



Published in final edited form as:

*Oral Oncol.* 2013 November ; 49(11): 1083–1087. doi:10.1016/j.oraloncology.2013.08.001.

## Dysplasia at the Margin? Investigating the Case for Subsequent Therapy in ‘Low-Risk’ Squamous Cell Carcinoma of the Oral Tongue

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### Abstract

**Purpose**—This is a retrospective analysis of the impact of moderate dysplasia at the resection margin for early stage cancer of the oral tongue.

**Materials and Methods**—Patients with T1-2N0 oral tongue cancer treated with surgery alone at Fox Chase Cancer Center (FCCC) from 1990 – 2010 were reviewed. Tumor and margin characteristics were abstracted from the pathology report.

Overall survival (OS), disease-free survival (DFS) and local control (LC) were calculated using the Kaplan Meier method. Predictors of LC, OS and DFS were analyzed.

**Results**—126 patients met the inclusion criteria. Dysplasia was present at the final margin in 36% of the cases (severe: 9%, moderate: 15%, mild: 12%).

Median follow-up was 52 months. 3 and 5-year actuarial LC for the entire cohort was 77 and 73%, respectively. Actuarial 5-year LC and DFS were significantly worse for patients with moderate or severe dysplasia at the margin vs. none or mild dysplasia at the margin (49 v 82%,  $p = 0.005$  and 49 v 80%,  $p = 0.008$ , respectively); 3-year comparisons were not significant. When analyzed separately, the detrimental local effect of moderate dysplasia at the margin persisted ( $p = 0.02$ ) and the effect of severe dysplasia at the margin was approaching significance ( $p = 0.1$ ). Mild dysplasia at the margin did not significantly impair LC or DFS.

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Abstract presented at the scientific session of the 54<sup>th</sup> annual meeting of the American Society for Radiation Oncology in Boston, MA, October 28-31; 2012.

Conflict of Interest Statement: None.

Multivariate analysis demonstrated worse LC (HR: 2.99,  $p=0.006$ ) and DFS (HR: 2.84,  $p=0.008$ ) associated with severe or moderate dysplasia at the margin.

**Conclusions**—Both severe and moderate dysplasia at the margin appear to be correlated with inferior LC and DFS. Additional therapy may be justified, despite added morbidity.

### Keywords

Oral tongue cancer; dysplasia; margin

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## Introduction

Pathologic margin is an important prognostic factor for relapse-free survival in head and neck cancer managed with primary surgery<sup>1-4</sup>. Given the prognostic significance of microscopic clearance of tumor, a ‘margin’ of grossly normal tissue is typically resected beyond the macroscopic tumor at the time of resection. Microscopic evaluation of the margin informs decisions regarding the application of postoperative therapy. Presence of tumor at a margin is an accepted indication for postoperative chemoradiation<sup>5,6</sup>. With a clear margin, in the absence of other risk factors, no additional treatment is needed<sup>7</sup>. What represents a “close margin” (defined as invasive carcinoma within a certain distance from the specimen limit) is institution-specific, ranging from 1 – 5 mm<sup>8-10</sup>. Despite the differences between centers in the definition of a “close” margin, retrospective analyses suggest that a close margin heralds increased locoregional failure<sup>11,12</sup>. While there are considerable data characterizing the influence of invasive carcinoma at the margin, the impact of dysplasia at the margin is less clear.

The concept of oral field cancerization was first promulgated in the 1950s<sup>13</sup>. It describes a situation in which, though clinical cancer is found in a seemingly discrete location (e.g. oral tongue, floor of mouth), the entire epithelial surface of the upper aerodigestive tract harbors multiple genetic abnormalities and potentially (pre)malignant lesions. The field effect has been attributed to multiple risk factors, most notably tobacco<sup>14</sup> and ethanol<sup>15</sup>. Premalignant changes are typically widespread and their relationship to invasive cancer may be uncertain. Additionally excising an area of dysplasia adjacent to an invasive cancer in the course of an extirpative procedure can affect quality of life—larger resections generally result in worse functional outcome<sup>16</sup>. In an effort to maximize the therapeutic ratio, historic multidisciplinary guidelines recommended that severe dysplasia (carcinoma in-situ) and invasive carcinoma at the margin be considered a ‘positive margin’<sup>17</sup> warranting the morbidity of additional resection, while both moderate and mild dysplasia at the margin did not warrant further therapy.

The prognostic importance of severe dysplasia at the margin appears significant, although the true impact is difficult to estimate because such cases are typically reported as ‘positive margin’ in retrospective reports. The prognostic importance of moderate and mild dysplasia at the margin is relatively unknown, because dedicated reports describing the outcomes of these patients are rare and management techniques range from re-excision for any dysplasia<sup>18</sup> to close observation<sup>19</sup>. Current CAP (College of American Pathologists) guidelines have recently been amended to recommend that both severe and moderate

dysplasia at resection margins of oral cavity cancers be characterized as “positive” margins<sup>20</sup>.

At this institution moderate dysplasia at the margin has not been considered an involved margin justifying further therapy (e.g. additional resection or postoperative radiotherapy). Hence, it is possible to perform a retrospective analysis of patients with early oral tongue cancer managed with surgery alone to evaluate the impact of dysplasia at the resection margin.

## Materials and Methods

We retrospectively identified 126 consecutive patients with early stage squamous cell carcinoma of the oral tongue who were treated with primary surgical resection alone from 1990 – 2010. Inclusion criteria were American Joint Committee on Cancer (AJCC) T1-2, N0 squamous cell carcinoma of the oral tongue with definitive surgical resection performed at Fox Chase Cancer Center. Patients who received postoperative radiation for accepted indications<sup>8</sup> were considered representative of a higher risk population and were excluded. Neck dissection was performed according to guidelines of acceptable surgical practice<sup>21</sup>. Patient demographics, tumor characteristics and treatment related outcomes were abstracted from the relevant medical records in accordance with a Fox Chase Cancer Center Institutional Review Board-approved protocol and the Health Insurance Portability and Accountability Act.

All patients underwent primary tongue surgery as definitive management of their cancer. Patients presenting from an outside institution after a diagnostic excisional biopsy were submitted to additional wide local resection/partial glossectomy to confirm adequate surgical clearance of tumor. In the instance of prior excisional biopsy, the margins from the institution’s definitive resection were considered the final margins.

In a typical case a glossectomy specimen was excised with clinically appropriate margins and sent to the Pathology laboratory for analysis. Additional specimens were taken from the patient’s clinically uninvolved tissue and sent for intraoperative frozen section analysis. Margins deemed close or involved (by the pathologist in discussion with the surgeon) were additionally excised. This process was repeated until any cancer or severe dysplasia was cleared (most commonly with a single additional excision) or anatomic constraints prevented further resection. Although the decision to re-resect a margin was based on frozen section analysis at the time of resection, it was the final, permanent section of the separately submitted margin that was interpreted as the true margin for this retrospective analysis. In instances when no re-excision of a margin was performed, the permanent margin of the oriented primary specimen was interpreted as the true margin.

Dysplasia was reported as either mild, moderate, or severe according to the World Health Organization criteria<sup>22</sup>. Severe dysplasia at an initial frozen-section margin was additionally excised, while severe dysplasia appearing on a final margin was recommended additional resection as a separate surgical procedure. During the study period moderate and/or mild dysplasia at the margin was not re-resected when assigned on frozen section analysis and

was not considered an indication for postoperative therapy when it appeared on permanent sections.

Tumor and margin characteristics were abstracted from the original surgical pathology analysis. A local recurrence was defined as one involving the tongue/floor of mouth – ‘elsewhere’ oral cavity tumors were interpreted as second tumors rather than as recurrences. Neck nodes above the supraclavicular fossa were interpreted as regional recurrences. All other recurrences were interpreted as distant. As there is no consensus threshold that separates true local recurrence from second primary tumors, we evaluated oral tongue cancers occurring both 3 and 5 years after initial resection as second primary tumors in separate analyses.

Overall survival (OS), disease-free survival (DFS) and local control (LC) were calculated using the Kaplan Meier method. The impact of any grade dysplasia at the margin was investigated as was the impact of either moderate or severe dysplasia (together) at the margin. Univariate and multivariate analyses were performed to evaluate potential predictors of OS, DFS and LC. Covariates investigated included: age, tobacco pack years, pathologic T stage, histologic grade, skeletal muscle involvement (intrinsic musculature of the tongue – a surrogate for depth of invasion), dysplasia at margin, tumor differentiation and neck dissection.

The endpoints of the study were Overall survival (OS), disease-free survival (DFS) and local control (LC) respectively. Patient demographic characteristics and tumor staging factors were assessed in regard of associations with the endpoints. Univariate analysis was performed using Kaplan-Meier estimation and log-rank test. Multivariable analysis (MVA) was done via a multiple Cox regression. Both analyses were performed on the three endpoints respectively. A p-value <0.05 was considered significant. All analyses were carried out with SAS 9.2.

## Results

A total of 126 patients with 131 tumors met the inclusion criteria. Patient, tumor and treatment characteristics are detailed in Table 1. The median patient age was 62 years (range: 20–98), 76% had a history of tobacco use including 24% who were actively using tobacco at diagnosis. Seventy-one percent of the primary surgical procedures were performed at our institution, while the remaining 29% were re-operations after excisional biopsies performed elsewhere. A neck dissection was undertaken on 51% of patients, and was defined as “supraomohyoid” in 90% of these patients. Pathologic evaluation revealed that 81% of our cohort had pT1 cancers, and that all close or positive margins were resected to tumor-free margins. Dysplasia was present at a final margin in 36% of the cases (severe: 9%, moderate: 15%, mild: 12%) and was identified only on permanent pathologic section in 50% of cases.

With a median follow-up of 52 months (range: 1–250), the 3- and 5-year actuarial LC, DFS and OS for the entire cohort was 77% and 76%, and 84% and 73%, 72% and 74%, respectively. Overall, 27 patients developed recurrent disease within 3 years of initial

surgery, including 16 local recurrences (12%), 10 regional recurrences (8%) and 1 distant failure (1%). Re-evaluation of outcomes within 5 years of the original operation increased local recurrences only (n = 19, 15%). The local control (80 v 71%, p = 0.43) and disease free survival (78 v 71%, p = 0.53) detriments of dysplasia at the margin were not significant at 3 years after complete resection but were approaching significance by 5 years of follow-up (LC: 80 v 60%, p = 0.12 and DFS: 78 v 60%, p = 0.17). Given the worsening LC and DFS as follow-up lengthened of patients with dysplasia at the margin the data were interrogated in terms of a 5-year determinant of true local failures.

We elected to initially evaluate moderate dysplasia and severe dysplasia at the margin together secondary to seemingly similar clinical behavior of the two variables (Figure 1). This conclusively demonstrated worse local control for moderate/severe dysplasia at the margin (82% v 49%, p = 0.005). Similar to local control data, the importance of either moderate or severe dysplasia at the margin influenced DFS (80% v 49%, p = 0.008). We then evaluated each degree of dysplasia at the margin separately. This demonstrated that, despite similar rates at five years, only moderate dysplasia at the margin (49% local control, p = 0.02) was still significant while severe dysplasia at the margin was approaching significance (54% local control, p = 0.1). This was thought to be secondary to less instances of severe dysplasia at the margin (n = 12) than moderate (n = 21). Other factors that approached significance were neck dissection performed (p = 0.16) and poor histologic grade (p = 0.09). Five year overall survival was 74% for the entire population and not influenced by the presence of dysplasia (Table 2) at the margin (p = 0.6).

Two multivariate analyses (MVA) of locoregional control and disease free survival were performed; one that evaluated moderate and severe dysplasia together and another that evaluated all degrees of dysplasia separately. When evaluated together, the MVA demonstrated that moderate and severe dysplasia at the margin (p = 0.007), an observed neck (p = 0.04) and poorly differentiated histology (p = 0.009) were predictive of locoregional recurrence (Table 3). Evaluation of disease-free survival with a similar MVA demonstrated that only moderate or severe dysplasia at the margin (p = 0.008) and poorly differentiated histology were significant (Table 4). A second MVA was then run that evaluated all degrees of dysplasia at the margin separately. This demonstrated that only moderate dysplasia at the margin (p = 0.036), poor histologic grade (p = 0.0078), and an observed neck (p = 0.04) were predictive of local recurrence (Table 3). Evaluation of DFS with a similar MVA demonstrated that both moderate dysplasia at the margin (p = 0.036) and poorly differentiated histology (p = 0.011) were associated with recurrence.

## Discussion

The pathologic evaluation of oral epithelial dysplasia, dependent upon the thickness of the involved epithelium, is subject to significant intra- and inter-observer differences in the grading of specimens. Institution of guidelines<sup>22</sup> has improved intra-observer grading<sup>23</sup>, but an undefined amount of subjectivity persists. Progression to invasive cancer is best characterized for severe dysplasia and carcinoma in situ<sup>24</sup>, and is thought to be mediated by p53 mutations<sup>25</sup>.

When dysplasia is encountered at the margin of a head and neck cancer resection, it has been common to extrapolate from the experience of dysplasia unassociated with invasive cancer to determine the need for further therapy. As a consequence, at Fox Chase Cancer Center, mild dysplasia at the margin is observed. All patients are counseled to discontinue exposure to potential environmental carcinogens (ethanol, tobacco, and mouth rinses containing alcohol). Similarly, severe dysplasia at the margin is re-resected until cleared during the initial operative procedure. In settings where severe dysplasia cannot be cleared, it is treated as a surrogate of residual disease and postoperative radiotherapy is typically recommended<sup>8</sup>.

Moderate dysplasia at the margin has not been widely interpreted as an indicator for additional therapy and has often been approached expectantly. Recently, CAP guidelines were updated to recommend that both moderate and severe dysplasia at the margin be considered “positive” margins<sup>20</sup>. This study evaluates the consequences of an expectant approach (observation) to moderate dysplasia at the margin. It relied upon dysplasia grading performed by multiple staff pathologists and fellows over a 20-year time period that was abstracted from the medical chart. There was no re-grading of material. Hence, these results reflect everyday practice at a National Cancer Institute designated Comprehensive Cancer Center. It suggests that moderate or severe dysplasia present at the final margin raises risk of local recurrence and worsens disease-free survival. A small number of patients ( $n = 12$ ) with severe dysplasia at the margin were recommended to receive further therapy (either re-resection or postoperative radiotherapy) and for a variety of reasons never received the proposed treatment. In addition to analyzing moderate and severe dysplasia together, we analyzed all degrees of dysplasia separately in an attempt to determine if the patients with severe dysplasia were influencing the results (as they did not receive recommended therapy). This demonstrated that moderate dysplasia at the margin was independently indicative of increased local recurrence ( $p = 0.02$ ) and worse disease-free survival ( $p = 0.03$ ). The effect of severe dysplasia was not significant for either local control ( $p = 0.12$ ) or disease free survival ( $p = 0.16$ ), despite a similar hazard ratio, likely secondary to limited patient numbers. As expected, mild dysplasia was not associated with worse local control ( $p = 0.63$ ) or disease-free survival ( $p = 0.57$ ).

To investigate potentially prognostic clinical and pathologic variables a multivariate analysis was undertaken. This evaluation is unique because all patients included were considered at ‘low risk’ and received no postoperative therapy. One might expect that no factors are independently associated with failure in such a cohort. However, three factors were found to be significant for locoregional failure - moderate or severe dysplasia at the margin, poor histologic grade, and no neck dissection performed. A disease-free survival MVA similarly demonstrated the significance of moderate dysplasia at the margin and poorly differentiated histology. A second MVA was performed to investigate the effect of both moderate and severe dysplasia at the margin separately. This demonstrated findings similar to when moderate and severe dysplasia were analyzed together, seeming to confirm that both moderate and severe dysplasia at the margin herald an increased risk of recurrence.

As the dominant mode of recurrence was local (63% of recurrences), it is difficult to interpret the significance of a local control detriment of a clinically observed neck, as this



variable would not be expected to influence local (tongue) failure, and is perhaps reflection of limited power in a relatively small data set. Nonetheless, it reinforces the importance of appropriate use of a neck dissection in seemingly ‘low-risk’ oral tongue cancers. Poor differentiation is a known risk factor for oral tongue treatment failure<sup>26</sup>. Oral tongue cancer depth of invasion is an accepted indication for elective therapy to the neck<sup>21,27,28</sup>. Given the retrospective nature of this analysis, we did not have depth of invasion data for all tumors. Skeletal muscle invasion, a surrogate for depth of invasion, demonstrated a detriment to DFS that was approaching significance, further suggesting that deeper tumors seem to display a higher propensity for failure, absent postoperative treatment. Finally, this analysis is the first to suggest that moderate dysplasia at the margin is suggestive of not just worse locoregional control, but also of worse disease free survival.

## Conclusions

The presence of moderate or severe dysplasia at the margin is strongly correlated with inferior local control and potentially with worse disease-free survival. In the absence of well-tolerated postoperative therapy with reversible toxicity additional excision in an effort to clear moderate dysplasia at the margin is justified, despite added morbidity. Whether postoperative radiotherapy or chemoprevention can improve the poor prognosis of patients with persistent dysplasia at the margin warrants prospective investigation.

## Acknowledgments

This publication was supported by grant number P30 CA006927 from the National Cancer Institute, NIH. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

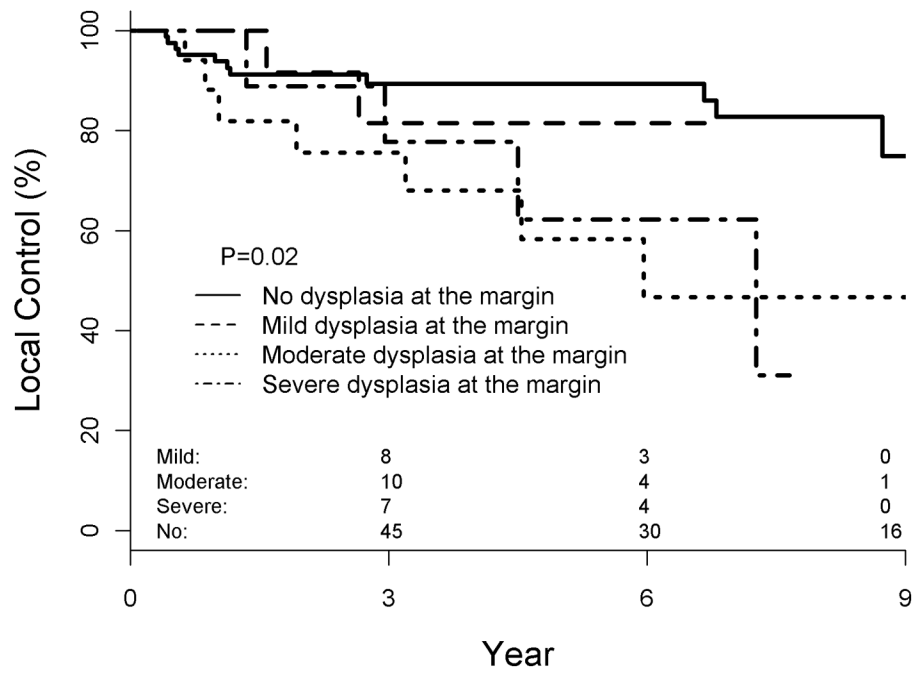
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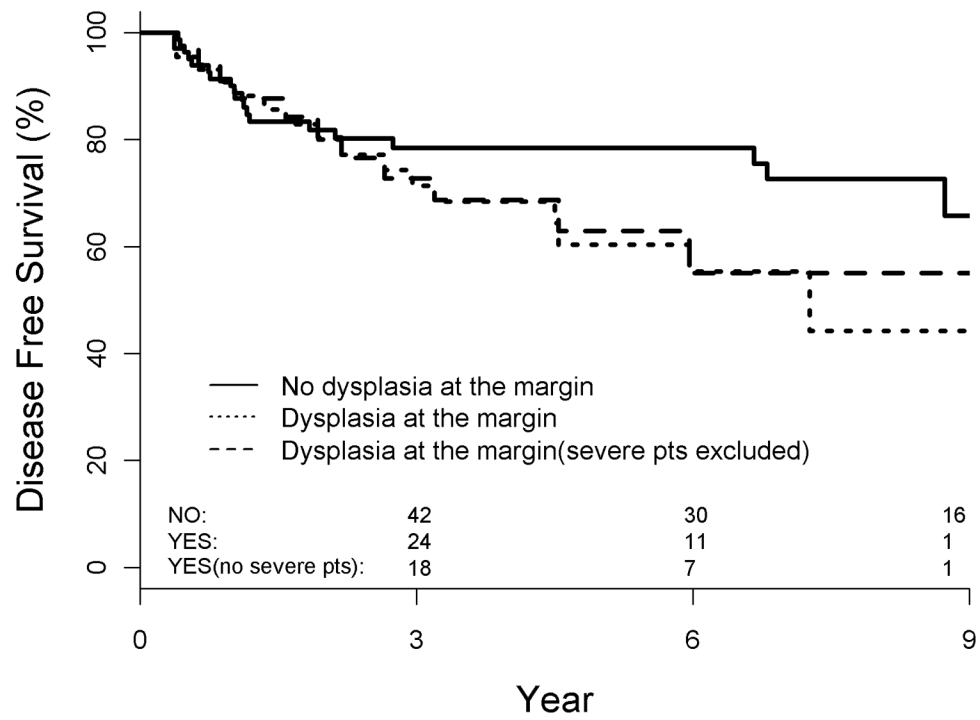
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**Figure 1.**  
Locoregional control as a function of dysplasia at the final surgical margin



**Figure 2.**  
Disease-free survival as a function of dysplasia at the final surgical margin

**Table 1**

## Clinical/pathologic characteristics

Characteristic	Number of Patients (%)
Age (years)	
<60	61 (47)
>60	70 (53)
Sex	
Male	73 (56)
Female	58 (44)
Tobacco use	
Current	32 (24)
History	68 (52)
Never	31 (24)
Clinical Tumor Stage	
cT1	86 (66)
cT2	29 (22)
cTx	16 (12)
Pathologic Tumor Stage	
pT1	105 (80)
pT2	23 (18)
pTx	3 (2)
Neck Dissection	
None	64 (49)
Supraomohyoid (SOH)	60 (46)
Modified Radical (MRND)	7 (5)
Histologic Grade	
Well	22 (19)
Moderate	68 (57)
Poor	21 (18)
n/a	8 (6)
Dysplasia at Final Margin	
No	83 (63)
Yes	48 (37)
Grade of Dysplasia at Final Margin	
Mild	15 (31)
Moderate	21 (44)
Severe	12 (25)

Characteristic	Number of Patients (%)
Skeletal (Intrinsic) Muscle Invasion	
No	91 (69)
Yes	40 (31)

**Table 2**

## 5-year actuarial outcomes

	<b>LC</b>	<b>DFS</b>	<b>OS</b>
Overall	73%	72%	74%
No dysplasia at the margin	80%	78%	72%
Any dysplasia at the margin	60%	60%	77%
Severe dysplasia at the margin	54%	54%	74%
Moderate dysplasia at the margin	49%	49%	77%
Mild dysplasia at the margin	81%	81%	76%



**Table 3**

Multivariate analysis of potentially predictive factors of local control

Variable	Comparison	Hazard Ratio	p- value	Hazard Ratio	p- value
Dysplasia at margin	Moderate/Severe v Mild/None	2.99 (1.35–6.61)	0.0067		
Dysplasia at margin	Severe v None			2.94 (0.91–9.49)	0.071
Dysplasia at margin	Moderate v None			2.72 (1.07–6.89)	0.036
Dysplasia at margin	Mild v None			0.62 (0.13–2.77)	0.53
Histologic Grade	Poor v Well/Mod/Unk	3.47 (1.36–8.83)	0.0090	3.63 (1.40–9.37)	0.0078
Pack years	Continuous	0.99 (0.98–1.01)	0.72	0.99 (0.98–1.01)	0.73
Neck Dissection	No vs yes	2.59 (1.03–6.49)	0.043	2.61 (1.05–6.55)	0.040
Age	Continuous	1.00 (0.98–1.03)	0.96	1.00 (0.98–1.03)	0.97
Skeletal Muscle	Yes v No	1.80 (0.82–3.94)	0.14	1.80 (0.82–3.94)	0.14
pT	2 v 1	1.76 (0.59–5.23)	0.31	1.70 (0.58–5.02)	0.34

**Table 4**

Multivariate analysis of potentially predictive factors of disease-free survival

Variable	Comparison	Hazard Ratio	p- value	Hazard Ratio	p- value
Dysplasia at margin	Moderate/Severe v Mild/None	2.84 (1.30–6.19)	0.0086		
Dysplasia at margin	Severe v None			2.57 (0.81–8.16)	0.11
Dysplasia at margin	Moderate v None			2.66 (1.07–6.64)	0.036
Dysplasia at margin	Mild v None			0.57 (0.13–2.54)	0.46
Histologic Grade	Poor v Well/Mod/Unk	3.21 (1.27–8.08)	0.013	3.34 (1.31–8.53)	0.011
Pack years	Continuous	0.99 (0.97–1.01)	0.86	0.99 (0.99–1.01)	0.90
Neck Dissection	No vs yes	2.18 (0.91–5.23)	0.082	2.20 (0.92–5.25)	0.077
Age	Continuous	1.01 (0.98–1.03)	0.66	1.01 (0.91–1.03)	0.65
Skeletal Muscle	Yes v No	1.97 (0.92–4.22)	0.08	1.98 (0.92–4.23)	0.080
pT	2 v 1	1.46 (0.51–4.24)	0.48	1.42 (0.49–4.09)	0.51