To evaluate disparity between clinical and pathological tumor-node-metastasis staging in oral cavity squamous cell carcinoma patients and its impact on overall survival: An institutional study

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Abstract

Background: Accurate clinical staging is important for patient counseling, treatment planning, prognostication, and rational design of clinical trials. In head and neck squamous cell carcinoma, discrepancy between clinical and pathological staging has been reported. **Objective:** To evaluate any disparity between clinical and pathological tumor-node-metastasis (TNM) staging in oral cavity squamous cell carcinoma (OCSCC) patients and any impact of the same on survival. **Materials and Methods:** Retrospective chart review from year 2007 to 2013, at a tertiary care center. **Statistical Analysis:** All survival analyses were performed using SPSS for Windows version 15 (Chicago, IL, USA). Disease-free survival curves were generated using Kaplan–Meier algorithm. **Results:** One hundred and twenty-seven patients with OCSCC were analyzed. Seventy-nine (62.2%) were males and 48 (37.8%) females with a mean age at presentation 43.6 years (29–79 years). The highest congruence between clinical and pathological T-staging seen for clinical stage T1 and T4 at 76.9% and 73.4% with pathological T-stage. Similarly, the highest congruence between clinical and pathological N-stage seen for clinical N0 and N3 at 86.4% and 91.7% with pathological N-stage. Of clinically early stage patients, 67.5% remained early stage, and 32.5% were upstaged to advanced stage following pathological analysis. Of the clinically advanced stage patients, 75% remained advanced, and 25% were pathologically downstaged. This staging discrepancy did not significantly alter the survival. **Conclusion:** Some disparity exists in clinical and pathological TNM staging of OCSCC, which could affect treatment planning and survival of patients. Hence, more unified and even system of staging for the disease is required for proper decision-making.

Key words: Disease-free survival, oral cavity squamous cell carcinoma, tumor-node-metastasis stage

Introduction

Accurate clinical staging is important for patient counseling, treatment planning, prognostication, and the rational design of clinical trials.[1] At the time of diagnosis, treatment strategies are largely based upon clinical staging. In head and neck squamous cell carcinoma (HNSCC), discrepancy between clinical and pathological staging has been reported. Upstaging from early stage N0 neck to node positive neck has been shown to occur in 34–44% of cases and has been shown to have a negative impact on survival.[2,3] This discrepancy is largely attributed to the clinical inaccuracy of lymph node staging. Clinical assessment by palpation has been shown to be 60–70% accurate, but the incorporation of computed tomography (CT) scanning can improve the accuracy to approximately 90%.[2-4]

At present, there is a very limited data on the discrepancy between the clinical and pathological tumor-node-metastasis (TNM) staging in oral cavity squamous cell carcinoma (OCSCC) and its overall impact on the survival of the patients with no single institutional study about the same. We, therefore, undertook a retrospective single institute cohort study to investigate the rate of staging discrepancy in TNM staging in OCSCC patients and whether this has any impact on disease-specific survival.

Materials and Methods

Patients

After obtaining ethical clearance from the Institutional Ethics Board, case records of 127 patients with OCSCC treated surgically at a tertiary care center from the year 2007 to 2013 were included in the study. The demographic data along with the clinical data were tabulated [Table 1].

The clinical and pathological TNM staging was compared and tabulated to determine upstaging, downstaging, or cases where no stage discrepancy occurred [Tables 2 and 3]. We classified patients into four groups for survival analysis: (1) Early stage patients with no pathological stage change, (2) early stage patients upstaged to advanced stage, (3) advanced stage patients with no stage change, and (4) advanced stage patients downstaged to early stage.

Table 1: Demographics of 127 patients with oral cavity squamous cell carcinoma

Demoghraphic character	Value
Age	
Mean	43.6 years
Range	29-79 years
Gender (%)	
Male	79 (62.2)
Female	48 (37.8)
Site of primary tumor	
Lip	2
Tongue	33
Floor of mouth	28
Buccal mucosa	29
Upper alveolus	12
Lower alveolus	15
Hard palate	8

OCSCC=Oral cavity squamous cell carcinoma

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Table 2: Correlation between T-stage clinical and pathological tumor staging in 127 patients

	pT1 (%)	pT2 (%)	pT3 (%)	pT4 (%)	Stage disparity in T-stage (%)			Total
					Upstaged	Unchanged	Downstaged	
cT1	30 (76.9)	5 (12.8)	3 (7.7)	1 (2.6)	9 (23.1)	30 (76.9)		39
cT2	7 (15.9)	19 (43.2)	15 (34.5)	3 (6.8)	18 (40.9)	19 (43.2)	7 (15.9)	44
cT3	3 (10.3)	4 (13.8)	11 (37.9)	11 (37.9)	11 (37.9)	11 (37.9)	7 (15.9)	29
cT4	1 (6.7)	1 (6.7)	2 (13.3)	11 (73.4)		11 (73.4)	4 (26.7)	15

Table 3: Correlation between N-stage clinical and pathological tumor staging in 127 patients

	pN0 (%)	pN1 (%)	pN2 (%)	pN3 (%)	Stage disparity in T-stage (%)			Total
					Upstaged	Unchanged	Downstaged	
cN0	23 (86.4)	3 (10.7)	2 (3.6)	0	5 (17.8)	23 (86.4)		28
cN1	9 (16.9)	21 (39.1)	23 (43.4)	0	23 (43.4)	21 (39.1)	9 (16.9)	53
cN2	0	1 (2.3)	17+24* (39.5)	0	24 (57.3)	17 (39.5)	1 (2.3)	42
cN3	0	0	1 (25)	3 (75)		3 (75)	1 (25)	4

*Includes 24 patients who were upstaged from N2a to N2b

Survival analysis

All survival analyses were performed using SPSS for Windows version 15 (Chicago, IL, USA). Disease-free survival curves were generated using the Kaplan–Meier algorithm.[5] To determine whether significant differences ($P < 0.05$) were present between these survival curves, we employed the log-rank test. Time zero was defined as the date of diagnosis, and surviving patients were included up to the date last known alive, according to time last seen in the outpatient Department of Otolaryngology-Head and Neck Surgery. Multivariate analysis was performed using Cox-regression, incorporating patient age and gender as variables.

Results

Of 127 patients with OCSCC analyzed, 62.2% were males, 37.8% were females, and the mean age at diagnosis was 43.6 years [Table 1]. These patients had tumors in various oral cavity subsites of which tongue and buccal mucosa were the most common. For each patient with an assigned clinical stage, the corresponding pathological stage is summarized in Table 2. The highest congruence between clinical and pathological staging was seen for clinical stages 1 and 4 at 76.9% and 73.4%, respectively. Lower levels of correlation were seen for clinical stages 2 (43.2%) and 3 (37.9%). This level of disparity is largely attributed to upstaging shown in 40.9% of clinically stage 2 patients and 37.9% of stage 3 patients.

Similarly, highest congruence between clinical and pathological N-stage was seen for clinical N0 and N3 at 86.4% and 91.7% with pathological N-stage. The lower level of correlation was seen for clinical N1 (39.1% with pathological) and N2 (39.5% with pathological) staging. This disparity largely attributed to upstaging shown in 43.4% of clinically N1 and 57.3% of N2 patients.

Staging discrepancy between early stages (stages 1 and 2) and advanced stage disease (stages 3 and 4) is summarized in Figure 1. Of the clinically early staged patients, 67.5% remained early stage, and 32.5% were upstaged to advanced stage following pathological analysis. Of the clinically advanced staged patients, 75% remained advanced stage, and 25% were pathologically downstaged.

Given the significant differences in treatment between early and advanced stage patients, we compared survival between these groups as a function of staging discrepancy. Kaplan–

Meir estimates of disease specific survival according to stage discrepancy is shown in Figure 1. In comparing the four groups, a statistically significant difference in survival ($P < 0.001$) was present between these groups according to the log-rank test. However, there was no significant difference between early stage patients not upstaged and early stage patients that were upstaged. Similarly, no significant survival differences were shown between advanced stage patients that remained advanced stage following pathological analysis and downstaged patients. Cox-regression analysis incorporating age and gender also showed no significant survival differences as a result of stage discrepancy.

Discussion

Analyses of clinical and pathological correlations in oral carcinoma, such as positive margins, nodal status, extracapsular spread, degree of invasion, and overall staging congruence are important to implement the most appropriate treatment pathways.[5-7] In our institutional analysis of patients, clinical and pathological staging was congruent in 21.9% of early stage patients upstaged and 7.9% of patients downstaged. Previous studies have shown the level of pathological upstaging in HNSCC patients with clinical N0 necks to be 34–44%,[2,3] and an estimated 20–30% of OCSCC harbor occult regional metastases.[8] This is clinically relevant in the context of recommendations by the American Joint Committee on Cancer, which state an elective neck dissection (END) may be performed where the risk of nodal metastasis is >20%.[9] A recent study also demonstrates that nodal disease is a strong independent predictor of outcome in OCSCC.[10] Taken together, although the level of upstaging in our study was relatively low, this lends support to perform END for OCSCC patients with clinically N0 necks.

Possible causes for staging discrepancy includes a delay between clinical diagnosis and pathologic analysis resulting in upstaging, pathologic interpretation of specimen, and lack of accuracy of clinical staging tools. Physical examination measures such as measurement of the tumor, node size, and manual palpation are relatively inaccurate and may be subjectively different based on surgeon experience. The lower limit of node palpation has been shown to be 0.5 cm in superficial areas and 1 cm in deeper regions.[3] The use of CT scanning does significantly improve the accuracy of staging, however, it does not detect micrometastasis and may have limited utility in differentiating nodal disease from
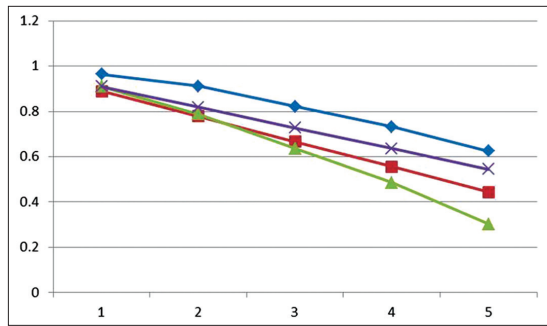
Figure 1: Kaplan–Meier survival estimates of disease-free survival according to stage discrepancy (diamond: Early stage patients with no change, square: Early stage patients who were upstaged, cross: Advance stage patients who were downstaged, triangle: Advance stage patients with no change)

submandibular gland in the submandibular region.[3,11] Therefore, microscopic deposits and extracapsular spread may not be clinically identified and can only be definitively assessed by neck dissection with the pathological assessment.

Given the current limitation in clinical staging even in combination with advanced imaging technology, initial surgical intervention for all patients with OCSSC may be warranted.[12] Some patients with early stage disease only treated with radiation will not have the benefit of appropriate staging to initiate multimodality treatments known to improve survival in advanced stage OCSCC.[13]

Our data suggests OCSSC patients pathologically upstaged or downstaged do not have a significantly altered disease-specific survival [Figure 1]. It is important to note that all patients in this study had surgery as part of their treatment pathway, which is necessary to enable appropriate staging. In the 32.5% of patients with early stage disease, upstaging may have enabled for appropriate adjuvant treatment. In 25% of advanced stage patients, downstaging may have prevented unnecessary adjuvant treatment if initially treated surgically. Thus, more studies are required to determine the role of stage discrepancy on the alteration of treatment pathways.

In contrast to other studies, although our data demonstrates staging discrepancy, we have found that this level of discrepancy does not significantly alter survival. However, similar levels of staging discrepancy with no statistical significance on the survival of the OSCCS patients was also demonstrated by a study conducted by Biron *et al.*[14]

In addition, most staging differences resulted in upstaging from early to advanced stage disease. In these cases, patients should have received appropriate postoperative radiation or chemoradiation and would, therefore, not be undertreated.

In a subset of patients, surgical treatment may provide more appropriate treatment for analysis of the pathological specimen, which might then upstage or downstage the disease. For instance, when a patient is upstaged from early stage disease following surgery, Chemoradiation may be added to the treatment protocol. Conversely, a patient being downstaged following surgery may have their therapy de-escalated. To further address these possibilities, a prospective analysis of patient outcomes following upstaging or downstaging should be performed.

Our study has a number of limitations. This is a retrospective

analysis of patients. In terms of survival analysis, one of the subgroups analyzed, namely downstaged patients was relatively small. This may, therefore, under represent a potentially significant difference in a larger sample size.

Conclusion

Some disparity exists in clinical, intra-operative, and pathological TNM staging of OCSCC, which could affect treatment planning and survival of patients. Hence, more unified and even system of staging disease required for proper decision-making.

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Conflicts of interest

There are no conflicts of interest.

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