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Independent Predictors of Prognosis Based on Oral Cavity Squamous Cell Carcinoma Surgical Margins

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Abstract

Objective.—Multivariate analysis of a large cohort of oral cavity squamous cell carcinoma (OCSCC) cases for independent predictors of local recurrence (LR) and overall survival (OS), with specific emphasis on the relationship between prognosis and main specimen permanent margins and intraoperative tumor bed frozen margins.

Study Design.—Retrospective cohort study

Setting.—Tertiary academic head and neck cancer program

Subjects and Methods.—This study included 426 patients treated with OCSCC resection between 2005–2014 at University of Iowa Hospitals and Clinics. Patients underwent excision of OCSCC with intraoperative tumor bed frozen margin sampling and main specimen permanent margin assessment. Multivariate analysis of the dataset to predict LR and OS was performed.

Results.—Independent predictors of LR included nodal involvement, histologic grade, and the main specimen permanent margin status. Specifically, the presence of a positive (OR 6.21, 95% CI 3.3–11.9) or <1mm/carcinoma-in-situ margin (2.41, 1.19–4.87) on the main specimen was an independent predictor of LR, whereas intraoperative tumor bed margins were not predictive of LR on multivariate analysis. Similarly, independent predictors of OS on multivariate analysis included nodal involvement, extracapsular extension (ECE), and a positive main specimen margin. Tumor bed margins did not independently predict OS.

Conclusion.—The main specimen margin is a strong independent predictor of both LR and OS on multivariate analysis. Intraoperative tumor bed frozen margins do not independently predict prognosis. We conclude that emphasis should be placed on evaluating the main specimen margins when estimating prognosis after OCSCC resection.

Keywords

oral cavity squamous cell carcinoma; intraoperative tumor bed frozen margins; main specimen margins; overall survival; local recurrence

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Introduction

Despite a fairly standardized practice in head and neck cancer of wide excision with the goal of microscopically clear margins, it remains unknown how prognosis is affected by patient and tumor variables. Specifically, it is difficult to fully interpret the impact of surgical margins and to advise patients accordingly regarding surveillance, adjuvant treatment, and expected prognosis. The objective of this study is to evaluate a large set of OCSCC cases for independent predictors of LR and OS based on multivariate analysis, with particular emphasis on the relationship between outcomes and main specimen permanent margins and intraoperative tumor bed frozen margins.

There is substantial controversy in the head and neck oncology literature about what constitutes a “positive” margin^{1,2}. This controversy extends into how to address main specimen permanent margins and intraoperative tumor bed frozen margins, how to interpret “clearance” of involved margins, and whether the main specimen permanent margin or the intraoperative frozen margins should be considered the “true” margin in the context of prognosis and further patient management^{3–8}. The majority of head and neck surgeons perform wide local excision of OCSCC followed by sampling of the tumor bed via frozen section for intraoperative margin assessment, however it is not evident how data derived from these techniques should be interpreted.

We published a large retrospective study with detailed examination of surgical margins and outcomes of LR and OS based on univariate analysis⁹. We paid particular attention to the variables of main specimen permanent margins and intraoperative tumor bed frozen margins, with evaluation of the prognostic significance of “clearing” involved tumor bed margins. In summary, this manuscript showed that the main specimen permanent margin has the stronger prognostic association with LR and OS than tumor bed frozen margins on univariate analysis. We also showed that there was no prognostic value in “clearing” involved intraoperative tumor bed margins. We also evaluated the association of LR with the specific millimeter close distance between invasive tumor and the permanent specimen margins¹⁰. This study showed that only a close margin of less than 1mm from invasive tumor was associated with a significantly increased risk of LR, with a rate of 28%.

The current study evaluates independent predictors of prognosis based on multivariate analysis for surgically treated OCSCC. In addition to clinical variables, particular attention has been placed on pathologic factors and surgical margin status when developing prognostic models of LR and OS. Development of independent predictor models has the capacity to aid surgeons and oncologists in decision-making regarding not only patient surveillance and expectations, but also possibly in recommending and tailoring adjuvant treatments.

Methods

Study Population

Approval for the study and a waiver of informed consent was obtained from the Institutional Review Board of the University of Iowa Hospitals and Clinics. A retrospective review of 540

patients who underwent en bloc resection of OCSCC between 2005 and 2014 was performed. Clinicopathologic data was obtained from the institutional tumor registry, operative report, pathology report, and clinic notes. Patients were excluded if they had a tumor outside the oral cavity, if pathology demonstrated histology other than squamous cell carcinoma or one of its variants, if there was no reported margin evaluation from the main tumor specimen, or if intraoperative tumor bed frozen sampling was not performed. Additional exclusion criteria were operation without curative intent or for recurrent disease, no cancer in the resection specimen, or gross disease remaining after surgery. Patients with multiple OCSCCs over time were included provided that primary tumors occurred at disparate locations. 426 patients remained in the dataset.

Variables included in the analysis were age, gender, oral cavity site, radiation, chemotherapy, reconstruction, mandibulectomy, neck dissection, prior radiation, T stage, any nodal involvement, extracapsular extension (ECS), perineural invasion (PNI), lymphovascular invasion (LVI), grade, bone invasion, initial tumor bed frozen margin, reresection performed, final intraoperative margin result, and the specimen margin. Outcome data including LR and OS were obtained from the institutional tumor registry and patient charts. Patients with missing data were excluded from analysis. LR was defined as return of cancer within five years at the same oral cavity subsite or a contiguous subsite. Patients without LR who did not survive six months after surgery were not included in LR analysis. Patients who developed distant and regional recurrence without noted local recurrence, which might have led to ignoring a local recurrence, were also excluded, resulting in 358 patients included in analysis of LR. Survival was measured from date of surgery to date of death or censor (last known follow-up), with 426 patients for OS analysis.

Surgical Resection and Pathologic Analysis

Surgical technique included wide local excision with attempted three-dimensional 1cm margins as able based on anatomic constraints. The main resection specimen was reserved for permanent margin analysis, and intraoperative tumor bed frozen margins were assessed. Involved tumor bed frozen margins were addressed by reexcision followed by evaluation of a second intraoperative margin, with attempts to obtain an uninvolved margin. Permanent margins on the main resection specimen were later reported by pathology. The results of this study are specifically applicable to a method of intraoperative margin sampling from the patient tumor bed and permanent margin sampling from the main specimen.

Definition of margin status includes positive if invasive cancer was present at the inked edge, very close if <1mm from the edge, close if 1–5mm from the edge, and negative if invasive cancer was >5mm from the edge. Carcinoma in situ (CIS) or dysplasia at the margin was also noted.

Adjuvant Treatment

Standard institutional practice was to discuss all patients in a multidisciplinary tumor board, with decisions made to recommend adjuvant treatments following surgery. Factors under consideration for adjuvant treatment recommendations include margin status, depth of invasion, perineural invasion, node metastasis, bone invasion, tumor size, and extracapsular

extension. Recommendations for adjuvant chemotherapy in addition to radiation therapy were based on either positive surgical margin status or extracapsular extension. Over the study time period, the guidelines for recommending adjuvant treatment have been consistent. Variance in practice on a case-by-case basis is possible and difficult to ascertain retrospectively, as well as patient choice of whether to pursue adjuvant treatment. It is also generally difficult to ascertain whether the final intraoperative margin status after frozen sections and additional resections was referenced as the surgical margin status, or what weight was placed on the permanent specimen margin assessment.

Statistical Analyses

A logistic regression model was used to predict LR, and a Cox proportional hazards model to predict OS. Model fitting was performed with Akaike information criterion (AIC)-based forward stepwise variable selection. A range of values was considered for the AIC penalty term that weights the number of variables in the models. Higher penalty values produce models with fewer variables. Predictive model accuracy was assessed with the concordance index estimated using 10-fold cross-validation. The concordance index ranges from 0 to 1 and can be interpreted as the probability that patients with events have higher predicted event probabilities in the case of logistic regression, and that patients who live longer have higher predicted survival rates in the case of Cox regression. Cross-validation was implemented as follows: the dataset was randomly split into ten folds, keeping the ratio of events to non-events constant; then, for each fold, a concordance index was computed based on the observed outcomes and values predicted from a model fit to the remaining folds. Concordance indices were averaged over folds to produce a final estimate of predictive performance.

The tumor bed frozen margin assessment and permanent margin status were of special interest for this study and were thus forced to remain in the models, along with the interaction between them. From the cross-validation results, it was determined that penalties of 4.75 and 5 should be used for the logistic model and the survival model respectively. These penalties resulted in concordance indices of 0.77 for the logistic model and 0.76 for the survival model. Final models were fit to the full dataset using the stepwise selection algorithm and the optimal penalties. Where reported, p-values are based two-sided statistical testing and assessed for significance at the 0.05 level. All statistical analyses were performed with R: A Language and Environment for Statistical Computing (R Foundation for Statistical Computing, 2015; <https://www.R-project.org>).

Results

Patient Characteristics

Study population, tumor characteristics, and their association with LR are described in Table 1. For both LR (N=358) and OS (N=426) the study population included 58% male and 42% female patients, with a mean age at diagnosis of 61 years. The most common primary site of OSCC was oral tongue (45%). Most commonly patients had T1 (45%), moderately differentiated SCC (63%) with no identified regional metastases (70%). Additionally, the majority of patients did not go on to receive adjuvant therapy (62%).

Multivariate Predictive Model for Local Recurrence

The pathologic factors significantly related to LR on univariate analysis were nodal involvement, ECE, higher tumor grade, PNI, LVI, and adjuvant chemotherapy treatment (Table 1).

A multivariate analysis was performed on the dataset in order to identify independent predictors of LR.

The final predictive model for LR contains the specimen margin variables, nodal involvement, and tumor grade (Table 2). In looking specifically at main specimen permanent margins, patients with CIS/very close (OR 2.4, 95% CI 1.2–4.9) or positive specimen margins (OR 6.2, 95% CI 3.3–11.9) were more likely to have a recurrence than patients with negative, mild or moderate dysplasia, or close main specimen margins. A positive specimen margin appears to have the strongest relationship with recurrence. Patients with nodal involvement were significantly more likely to have LR than patients without nodal involvement (OR 2.8, 95% CI 1.5–5.1), and with a grade of ‘poor’ are more likely to have a recurrence than patients with a grade of ‘moderate’ (OR 3.5, 95% CI 1.8–6.9). The AIC for this model is 333.19. Another model was fit: one forcing specimen margin, frozen margin, and final margin into the model resulted in an AIC of 334.04. Both models have a higher AIC than the final selected model, meaning the fit is not as good. When included in the model, a positive intraoperative tumor bed frozen margin does not have a significant association with LR (OR 1.57, 95% CI 0.6–4.1), nor does a positive final operative margin status (OR 2.95, 95% CI 0.4–24.7). The independent predictor model for LR is shown in graph format in Figure 1.

Multivariate Predictive Model for Overall Survival

Similar to evaluation of LR, a multivariate analysis was performed on the OCSCC dataset to identify independent predictors of OS, including all clinicopathologic variables and with attention to margins. Multivariate analysis of the dataset revealed the independent predictors of death to be increased age, any nodal involvement, extracapsular spread, and a positive specimen margin (Table 3). In this case, only patients with positive main specimen margins were at an increased risk of death, rather than patients with negative, mild or moderate dysplasia, CIS, close, or very close margins. The intraoperative tumor bed frozen margins, either taken alone or in combination with main specimen margin variables, was not a significant independent predictor of OS on multivariate analysis. These data are also shown in graph format in Figure 2.

The multivariate analysis performed for LR and OS highlight the prognostic importance of the main specimen permanent margin in predicting prognosis. Although intraoperative tumor bed frozen margins are routinely tested and emphasized for accomplishing tumor “clearance,” in this multivariate analysis the intraoperative frozen sections were unable to independently predict important prognostic outcomes. In addition, other factors were also not independent predictors of outcome, such as T-stage, bone invasion, perineural invasion, or lymphovascular invasion. Depth of invasion was not included in the modeling as accurate assessment was missing for over 30% of this retrospective cohort.

Internal validation of the prognostic models was performed via cross-validation, with application of appropriate penalty terms, resulting in concordance indices of 0.77 for the local recurrence model and 0.76 for the survival model. These models have not been validated in an external dataset.

Adjuvant Treatment

In a retrospective cohort study, it is difficult to control for the effects of additional treatment, such as radiation and chemotherapy, which may be subject to selection bias and confound outcome analysis. The criteria for selecting patients for adjuvant treatment is fairly standardized, and consistent during the time period of this study. It is not surprising that a number of factors are related to adjuvant radiation treatment on univariate analysis, including age, gender, T-stage, N-stage, ECS, PNI, LVI, grade, bone invasion, and the specimen margin. The initial intraoperative frozen margin, nor the final operative margin status were associated with adjuvant radiation treatment. In the multivariate model of LR, forcing adjuvant treatment into the model build resulted in an AIC of 336.0, which implies worse model fit. In this model, neither adjuvant radiation (OR 0.67, 95% CI 0.33–1.38) nor adjuvant chemoradiotherapy (OR 0.77, 95% CI 0.29–2.04) independently predicted LR, while the effect sizes of the specimen margin, nodal disease, and grade were relatively unchanged. In the OS multivariate model, neither was adjuvant radiation (HR 0.80, 95% CI 0.56–1.14) or chemoradiation (HR 0.76, 95% CI 0.47–1.23) a significant predictor of survival.

Discussion

In this large, retrospective study of surgically treated OCSCC with focus on surgical margin assessment we have demonstrated which variables serve as independent predictors of prognosis, and emphasize the importance of the main surgical specimen margins, node status, extracapsular extension, and histologic grade. This study pertains to a technique of resection including wide local excision of OCSCC with intraoperative tumor bed frozen margin sampling and subsequent permanent margin evaluation on the main specimen. There was a relatively homogenous technique among surgeons as well as a broad sample of oral cavity primary sites, stages, and outcomes. One limitation of this study is that it is retrospective in nature. Furthermore, data are obtained from a single institution and a relatively small number of surgeons. This study is also limited by our inability to evaluate the less commonly utilized technique of assessing intraoperative frozen sections directly from the main specimen as opposed to the tumor bed.

Although there are a number of studies looking at univariate predictors of outcomes for OCSCC, studies with multivariate prognostic modeling are fairly limited. Gross et al. published a study looking at locoregional recurrence-free survival (LRFS) of 590 patients with OCSCC¹¹. They created a predictive nomogram to predict the likelihood for LRFS within five years from surgery. Independently predictors of LRFS included lymph node involvement (N1, >N1), T stage (T2, >T2), and close/positive margin. One major difference between that study and the current study is in the definition and detail of margins; in the nomogram provided by Gross et al., surgical margins were defined as “close” if within one

high-powered field of the resection margin, and this was grouped with “positive” margins. There is no further detail provided as to how these margins were specifically obtained or assessed, or if intraoperative frozen margins were sampled and addressed. Furthermore, factors such as CIS and dysplasia were not taken into account. Other important variables, including ECS, PNI, and LVI were not available for evaluation. The method of variable selection for model inclusion in our current paper was based on information criterion, with penalties imposed for overselection based on cross-validation, while in the Gross et al. study all variables selected by the authors were included in the model. A final difference is the patients in the prior study were treated between 1985 and 1996, which importantly does not include the period of time where chemotherapy was routinely introduced in the adjuvant setting for an indication of positive margins. This current study spans the years 2005 to 2014, where chemotherapy was routinely recommended in the adjuvant setting with radiation for positive margins.

Two additional prognostic models for OCSCC were published in 2013, the first of which was an extension of the dataset used by Gross et al. in 2008, intended to further examine the effect of adjuvant radiotherapy on LRFS, but with the same data limitations as discussed above¹². The authors used propensity score weighting to control for selection bias in adjuvant radiation treatment, and found that patients with positive margins and/or N2/N3 disease would be expected to gain the most LRFS benefit from adjuvant radiotherapy¹². A second paper by Montero et al. used a dataset of 1600 OCSCC patients from 1985–2009 to develop a nomogram for prediction of OS, cancer specific mortality probability (CSMP), and locoregional recurrence-free survival¹³; they found the most influential predictors were clinical nodal involvement, tumor size, oral cavity subsite, and bone invasion. This model was developed with information only available prior to surgery, thus does not include margin status, PNI, LVI, ECS, grade, or pathologic node status. As reflected in a c-index of 0.60 for predicting locoregional recurrence, the model does a poor job of discriminating the likelihood of recurrence based on preoperative clinical information alone, highlighting the importance of prognostic information obtained from the pathologic assessment of OCSCC surgical specimens.

A multivariate model for predicting recurrence and survival based on histologic assessment was reported in 2005, which included the pattern of invasion, lymphocytic response, and size of perineural invasion¹⁴. Interestingly, that study did not find margin status correlated with outcomes, though important differences exist in the assessment and definition of margins in that study where the resection specimen margins were intraoperatively assessed by surgeon and pathologist, and additional margin clearance from the tumor bed obtained for questionably close margins. The authors hypothesized that this was effective in removing any prognostic impact of the involved specimen margin, and dependent on the techniques employed by the surgeon-pathologist team. In a followup validation study of the histologic risk model in a new multi-institutional patient cohort, on multivariate regression they found that a positive surgical margin was a stronger predictor of survival than the histologic risk score, possibly related to inherent variability in techniques related to surgical margins between institutions¹⁵.

The primary strength of the current study is the emphasis on and clear definition of surgical margin variables in determining independent prognostic predictors of OCSCC outcomes. This analysis revealed an independent predictor of LR and OS on multivariate analysis was a positive specimen margin. Neither a positive intraoperative tumor bed frozen margin, or a positive final intraoperative margin status serves as an independent predictor of LR or OS, questioning the prognostic value of the information gained from intraoperative tumor bed sampling. This message is similar to other recent reports evaluating the benefit of surgical margin sampling from the tumor bed, versus the main resection specimen. The group from the University of Pittsburgh, in two related publications, compared patients treated by glossectomy for early stage tongue SCC with either intraoperative margin assessment from the tumor bed, or assessment of the glossectomy specimen margins^{16,8}. In the first study, including 126 patients, they found that the glossectomy specimen margin status predicted local recurrence outcome, while the tumor bed sampling and final operative margin status did not¹⁶. In that study, only early T-stage tongue cancers without pathologic node metastases were included, while our study reports a similar finding of the importance of the specimen margins relative to tumor bed sampling, even in the setting of other high-risk pathologic findings such as node metastases and extracapsular extension. In an expanded second study including twice the number of patients from multiple institutions, they report a similar finding⁸. In addition to emphasizing the prognostic importance of the glossectomy specimen margin status, these two studies answer an important question: even with intraoperative recognition of a positive margin on the glossectomy specimen, revision of margins with additional resection from the tumor bed is still associated with worse local control.

It is also interesting to note clinicopathologic factors which are significantly associated with outcomes on univariate analysis, but on multivariate analysis are not as important as the specimen margin, node status, grade, or extracapsular extension. It is noteworthy that this includes t-stage, as well as bone involvement itself, as well as perineural and lymphovascular spread. If validated in additional patient cohorts, this should influence the refinement of surgically treated oral cavity tumor staging systems.

An important caveat is that based on this study alone, it would be a mistake to definitively conclude that tumor bed margin sampling does not have some utility in practice. Though we have demonstrated that the main specimen margins correlates more strongly with eventual outcomes than the sampled tumor bed margins, this study only includes patients who underwent this type of margin assessment, and therefore we cannot rule out that some benefit was achieved for certain individual patients, if they underwent further margin clearance intraoperatively based on tumor bed margin sampling. We are unable to compare to a different technique of intraoperative margin assessment (such as from the main specimen), as it was not utilized in our patient sample. As well, in some instances the practical manner to check intraoperative margins is by sampling the tumor bed, such as for complex specimens and when bone is included in the main specimen. Therefore, the message of this study emphasizes the critical importance of the main specimen permanent margins for patient prognosis, as opposed to making decisions based on the status of the tumor bed margins and belief of tumor bed “clearance” intraoperatively. Though certainly,

this and similar studies may influence head and neck surgeons to pursue intraoperative margin assessment more selectively and alter the specific sampling technique.

Future prospective studies would be valuable to evaluate margin status and risk stratification in patients with OCSCC. The strength of our study is a very clear and detailed definition of surgical technique and margin sampling, which helps to make this study applicable to the common cases where intraoperative tumor bed frozen margins are assessed, followed by main specimen margins assessment on permanent pathology. Our data emphasizes the prognostic importance of the main specimen margin over tumor bed margins; it is easy to believe clinical scenarios exist where patients are falsely expected to have a good prognosis leading to undertreatment from an adjuvant therapy standpoint, based on the belief that intraoperative tumor bed margins are uninvolved. The predictive models we report may provide clinicians and researchers guidance in tailoring practice and organizing future trials to better understand how to treat OCSCC patients.

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Figure 1.

Predictive models of local recurrence. A model was created based on multivariate analysis of independent predictors of LR. Depicted are odds ratios for variables with 95% confidence intervals. $P < 0.05$ is statistically significant.

Figure 2.

Predictive model and nomogram of overall survival. A model was created based on multivariate analysis of independent predictors of OS. Depicted are hazard ratios for variables with 95% confidence intervals. $P < 0.05$ is statistically significant.

Table 1.

Patient Characteristics and Association with Local Recurrence

		Overall N=426	Local Recurrence (n=358)		
			No N=274	Yes N=84	P value
Age, mean (range)		61 (53–71)	61 (54–71)	62 (53–71)	0.57
Gender	Male	248 (58%)	163 (59%)	45 (54%)	0.34
	Female	178 (42%)	111 (41%)	39 (46%)	
Tumor Subsite	Oral tongue	193 (45%)	118 (43%)	41 (49%)	0.23
	Alveolus	87 (20%)	69 (25%)	15 (18%)	
	FOM	79 (19%)	54 (20%)	11 (13%)	
	Palate	10 (2%)	4 (1%)	2 (2%)	
	Buccal	23 (5%)	11 (4%)	7 (8%)	
	RMT	31 (7%)	16 (6%)	8 (10%)	
	Other	3 (1%)	2 (1%)	0 (0%)	
Differentiation Grade	Well	84 (20%)	60 (22%)	16 (19%)	<0.001
	Moderate	270 (63%)	182 (66%)	40 (48%)	
	Poor	72 (17%)	32 (12%)	28 (33%)	
T Stage	T1	193 (45%)	134 (49%)	36 (43%)	0.47
	T2	88 (21%)	55 (20%)	16 (19%)	
	T3/4	145 (34%)	85 (31%)	32 (38%)	
Neck Dissection	Yes	293 (69%)	181 (66%)	61 (73%)	0.26
	No	133 (31%)	93 (34%)	23 (27%)	
Any Positive Node	Yes	126 (30%)	51 (19%)	38 (45%)	<0.001
	No	300 (70%)	223 (81%)	46 (55%)	
N Stage	N0	300 (70%)	223 (81%)	46 (55%)	<0.001
	N1	43 (10%)	19 (7%)	10 (12%)	
	N2a	4 (1%)	2 (1%)	1 (1%)	
	N2b	60 (14%)	24 (9%)	21 (25%)	
	N2c	17 (4%)	6 (2%)	5 (6%)	
	N3	2 (0%)	0 (0%)	1 (1%)	
ECE	Yes	74 (17%)	24 (9%)	25 (30%)	<0.001
	No	352 (83%)	248 (91%)	59 (70%)	
LVI	Yes	118 (28%)	60 (22%)	27 (32%)	0.055
	No	308 (72%)	214 (78%)	57 (68%)	
PNI	Yes	153 (36%)	77 (28%)	41 (49%)	<0.001
	No	273 (64%)	197 (72%)	43 (51%)	
Bone Invasion	Yes	106 (25%)	67 (24%)	18 (21%)	0.57
	No	320 (75%)	207 (76%)	66 (79%)	
Adjuvant RT	Yes	174 (41%)	98 (36%)	39 (46%)	0.079

		Overall N=426	Local Recurrence (n=358)		
			No N=274	Yes N=84	P value
	No	252 (59%)	176 (64%)	45 (54%)	
Adjuvant CRT	Yes	53 (12%)	24 (9%)	17 (20%)	0.004
	No	373 (88%)	250 (91%)	67 (80%)	
UADT Second Primary	Yes	75 (18%)	42 (15%)	20 (24%)	0.07
	No	351 (82%)	232 (85%)	64 (76%)	
Initial frozen margin result	Negative	239 (56%)	160 (58%)	39 (46%)	0.019
	Positive	77 (18%)	38 (14%)	24 (29%)	
	Severe/CIS	74 (17%)	53 (19%)	14 (17%)	
	Mild/Mod	36 (8%)	23 (8%)	7 (8%)	
Additional excision	Yes	143 (34%)	80 (29%)	40 (48%)	0.002
	No	283 (66%)	194 (71%)	44 (52%)	
Final operative margin status	Negative	338 (79%)	215 (78%)	66 (79%)	0.054
	Positive	10 (2%)	3 (1%)	5 (6%)	
	Severe/CIS	31 (7%)	23 (8%)	5 (6%)	
	Mild/Mod	47 (11%)	33 (12%)	8 (10%)	
Tumor specimen margin on permanent	Negative	102 (24%)	79 (29%)	9 (11%)	<0.001
	Positive	99 (23%)	41 (15%)	39 (46%)	
	Severe/CIS	20 (5%)	11 (4%)	5 (6%)	
	Mild/Mod	7 (2%)	3 (1%)	0 (0%)	
	Close (1–5mm)	135 (32%)	101 (37%)	17 (20%)	
	Very close (<1mm)	63 (15%)	39 (14%)	14 (17%)	

Abbreviations: ECE, extracapsular extension; LVI, lymphovascular invasion; PNI, perineural invasion; RT, radiation; CRT, chemotherapy; UADT, upper aerodigestive tract; CIS, carcinoma in situ; Mod, moderate dysplasia.

Table 2.

Independent Predictors of Local Recurrence Based on Multivariate Analysis

Covariate	Level	N	Local Recurrence			
			Odds Ratio	95% CI		OR P-value
Any Nodal Involvement	Yes	89	2.77	1.50	5.12	<0.01
	No	269	-	-	-	-
Grade	Poor	60	3.49	1.76	6.94	<0.01
	Well	76	1.97	0.94	4.09	0.07
	Moderate	222	-	-	-	-
Specimen Margin	CIS/Very Close	69	2.42	1.19	4.87	0.01
	Positive	80	6.21	3.30	11.93	<0.01
	Negative/Dysplasia/Close	209	-	-	-	-

Abbreviations: CIS, carcinoma in situ; CI, confidence interval; OR, odds ratio.

Table 3.

Independent Predictors of Overall Survival Based on Multivariate Analysis

Covariate	Level	N	Overall Survival			
			Hazard Ratio	95% CI		OR P-value
Age		426	1.02	1.01	1.04	<0.01
Any Nodal Involvement	Yes	126	3.31	1.95	5.65	<0.01
	No	300	-	-	-	-
Extracapsular Spread	Yes	74	2.10	1.24	3.55	0.01
	No	352	-	-	-	-
Specimen Margin	CIS/Very Close	83	1.38	0.79	2.41	0.26
	Positive	99	2.87	1.83	4.49	<0.01
	Negative/Dysplasia/Close	244	-	-	-	-

Abbreviations: CIS, carcinoma in situ; CI, confidence interval; OR, odds ratio.