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A Nomogram based prognostic score that is superior to conventional TNM staging in predicting outcome of surgically treated T4 buccal mucosa cancer: Time to think beyond TNM

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ABSTRACT

Background and objectives: T4 squamous cell carcinomas of the buccal mucosa is known to have ominous outcome. The aim of this study was to develop a nomogram for T4 buccal mucosa cancer patients and demonstrate the difference in survival based on prognosticators beyond those covered by the traditional TNM staging system.
Methods: We examined medical records of treatment naïve 205 T4 buccal mucosa cancer patients operated between January 1, 2009, and December 31, 2014. A nomogram was developed using multivariate cox-regression. The nomogram was validated internally by bootstrapping and externally in an independent validation set.
Results: The nomogram for predicting 3-year overall survival was built using Tumor differentiation, Pathological Lymph node involvement, Bone and Perineural invasion. Based on nomogram, a score was assigned to each patient and they were divided into two groups based on Youden derived cut-off value (13.5). These two groups in training and validation set showed significant difference in survival.
Conclusion: We developed a high performance, accurate and efficient nomogram to predict the probability of 3-year survival in T4 buccal mucosa cancer patients. Intensification of adjuvant treatment in these advanced cancer patients with poorer score might improve their survival.

Introduction

TNM staging system since 1953, when it was first proposed by French surgeon, Denoix [1,2], to Union for International Cancer Control (UICC) for staging and prognostication of solid tumors, has fulfilled its original mandate remarkably. Initially, based on the simple theory that outcomes worsened as the tumor progressed from the primary site (T) to regional lymph nodes (N) and then to distant organs (M), TNM system has evolved over the years [2]. The American joint committee on cancer (AJCC) and UICC versions of the TNM system were unified in 1987 and since then through continuous collaboration these organizations have maintained a liaison to ensure compatibility of subsequent revised staging classifications. The AJCC/UICC TNM staging system is now in its seventh version and the next edition is due for publication in near future.

The TNM consists of (1) the size of the primary tumor (T stage), (2) description of regional Nodal metastasis (N stage), and (3) distant metastasis (M stage) [3]. Consequently, various subsets of TNM categories are clustered into four stages to stratify patients according to prognosis and to simplify communication. But this clustering results in a loss of accuracy because, for example, a patient with a T4N0M0 carcinoma may biologically be very different from a patient with a T1N2M0 carcinoma, but both these tumors are classified as stage IV diseases [4]. Furthermore, multiple other factors which influence cancer survival have been identified in the literature, including age [5], tumor thickness [6] grade [7], pathological nodal (N) classification [8,9], extracapsular spread (ECS) [10], margin status [11], perineural invasion [12]. The increasing assertion of the impact of these clinical and pathological factors on survival has stimulated the need for better prognostication tools. However, the rigid configuration of TNM inhibits the addition of a new variable, as any attempt to include new variables exponentially increases the number of categories, multiplies the stage options, and makes the system unwieldy [3,13]. Thus, though TNM staging is currently the mainstay of clinical decision making, predicting outcome and patient counseling, it suffers from many drawbacks viz. relative lack of predictive power, inhomogeneity within groups, lack of

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differentiation between groups, failure to account for other tumor factors and inability to reflect important host characteristics [2].

Accurate and individualized estimation of survival in patients with Head and Neck Squamous Cell Carcinoma (HNSCC) can undoubtedly lead to an improvement in therapeutic and care strategies, thus minimizing risks of under-treatment or over-treatment. Nomogram is one such predictive tool that creates a simple graphic representation of a statistical predictive model that generates a numeric probability of a clinical event. Nomograms are widely used for cancer prognosis [14–16], primarily because of their ability to reduce statistical predictive models into a single numeric estimate of the probability of an event that is tailored to the profile of an individual patient. Additionaly, user-friendly graphic interfaces can facilitate the use of nomograms during clinical encounters for informed clinical decision-making [17].

Cancers staged as T4 based on American Joint Committee on Cancer (AJCC) classification [18] are conventionally considered advanced and are known to have poor prognosis [19]. Frequently, in stage T4 tumors neither a clear preoperative tumor infiltration is ascertainable clinically or by imaging nor an adequate surgical margin is achievable during surgical procedures, resulting in unsatisfactory survival [20]. However, apart from anatomical extension there are several other factors which affect survival in these patients [21]. Therefore, timely identification of patients with adverse characteristic can assist in providing more aggressive treatment and prevent ominous outcome. Studies reporting survival statistics specifically on buccal mucosa cancer are sparse. Few researchers have studied buccal mucosa cancer and even fewer have studied prognostic factors exclusively in T4 buccal mucosa cancer patients. In the present study we demonstrate intragroup survival heterogeneity among T4 buccal mucosa cancer patients and present a nomogram developed and validated on one of the largest sample of exclusively T4 buccal mucosa cancer patients.

Materials and methods

Patient's recruitment and data collection

Medical records of 205 T4 buccal mucosa (ICD 10 code C06.0) (as per seventh edition of the Union for International Cancer Control/ American Joint Committee on Cancer TNM classification system) cancer patients, who were diagnosed and surgically treated at Tata Memorial Hospital between January 1, 2009, and December 31, 2014, were retrospectively analyzed. Consequent patients were included in the sample except for patients who had received any form of cancer directed therapy before registering in Tata Memorial Hospital, they were excluded from the study. Patient and tumor characteristics were recorded from the medical records. Microscopic features such as, pathological lymph node involvement, degree of differentiation, status of surgical margin, bone infiltration, skin involvement, presence of perineural invasion and extracapsular spread were recorded from the histopathological report of surgical specimen. In addition, external validation of the nomogram was done using historical patient data archived at our institute. The validation set comprised of 198 treatment naïve T4 buccal mucosa cancer patients who were surgically treated at Tata Memorial Hospital between January 1, 2006, and December 31, 2008. The study had the approval of the research ethics committee of the Institute.

Data analysis and statistical methods

Patients' overall survival (OS) was defined as the time interval between the date of diagnosis and the date of death or the date of the last follow-up, whichever was earlier. The closing date for recording the last follow-up was taken as December 31, 2015. The Kaplan–Meier method was used to calculate survival. The Cox-regression model was used to investigate the effect of selected factors simultaneously on overall survival in a multifactorial setting. Statistical analyses were performed using SPSS software version 21.0 (SPSS, Chicago, IL) and STATA version 12.0 with the Nomocox package added [22]. Statistical significance was considered at $p < 0.05$.

Nomogram development and validation

The following variables were analyzed as predictors of prognosis: age at diagnosis, "T" classification, pathological lymph node involvement, degree of differentiation, status of surgical margin, bone infiltration, presence of perineural invasion and extracapsular spread. Among these clinicopathological variables, for statistical analysis, age was modeled as continuous variable and other factors as categorical variables. Multivariate analysis on these variables was performed using Cox proportional hazards regression. The stepdown reduction method was used to select the statistically most influential predictors for inclusion in the final nomogram. Nomogram was developed from the final selected model for prediction of OS in patients with T4 buccal mucosa cancer.

The discrimination ability of the nomogram was evaluated by Harrell's concordance index (c-index), which provides the probability that for 2 randomly drawn patients, when 1 patient dies before the other, the patient who dies first has a poorer predicted outcome, as determined using the nomogram. It has a scale of 0 to 1 with 1 representing perfect discrimination and 0 for no discrimination ability [23]. Thus, the discrimination ability of the nomogram was internally validated using estimation of bootstrap-adjusted c-index with 1000 bootstrap resamples. The performance of our nomogram was further evaluated externally for discrimination by the area under receiver operating characteristic curve (AUC) for both the training set ($N = 205$) and the external validation set ($N = 198$). A 95% confidence interval (CI) was calculated for each AUC.

In addition to survival probability, in both training and the validation sets a score for each patient was calculated from the nomogram. Patients based on these scores were then grouped into 2 categories as per cutoff value, derived from the Youden index (ROC analysis). The Kaplan–Meier method was then used to compare survival among these two groups. Furthermore, nomogram performance in predicting dichotomous outcomes (alive/dead) was also evaluated in the training and validation sets by two-way contingency table analysis.

Results

The patient's characteristics of training and validation sets are summarized in Table 1. In the training set, the median age was 50 years (range, 23–76 years), and the percentage of men and women were 82.4% and 17.6%, respectively. At the end of follow-up (December 31, 2015), among these 205 patients 84 had died, and 121 were censored. The median follow-up period was 21 months (range, 2–68 months). The three year OS of the cohort was 59.5%. By multivariate logistic regression analysis using the stepdown model reduction method, pathological lymph nodal status, tumor differentiation, perineural invasion and bone involvement were found to be independently associated with OS ($p < 0.05$; Table 2). Based on this Cox proportional hazard model, a nomogram was developed to calculate the probability of survival within three years (Fig. 1). For example, T4 buccal mucosa cancer patient who has undergone surgery with tumor histology showing moderate differentiation (7 points), pN2b lymph node classification (8 points) with perinueral invasion (5 points) and no bone involvement (0 point) would have (22 total points) 35% probability of three year survival. The nomogram was found to have a c-index of 0.7266 for predicting the three year OS.

Nomograms show the probability of three year survival as a percentage; however, dichotomous outcomes for survival/ death are likely to be a user friendly option in practice. Therefore, the nomogram was used to calculate a total score for each patient by adding the score obtained from individual characteristics. Thereafter, we assigned a