Treatment guidelines and patterns of care in oral cavity squamous cell carcinoma: Primary surgical resection vs. nonsurgical treatment

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ABSTRACT

Background: The 2017 National Comprehensive Cancer Network Clinical Practice Guidelines recommend surgical resection or definitive radiation therapy for early-stage oral cavity malignancies, and surgical resection or multimodality clinical trials for late-stage disease. Few studies have been conducted to identify predictors of choice of treatment modality for oral cavity malignancies.
Methods: All patients in the National Cancer Data Base (NCDB) diagnosed with oral cavity squamous cell carcinoma (OCSCC) between 1998 and 2011 were identified. Chi-square and binary logistic regression were used to identify factors predictive of surgical or nonsurgical treatment; multiple imputation was used for missing data. Cox proportional hazards models were generated to identify associations between treatment modality and overall survival (OS).
Results: Of 23,459 patients, 4139 (17.6%) underwent primary nonsurgical treatment. Among NCDB-registered facilities, there has been a decrease in use of nonsurgical treatment for OCSCC (OR 0.97, $p < 0.001$). Older age, non-white race, Medicaid insurance, low income, low education, and later-stage disease were associated with nonsurgical therapy, while patients at academic/research programs were more likely to undergo surgery (OR 0.38, $p < 0.001$). Nonsurgical treatment was associated with decreased OS (HR = 2.02, $p < 0.001$); this was upheld on subgroup analysis of early- and late-stage disease.
Conclusions: Use of primary nonsurgical treatment for OCSCC has decreased over time among NCDB-registered facilities and is associated with factors related to access to care. Surgical resection for the primary treatment of oral cavity cancer may be associated with improved OS, though conclusions regarding survival are limited by the non-randomized nature of the data.

Introduction

The 2017 National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines provide level 2A recommendations for surgical excision with neck dissection or for definitive radiation therapy (RT) in early-stage oral cavity cancers, as well as 2A recommendations for surgery with postoperative adjuvant therapy or multimodality clinical trials for resectable late-stage oral cavity lesions [1]. Despite this, with significant advancements in recon-

structive techniques and subsequent improvements in functional outcomes, surgical resection has become the preferred treatment modality for resectable oral cavity malignancies [2,3]. However, evidence comparing primary surgical and nonsurgical treatment modalities for oral cavity squamous cell carcinoma (OCSCC) is sparse, and the most recent Cochrane review on surgical intervention for OCSCC found insufficient evidence to draw any specific conclusions comparing surgical to nonsurgical treatment [4–6]. We identified only two RCTs comparing surgery to definitive RT/CRT. The first was initiated in the UK in 1998 but closed after enrolling 35 patients because of technical and ethical concerns; additionally, over half of patients randomized to RT did not receive the planned course [7]. The second randomized patients with advanced, non-metastatic head and neck squamous cell carcino-

mas to surgery or concurrent CRT [8]. Although significant differences in disease-specific survival (68% vs. 12%, $p = 0.038$) were observed, the trial enrolled exclusively advanced-stage malignancies and was relatively small, randomizing only 19 patients to the surgical arm and 13 to the CRT arm with OCSCC.

Similarly, there are limited numbers of retrospective studies comparing treatment modalities for patients diagnosed with resectable OCSCC, and little analysis has been conducted on patient and tumor factors predicting treatment modality choice for patients with oral cavity cancers. In a retrospective study of 42 patients undergoing intensity-modulated RT postoperatively or as definitive therapy due to surgical contraindications, Sher et al. found that postoperative RT was associated with improved locoregional control (LRC), overall survival (OS), and lower toxicity rates, but no multivariate analysis was conducted to control for patient or tumor factors.[9] Most recently, Cannon et al. compared surgery, surgery with adjuvant RT, and definitive RT for advanced-stage OCSCC using the SEER database [10]. After excluding unresectable tumors with T4b classification, the authors found increasing prevalence of nonsurgical therapy over time in advanced-stage disease and that nonsurgical therapies were associated with the hard palate and patients who were black, single, or divorced. Other single-institution studies excluded patients with unresectable disease on chart review and have shown worse outcomes with nonsurgical therapy, though again did not identify sociodemographic factors associated with undergoing particular treatment regimens [11–14].

Although recent literature has identified factors associated with worse outcomes in OCSCC [15,16], to our knowledge little analysis has been conducted to identify national trends and patterns of care in the initial treatment plans of patients with OCSCC and to compare surgical to nonsurgical treatment regimens nationally. The primary purpose of the present study is twofold: (1) to identify national trends on the use of nonsurgical therapy for OCSCC using the National Cancer Data Base (NCDB) and (2) to identify factors associated with increased use of definitive RT/CRT or primary surgical resection. As a secondary focus, survival outcomes of nonsurgical therapies relative to definitive surgical resection will be assessed in this non-randomized population.

Materials and methods

This study uses the NCDB Participant User Files and was exempt for approval by the Yale University institutional review board. The NCDB is a nationwide, facility-based, comprehensive clinical surveillance resource oncology dataset that captures approximately 70% of all newly diagnosed malignancies in the United States annually [17]. All patients diagnosed or first treated for oral cavity squamous cell carcinoma at an NCDB site from 1998 to 2011 were identified (n = 82,628). Patients were excluded from analysis for: (i) multiple cancer diagnoses; (ii) primary tumor site at the outer lip; (iii) not treated at the reporting facility; (iv) incomplete clinical staging; (v) T0 or Ti classification; (vi) unresectable disease, defined as cT4b classification; (vi) M1 classification; (vii) untreated or unknown treatment regimen or treatment sequence; or (viii) treated with chemotherapy alone. In addition, surgery was not recommended or performed in 286 patients in the nonsurgical treatment group due to contraindications; these patients were excluded from analysis in order to limit potential biases in the intent of the chosen treatment between the surgical and nonsurgical groups. Clinical staging and T and N classifications were used throughout this analysis.

Patients treated with surgical resection with or without adjuvant therapy were compared to those who underwent nonsurgical treatment, which was defined as either definitive RT or CRT. Logistic regression was used to analyze temporal trends in treatment. In order to identify factors predictive of undergoing either treatment, univariate analysis was conducted using chi-square analysis. Education was estimated in the NCDB Participant User Files by the percentage of adults in a patient's zip code who did not graduate from high school; higher quartiles had increased percentage of adults who did not graduate high school. Income was estimated by the median household income in a patient's zip code at the time of diagnosis. In addition to clinical AJCC stage and Charlson-Deyo scores (0, 1, or 2) which were identified beforehand as clinically meaningful covariates, factors with $p < 0.20$ on univariate analysis were included in multivariate analysis. Because a substantial number of patients had missing comorbidity data, multiple imputation using an ordinal logistic imputation method was utilized, with the assumption that the missing data were missing at random (MAR) [18]. All other variables to be included in the multivariate analysis were included as covariates within the imputation prediction equation [19,20]. A binary logistic regression model was then conducted for multivariate analysis to identify sociodemographic and treatment factors independently predictive of nonsurgical treatment.

As a secondary outcome, we identified whether treatment modality was associated with differences in overall survival (OS). Univariate survival analysis was conducted by log-rank test. Cox proportional hazards models were generated to determine whether different treatment modalities were associated with significant differences in OS. Factors with $p < 0.20$ were included in the Cox proportional hazards model. Multiple imputation was utilized as described above to account for missing Charlson-Deyo scores. All statistical analysis was performed using Stata 14.2 (StataCorp, College Station, TX).

Results

Patient, tumor, and treatment characteristics

The final analysis included 23,744 patients, of whom 4424 patients (18.6%) were treated nonsurgically. Of the nonsurgical patients, 2207 (49.9%) underwent RT alone, and the remainder received CRT. Surgery was not performed for the following reasons: (1) it was not part of the planned first course of treatment (86.2%); (2) it was recommended but not performed without a reason given (3.2%); and (3) it was recommended but refused by the patient (10.6%). Of surgical patients, 12,624 (65.3%) underwent surgical resection without adjuvant therapy, and the remainder received adjuvant therapy. Patient, tumor, and treatment characteristics stratified by treatment modality, in addition to the results of univariate analysis, are detailed in Table 1.

Patterns of care

From 1998 to 2009, there was a decrease in rate of nonsurgical treatment for OCSCC (Fig. 1). In 1998, 21.2% of OCSCC patients underwent nonsurgical management, compared to 13.7% of patients in 2009. For AJCC clinical stage I and II cancers, nonsurgical therapy utilization decreased from 9.8% to 5.7% between 1998 and 2009; similarly, over the same time, non-surgical therapy utilization decreased for late-stage OCSCC from 36.7% to 23.7%. On logistic regression, these data reveal a significant decrease in non-surgical therapy for OCSCC ($p < 0.001$, OR 0.97); this difference was significant on subset analysis for early-stage ($p < 0.001$, OR 0.97) and late-stage ($p < 0.001$, OR 0.97) tumors.