that all patients did not underwent radiological examination for detection of occult metastasis as per our institute policy which would not insist for radiological neck assessment in early oral cancer unless essentially required. Wide excision of tumor along with neck dissection was the primary modality of treatment for all the patients. Unilateral neck dissection was done in 330 (93.2%) cases; bilateral neck dissection was done in 24 (6.8%) cases. Postoperative radiotherapy (RT) or concurrent chemo-radiotherapy (CCRT) was offered as per the standard guidelines. Adjuvant CCRT was used in patients with positive margins and/or nodes with extracapsular spread (ECS). Adjuvant RT was given in 164 (46.3%) patients, adjuvant CCRT in 51 (14.4%) patients and 139 (39.3%) patients did not require further adjuvant treatment. The clinical and demographic details, as well as histopathological data of these patients, were obtained from the electronic medical records. Lymph nodes ratio (LNR), defined as the ratio of the number of positive lymph nodes to the total number of lymph nodes dissected, was calculated for each patient.

Statistical analysis

Statistical analysis was done using the software SPSS20.0 (IBM, Armonk, NY). To identify factors associated with ECS, univariate analysis was done using chi-square test. Multivariate analysis was done using binary logistic regression. Information regarding patient survival and disease status was also retrieved from medical records. Disease-free (DFS) and overall survival (OS) was calculated by Kaplan Meier method. We defined DFS as the period from the date of diagnosis until date of the first recurrence: loco-regional or systemic. The OS was defined as the period from the date of diagnosis until death, from any cause. Dates of disease recurrence were collected from the medical records when they were diagnosed histologically or radiologically. For survival analysis, the variables for univariate analysis were selected based on their clinical relevance as well as those previously described in literature and analyzed using log-rank test. All significant ($p < 0.05$) variables were subsequently tested (multivariate) with cox-regression analysis using forward stepwise selection.

Results

The median age of the patients in the study group was 50.5 years. Most of the patients were males (77.7%) with male to female ratio of 3.4:1. Tongue (47.5%) was the most common sub-site involved, followed by buccal mucosa (28.5%). The incidence of occult nodal metastasis was 28.5% (101/354). The demographic and tumor characteristics of the patients in the study group are given in Table 1. Among them, extracapsular spread (ECS) was seen in 15.3% (54/354) patients. None of the patients had contralateral nodal neck node metastasis. The mean lymph node yield i.e. the mean number of nodes dissected during ipsilateral neck dissection was 25.16 and mean lymph node yield during contralateral neck dissection was 19.9. The incidence of ECS in T1 and T2 lesion was 13.4% (21/157) and 16.8% (33/197), respectively. ROC curves (Receiver Operating Characteristic) were utilized to identify the ideal cut off of a metastatic nodal size and LNR having the best sensitivity and specificity for ECS. The ideal cut off, as per ROC, was 15 mm and 0.05 for metastatic nodal size and LNR, respectively. LNR was not found to be a predictor of ECS. Mean metastatic nodal size in patients with ECS was 14 mm and mean metastatic nodal size in patients without ECS was 12 mm (p value- 0.00). We found that tumor depth of invasion of more than 5 mm was the only factor predicting occult nodal metastasis (p value-o. 000) (Table 2). Interestingly, we found that tumor depth of invasion (> 5 mm; p-0.027) and node (metastatic) size of more than 15 mm (p-0.018) were significant predictors of ECS on multivariate analysis (Table 3). The Spearman correlation coefficient between ECS and increasing size of the metastatic node was 0.78 (p-0.022). In our study, p N2b disease was seen in 41/

Table 1

Tumor and histopathological characteristic of the patients in the study group.

Tumor and patient characteristics	Total -354 patients (percentage)
Age	
Median	50.5 years (range19-81)
Gender	
Male	275 (77.7)
Female	79 (22.3)
pT stage	
T1	157 (44.4)
T2	197 (55.6)
Site of Tumor	
Tongue cancers	168 (47.5)
Non tongue oral cancers	186 (52.5)
Lymphovascular Emboli (LVE)	
Yes	5 (1.4)
No	349 (84.7)
Perineural Invasion (PNI)	
Yes	66 (18.6)
No	288 (81.4)
Grade	
Well differentiated	62 (17.5)
Moderately differentiated	237 (66.9)
Poorly differentiated	55 (15.5)
Nodal status	
Node positive	101 (28.5)
Node negative	254 (71.75)
Extracapsular spread	
Yes	54 (15.3)
No	300 (84.7)
Margin status	
Adequate (> 5 mm)	336 (94.9)
Close/positive (< 5 mm)	18 (5.1)
Neck node status	
pN0	253 (71.5)
pN1	60 (16.9)
pN2b	41 (11.6)
Type of tumor	
Ulceroproliferative	159 (44.9)
Ulceroinfiltrative	124 (35.0)
Ulcerative	60 (16.9)
Verrucous	11 (3.1)
Number of lymph nodes dissected ipsilateral	
Mean	25.16, range (6–51)
Median	23.5
Number of lymph node dissected contralateral	
Mean	19.9 range (9–40)
Median	18.00
Size of positive lymph node	
Mean	14.04 mm (3–3.2)
Median	13.00
LNR	
0–0.05	49 (13.8)
> 0.05	305 (86.2)

354 (11.6%) of which 31/354 (8.7%) had ECS, i.e. 75.6% of pN2b patients been ECS positive (p-0.000).

Survival analysis

Follow-up details were available for 97.17% patients with a median period of 36 months. At last, follow up, 69.77% (247/354) were alive and disease free, 6.21% (22/354) were alive with disease, 20.05% (71/354) died due to cancer and 1.12% (4/354) patients died due to other causes. It was seen that nodal metastasis (p = 0.048, HR = 1.54, CI: 1.00–2.37) (HR: Hazard ratio, CI: Confidence interval), poorer grade of differentiation (p- value: 0.023, HR:1.74, CI:1.07–2.82), tumors with