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Clinical and Histological Determinants of Mortality for Patients with Barrett's Esophagus-related T1 Esophageal Adenocarcinoma

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Abstract

BACKGROUND & AIMS—Superficial (T1) esophageal adenocarcinoma (EAC) is commonly treated by endoscopic resection, yet little is known about factors that predict outcomes of this approach. We assessed clinical and histologic variables associated with overall survival times of patients with T1 EAC who received therapy.

METHODS—In a retrospective analysis, we collected data from patients who underwent endoscopic mucosal resection (EMR) for T1 EAC (194 with T1a and 75 with T1b) at the Mayo Clinic, from 1995 through 2011. EMR specimens were systematically reviewed for depth of invasion, presence of lymphovascular invasion, grade of differentiation, and status of resection margins. Kaplan-Meier curves and proportional hazards regression models were used in statistical analyses.

RESULTS—Demographic characteristics were similar between patients with T1a and T1b EAC. Overall survival at 5 years following EMR was 74.4% for patients with T1a (95% confidence interval [CI], 67.6%–81.8%) and 53.2% for patients with T1b EAC (95% CI 40.3%–70.1%). Of surviving patients with T1a EAC, 94.1% remained free of cancer (95% CI, 89.8%–98.5%), and

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94.7% of surviving patients with T1b EAC remained free of cancer (95% CI, 85.2%–100%). A multivariable model associated older age (per 10-year increment), evidence of lymphovascular invasion, and deep margin involvement with reduced overall survival in patients with T1 EAC

CONCLUSION—Systematic assessment of EMR specimens can help predict mortality and potentially guide treatment options for patients with T1 EAC.

Keywords

tumor progression; endoscopic therapy; esophageal cancer; prognostic factor

BACKGROUND

Endoscopic therapy has gained acceptance as the treatment of choice for Barrett's esophagus (BE) with intramucosal esophageal adenocarcinoma (T1a EAC).¹ Overall survival in patients treated endoscopically is comparable to patients treated with esophagectomy with lower morbidity and mortality.^{2–6} Endoscopic therapy involves a combination of endoscopic mucosal resection (EMR) of visible lesions followed by endoscopic ablation. EMR serves both diagnostic and therapeutic purposes, as the EMR specimen(s) allow accurate evaluation of depth of invasion and margin assessment, in addition to providing other histological prognostic variables such as grade of differentiation and presence or absence of lymphovascular invasion (LVI).⁷

Several surgical series have looked at the depth of invasion and its association with lymph node metastases (LNM). A recent meta-analysis showed that T1a EAC is associated with low rates of metastatic lymphadenopathy (<2%).⁸ In contrast, rates are higher with sub-mucosal invasion (20–30%).^{9–12} Other histological factors that have been associated with a greater rate of LNM include the presence of LVI and poor grade of differentiation.^{9, 13}

Few studies have looked at the influence of histologic characteristics and other clinical variables on overall survival of subjects treated endoscopically for T1 EAC.¹⁴ Identification of prognostic determinants on long-term outcomes in subjects with T1 EAC may help with patient risk stratification and tailoring of treatment. For this purpose, we aimed to comprehensively assess the influence of clinical and histological variables on overall survival in a large cohort of patients treated endoscopically at our institution's specialized BE Unit.

METHODS

Study Population and Study Design

This is a retrospective cohort study using data from a prospectively maintained database of patients with T1 EAC who underwent EMR between 1995 through 2011 at our institution. Patients were referred for endoscopic treatment of T1 EAC or were enrolled in a multidisciplinary treatment program. Patients were treated with a combination of EMR followed by ablative techniques. Baseline clinical characteristics were obtained at time of EAC diagnosis. Patients were followed from diagnosis to date of last clinical encounter or death.

Endoscopic Evaluation

All patients underwent esophagogastroduodenoscopy (EGD) with a detailed examination of the Barrett's mucosa and standardized surveillance consisting of four quadrant biopsies every 1–2 cm every 3 months. Mucosal irregularities were targeted with the Duette multiband mucosectomy (Cook Ireland, Limerick, Ireland), EMR cap (EMR-001, Olympus America Inc, Center Valley, PA), variceal ligation with snare (Bard Interventional Products, Billerica, MA) or snare alone techniques.¹⁵ Endoscopic characteristics of the lesions including number, size and appearance were reported. Endoscopic ultrasound (EUS) was used to assess the extent of disease (using standard TNM criteria). Fine needle aspiration of suspicious lymph nodes was preformed when clinically indicated. Computerized tomography (CT) scans of the chest, abdomen and pelvis and/or positron emission tomography (PET) scans were used to exclude distant metastasis (performed since 2003).

Histopathological Assessment

The initial diagnosis of T1 EAC in this patient cohort was established by two experienced gastrointestinal pathologists following a published protocol.¹⁵ T1a EAC was defined as tumor demonstrating invasion into the lamina propria (LP) or muscularis mucosae (MM). T1b EAC was defined as tumor invading the submucosa (SM). EMR histology was systematically reviewed to assess (1) tumor grade (well, moderate or poorly differentiated), (2) depth of invasion (LP, MM, SM), (3) presence or absence of LVI, (4) status of deep and lateral margins (positive or negative for carcinoma). Tumor grade was based upon standard histologic features, including percent of gland formation, growth pattern, and degree of cytologic and nuclear atypia. (Figure 1)

LP invasion was defined as penetration of the basement membrane by neoplastic cells, which included isolated malignant cells within the LP as well as larger proliferations of glands demonstrating architectural complexity which exceeded that of high grade dysplasia. MM invasion was defined as the presence of infiltrative glands within the smooth muscle fibers of a single MM, the space between duplicated layers of the MM, or the outer layer of the MM. The majority of EMR specimens do not extend to the level of the MP. Mistaking a duplicated layer of MM for MP is a known pitfall of EMR evaluation given the variable depth of endoscopic mucosal resection.¹⁶ To minimize the chances of overcalling invasion into the space between duplicated MM as true submucosal invasion, we classified a tumor as demonstrating SM invasion when it (1) extended beyond a duplicated layer of MM, (2) involved a tissue plane containing submucosal glands, or (3) was adjacent to large caliber arterial branches which would not be present in the mucosa. Surgical resection specimens were reviewed to confirm depth of invasion in those patients who subsequently underwent esophagectomy.

LVI was defined as the presence of clusters of malignant cells within an endothelial-lined vascular channel. In clinical practice, LVI determination is an H&E diagnosis so immunohistochemical studies to highlight lymphatic or vascular spaces were not used. Any case which may have represented retraction artifact was excluded. All foci of LVI were agreed upon with consensus of both pathologists.

EMR specimens were inked at the time of grossing and serially sectioned in a previously reported protocol.¹⁵ A margin was considered positive for carcinoma if malignant glands extended to the inked surface or into the cautery zone of the EMR.

Survival Data

Survival data (vital status and death date as of November 30th, 2011) information was assessed by using an institutionally approved internet research and location service (www.accurint.com). Cause of death was obtained from either medical records or review of death certificates. Cancer free survival was assessed by reviewing endoscopy and histology reports. Cancer remission was defined as the absence of carcinoma or dysplasia at surveillance biopsies on two consecutive follow-up endoscopies. Recurrence of cancer was established when surveillance biopsies showed evidence of carcinoma following remission.

Statistical Analyses

Baseline characteristics are summarized as mean (SD) or median (IQR) for continuous variables and proportions for categorical variables. The Kaplan-Meier method was used to summarize overall and cancer free survival. The association of tumor status (T1a EAC vs T1b EAC) with endoscopic and histologic characteristics was assessed using contingency table analysis for discrete characteristics and the Wilcoxon rank sum test for quantitative characteristics.

Predictors of overall and cancer free survival in T1a EAC were assessed using proportional hazards regression models. The predictors included age (per 10 years), gender, length of BE segment, grade of differentiation (well, moderate, poor), LVI (yes, no), deep margin involvement (positive, negative) and lateral margin involvement (positive, negative). A model adjusting for age and gender was used to assess the association of length of BE segment, grade of differentiation, LVI, deep and lateral margin involvement with overall survival.

RESULTS

A total of 269 patients diagnosed with T1 EAC were identified and included in the study. Overall, 194 (72.1%) patients were diagnosed with T1a EAC while 75 (27.9%) had T1b EAC. (Figure 2) The majority of patients (86%) were male with a mean (SD) age at time of diagnosis of 70 (10) years. Baseline patient characteristics are summarized in Table 1. Patients were followed for a median (range) of 4.2 (3.0) years since time of EAC diagnosis. A total of 118 patients treated with endoscopic therapy were alive at time of study conclusion of which 109 (93%) had endoscopic surveillance at our institution.

Patients with T1a EAC had a longer BE segment compared to patients with T1b EAC (4.9 versus 4.4 cm, respectively) ($p=0.14$). The mean (SD) number of mucosal lesions identified per EGD was 1 (0.5) with a mean (SD) size of 0.8 (0.9) cm. The mean (SD) number of EMRs per EGD was 2.5 (1.6). Cancer staging performed with a combination of EUS, CT of the chest, abdomen and pelvis and/or PET CT is described in supplementary table 1.

A total of 152 (78%) patients with T1a EAC were treated with endoscopic therapy alone and did not undergo subsequent esophagectomy. From this group, 81 (53%) patients received ablative therapy of which 52 (64%) received photodynamic therapy alone, 25 (31%) received radiofrequency ablation alone and 4 (5%) a combination of both. A total of 39 (52%) patients with T1b EAC were treated with endoscopic therapy alone of which 24 (62%) patients were not considered appropriate surgical candidates for esophagectomy, 12 (31%) patients did not wish to pursue surgery and 3 (7%) patients were lost to follow-up. A total of 18 (24%) patients with T1b EAC were treated with ablative therapy of which 12 (67%) received photodynamic therapy alone, 5 (28%) received radiofrequency ablation alone and 1(5%) a combination of both.

Overall, 42 (22%) patients with T1a and 36 (48%) patients with T1b EAC underwent esophagectomy. 4 patients in the T1a group and 9 patients in the T1b group received endoscopic therapy (defined as >1 endoscopic session involving EMR and/or ablative therapy) prior to esophagectomy. A total of 28 of 42 subjects with T1a EAC underwent esophagectomy before 2005, likely in accordance with the standard of care at the time, without additional EMR or ablation sessions. The indication for esophagectomy in the remaining T1a EAC patients was multifocal disease (N=6), failure of endoscopic therapy (N=4) and patient's personal choice (N=4). A total of 25 (60%) esophagectomy specimens from T1a patients showed residual EAC (T1, N=20; T2, N= 5) of which 8 (19%) had evidence of LNM. A total of 19 (53%) esophagectomy specimens from T1b patients showed residual EAC (T1, N=17; T2, N=2) of which 6 (17%) had evidence of LNM. 18 patients with LVI on EMR underwent esophagectomy with 4 (22%) patients having evidence of LNM in their surgical specimens (T1a EAC, N=2; T1b EAC, N=2).

Histological assessment of EMR specimens indicated a significant association ($p<0.001$) with tumor status, most T1a cancers (81%) were well or moderately differentiated compared to a lower proportion of T1b EAC (60%) tumors. Depth of invasion into the LP and MM was present in 43 (22%) and 151 (78%) of T1a EAC cases respectively. A significant association of tumor status with LVI was observed ($p<0.001$), with 23 (12%) T1a and 30 (40%) T1b EAC cases showing evidence of LVI. Deep and lateral EMR margins were positive in 39 (20%) and 113 (59%) of T1a EAC cases and 50 (67%) and 66 (88%) of T1b EAC cases respectively, ($p<0.001$, for both).

Complete remission of dysplasia was significantly associated with tumor status ($p<0.001$). 70.2% of patients in the T1a EAC and 26.7 % in the T1b EAC group achieved remission by 12 months, respectively. There was no significant association of tumor status with recurrence of cancer ($p=0.72$).

Histopathology at time of last endoscopic follow up for T1 groups is described in Figure 2. There was a significant association of tumor status with histopathology at the time of last endoscopic follow-up, ($p<0.001$). A total of 9 patients (T1a EAC, N=8; T1b EAC, N=1) had recurrence of carcinoma and 11 patients (T1a EAC, N=10; T1b EAC, N=1) had recurrence of dysplasia that was managed with endoscopic mucosal resection.

In patients with T1a EAC the overall survival and cancer free survival at 5 years was 74.4% (95% CI 67.6–81.8) and 94.1% (95% CI 89.8–98.5) respectively. In patients with T1b EAC the overall survival and cancer free survival at 5 years was 53.2% (95% CI 40.3–70.1) and 94.7% (95% CI 85.2–100) respectively. Figure 3 shows overall and cancer free Kaplan-Meier estimated survival curves in T1 EAC patients with and without evidence of LVI.

The cause of death was identified in 32 out of 91 patients. We were unable to obtain death certificates from 59 patients who passed away in 12 states due to privacy laws. The cause of death per group is described in Table 2. There was no association between availability of death certificates and any of the prognostic variables assessed. (Supplementary Table 2) The baseline characteristics of the 10 patients who died of EAC were found to be comparable between T1a and T1b EAC groups. (Supplementary Table 3)

A multiple variable model assessing predictors of overall survival in T1 EAC indicated that older age (age per 10 year increment) (HR 1.71 95%CI 1.36–2.17, $p<0.001$), presence of LVI (OR 1.95 95%CI 1.18–3.22 $p=0.009$) and deep margin involvement by carcinoma (HR 1.67 95%CI 1.09–2.55 $p=0.02$) were associated with decreased overall survival. A model for T1aEAC patients indicated an association between decreased overall survival and age (age per 10 years) (HR 1.85 95%CI 1.38–2.47 $p<0.001$) and a model for T1bEAC patients indicated an association between decreased overall survival, age (age per 10 years) (HR 1.46 95%CI 0.99–2.15, $p=0.05$) and presence of LVI (OR 2.16 95%CI 0.99–4.72, $p=0.05$). (Table 3) The remaining factors including gender, length of BE segment, grade of differentiation and lateral margin involvement were not significantly associated with overall survival. Univariate analysis of predictors of cancer free survival revealed a borderline significant association with lymphovascular invasion (HR 3.68, 95% CI 0.89, 15.22, $p=0.07$) and increased BE segment length (HR 1.14 (95% CI 0.98, 1.32, $p=0.10$) for predicting increased risk of recurrence (Supplementary Table 4).

A multiple variable model assessing histological predictors for LVI including depth of invasion and grade of differentiation did not find a significant association between these variables and the presence of LVI.

DISCUSSION

Endoscopic therapy is considered an effective alternative to esophagectomy for a select patient population with early EAC.^{2–6} In the present study we aimed to determine the influence of demographic and histological variables on overall survival in a cohort of patients treated with endoscopic therapy for T1 EAC. EMR specimens were meticulously reviewed to assess histologic variables. We determined that older age, evidence of LVI and deep margin involvement were histological factors associated with decreased overall survival in patients with T1 EAC. Presence of LVI and a longer BE segment may predict higher recurrence risk.

Surgical series have shown that increased tumor size, poor differentiation and presence of LVI are histological characteristics associated with the risk of LNM.^{9,10, 11, 14} A surgical series of 258 patients who underwent esophagectomy for T1 EAC found LVI to be the

strongest predictor of LNM based on a scoring system that incorporated tumor size, depth of invasion and grade of differentiation.¹¹ Evaluation of LNM in series on endoscopic therapy for T1 EAC has been limited by the detection accuracy of imaging modalities including EUS, CT and PET CT.¹⁷ The focus of these series has, by the most part, been on the association of clinical and demographic risk factors on overall survival and recurrence of neoplasia.^{15, 18, 19} Risk stratification is important when selecting therapeutic options for patients with T1 EAC. Our study demonstrates that careful and systematic evaluation of EMR specimens can offer insight into patient outcomes and may help guide therapeutic decision making.

Our findings suggest that assessment for LVI is important as it is associated with a decreased overall and cancer free survival in patients with T1 EAC - this association appears to be stronger among patients with T1b EAC. In a surgical series overall survival of T1 EAC patients with LVI was lower (36%) compared to patients without LVI (85%).¹⁴ To our knowledge, this is the first study to demonstrate this in subjects treated endoscopically. In our cohort, a total of 23 (11.9%) T1a and 30 (40.4%) T1b EAC cases showed evidence of LVI. This is comparable to previously published estimates (0–18%).⁸ 18 patients with LVI on EMR underwent esophagectomy and 4 (22%) patients had evidence of LNM in their surgical specimens (T1a EAC, N=2; T1b EAC, N=2). The prevalence of LNM following surgical resection in patients with LVI on EMR specimens was comparable to a surgical series of 126 T1EAC patients where LNM was found in 35.7% of patients with LVI on esophagectomy specimens.⁹ This suggests that assessment for LVI is feasible using EMR specimens despite differences in size between EMR and esophagectomy specimens.

Given the observed association between LVI and mortality, we looked for histological predictors for LVI including depth of invasion and grade of differentiation in a model adjusted for age and gender and did not find a significant association between these variables and the presence of LVI.

A recent meta-analysis suggests that the strongest risk for LNM appears to be depth of invasion in T1 EAC.⁸ Our study confirms this finding as we observed a survival advantage in T1 EAC patients who lacked deep margin involvement. This association was not statistically significant when the patients were divided into T1a and T1b EAC subgroups likely due to loss of power to model this effect in the individual subgroups.

The overall survival at 5 years for patients with T1a EAC (74.4%) was superior to that of patients with T1b tumors (53.2%) in our study and comparable to 5 year survival rates from previous endoscopic and surgical series.¹⁵ Though we observed a higher than expected rate of LNM among T1 patients who underwent esophagectomy (T1a, 19%; T1b, 16%), it is important to recognize that the majority of T1a patients (78%) were successfully treated with endoscopic therapy alone as compared to T1b patients (52%) and in this context, the rate of LNM among all T1 patients (T1a, 4.1%; T1b, 8%) was similar to previously published series.^{9, 11} Several patients with T1a EAC who were treated with esophagectomy were those who failed endoscopic therapy or had multifocal disease. These patients likely had a more biologically aggressive phenotype compared to those who responded to endoscopic therapy. Patients with T1a EAC who underwent esophagectomy in this study

had a higher rate of poor prognostic factors such as poor differentiation, LVI and positive deep and lateral margins. (Supplementary Table 5) Also, patients who died of EAC had a higher prevalence of LVI and deep margin positive resections. (Supplementary Table 6) This likely accounts for the higher rate of LNM in this cohort of subjects compared to earlier reports from our center.

We performed an extensive search for cause of mortality that was limited in part by individual state privacy laws. However we did not find any association between the availability of a death certificate and prognostic factors assessed, making the likelihood of a selection bias low. From the partial information we acquired we were able to determine that 4 patients in the T1a group and 6 patients in the T1b group died of metastatic EAC. It is also likely that overall mortality is influenced by medical comorbidities.

The management of BE has changed significantly over the past decade with potential implications on overall mortality and cancer specific survival. We performed a univariate analysis stratified by date of initial cancer diagnosis (1995–2004, 2005–2011) and treatment modality (esophagectomy versus endoscopic therapy) that did not show a difference in overall mortality between groups suggesting our results to be independent of these variables. (Supplementary Table 7)

Our study has several strengths including the systematic review of EMR specimens by two experienced gastrointestinal pathologists following a published protocol.¹⁵ This includes assessment for duplication of the MM to minimize the chances of overdiagnosing submucosal invasion. Our histological assessment of EMR specimens did not rely on immunohistochemical studies and hence can be directly translated into clinical practice. Furthermore, we used a prospectively maintained database of T1 EAC patients and performed a comprehensive review of medical records for demographic and clinical information.

In conclusion, the present study assessed cancer remission and overall survival in a cohort of patients treated with endoscopic therapy for T1 EAC. We demonstrate that systematic assessment of EMR specimens can help predict mortality and potentially guide treatment options in this patient population. We propose that the presence of LVI in EMR specimens should be regarded as a risk factor for mortality and patients with permissive co-morbidities should be referred for evaluation for esophagectomy. It is likely safe to continue endoscopic therapy in patients without LVI and deep margin involvement in EMR specimens and who otherwise have no evidence of invasive EAC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

BE	Barrett's esophagus
CI	Confidence interval
CT	Computed tomography
EAC	Esophageal adenocarcinoma
EGD	Esophagogastroduodenoscopy
EMR	Endoscopic mucosal resection
EUS	Endoscopic ultrasound
HR	Hazards ratio
LVI	Lymphovascular invasion
LM	Lamina propria
LNM	Lymph node metastasis
MM	Muscularis mucosae
PET	Positron emission tomography
SM	Submucosa

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FIGURE 1.

Histopathological assessment of endoscopic mucosal resections. (A) T1a esophageal adenocarcinoma was defined as tumor demonstrating invasion into the lamina propria or muscularis mucosa. (B) T1b esophageal adenocarcinoma was defined as tumor that invades through the muscularis mucosa into the submucosa. (C) Lymphovascular invasion was defined as the presence of clusters of malignant cells within an endothelial-lined vascular channel.

FIGURE 2.

Flow diagram showing number of T1a and T1b EAC patients who underwent esophagectomy versus endoscopic therapy with histology at last endoscopic follow-up.

FIGURE 3.
(A) Overall and (B) Cancer Free Survival of T1 Esophageal Adenocarcinoma Subjects with and without Lymphovascular Invasion.

TABLE 1

Baseline Demographic and Histological Characteristics

Variable	T1a EAC N=194	T1b EAC N=75
Mean (SD) age at diagnosis of cancer	70 (10)	69 (10)
Male gender, n(%)	163 (84.0%)	67 (89.3%)
Mean (SD) BE length, cm	4.9 (3.6)	4.4 (4.0)
Grade of differentiation		
Well	29 (15.0%)	9 (12.0%)
Moderate	128 (66.0%)	36 (48.0%)
Poor	37 (19.1%)	30 (40.0%)
Depth of Invasion		
Lamina Propria	43 (22.3%)	
Muscularis Mucosae	151 (77.8%)	
Submucosa		75 (100%)
Lymphovascular invasion present n (%)	23 (11.9%)	30 (40.4%)
Deep margin positive	39 (20.4%)	50 (66.7%)
Lateral margins positive	113 (58.6%)	66 (80.0%)
Esophagectomy N (%)	42 (21.3%)	36 (48.0%)

TABLE 2

Cause of Death

Cause of Death*	T1a EAC N=21	T1b EAC N=11
Pneumonia/respiratory failure	8	1
Myocardial infarction/arrhythmia/Congestive heart failure	4	3
End-stage renal disease	2	0
Esophageal adenocarcinoma	4	6
Other malignancy	2	1
Cerebrovascular accident	1	0

* We were unable to obtain death certificates from 59 patients who passed away in the following states due to privacy laws: Iowa, Illinois, Indiana, North Dakota, Kansas, Louisiana, Montana, Nebraska, Nevada, Oklahoma, Oregon and Wyoming.

TABLE 3

Predictors of Overall Mortality in T1 EAC

Variable	OVERALL N = 269		T1a EAC N = 194		T1b EAC N = 75	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age per 10 years	1.71 (1.36,2.17)	<0.001	1.85 (1.38,2.47)	<0.001	1.46 (0.99, 2.15)	0.05
Male Gender	1.32 (0.72,2.44)	0.37	1.31 (0.64,2.68)	0.45	1.13 (0.34, 3.81)	0.84
Length of BE (continuous) *	1.00 (0.94,1.05)	0.86	1.00 (0.93,1.07)	0.99	1.00 (0.91, 1.10)	0.96
Grade of differentiation *						
Well	1.0 (ref)		1.0 (ref)		1.0 (ref)	
Moderate	0.74 (0.40,1.38)	0.35	0.63 (0.32,1.24)	0.18	1.12 (0.25, 5.04)	0.88
Poor	1.64 (0.84,3.19)	0.15	1.31 (0.59,2.90)	0.51	2.69 (0.60, 12.17)	0.20
Lymphovascular invasion *						
Yes	1.95 (1.18,3.22)	0.009	1.72 (0.77,3.85)	0.19	2.16 (0.99, 4.72)	0.05
No	1.0 (ref)		1.0 (ref)		1.0 (ref)	
Deep margin *						
Positive	1.67 (1.09, 2.55)	0.02	1.48 (0.85,2.58)	0.17	1.69 (0.68, 4.19)	0.26
Negative	1.0 (ref)		1.0 (ref)		1.0 (ref)	
Lateral margins *						
Positive	1.44 (0.90, 2.30)	0.13	1.40 (0.59,2.37)	0.21	0.94 (0.28, 3.16)	0.91
Negative	1.0 (ref)		1.0 (ref)		1.0 (ref)	

* models adjusted for age and gender