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Do we need a different staging system for tongue and gingivobuccal complex squamous cell cancers?

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Abstract

Objectives—To determine the need for a separate staging system for gingivobuccal complex squamous cell cancers (GBCSCC) based on 5-year overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS) data from one institution.

Patients and Methods—An Institutional Review Board (IRB)-approved retrospective analysis was performed on an oral cavity cancer patient database. Patients from 1985–2012 with primary surgical treatment for biopsy-proven squamous cell cancer (SCC) from either the oral tongue (TSCC Group) or gingivobuccal complex (GBCSCC Group), were selected as two separate subgroups. The clinicopathologic data were used to stage the patients based on the American Joint Committee on Cancer 7th edition. Survival outcomes including 5-year OS, RFS, and DSS were calculated and analyzed. A multivariate analysis was performed to identify if subsite was an independent predictor for the survival outcomes, adjusting for other variables. A p-value of less than 0.05 was considered statistically significant.

Results—936 patients with TSCC and 486 patients with GBCSCC were considered eligible for the analysis. Patients with GBCSCC were more likely to be older ($p < 0.001$) and presented with more advanced disease ($p < 0.001$) compared to patients with TSCC. Unadjusted hazard ratio (HR) suggested GBCSCC had poor OS compared to TSCC. However, after adjusting for other variables, the adjusted HR was not significant ($p = 0.593$). There was no difference in 5-year DSS or RFS in either of the study groups.

Conclusion—With similar survival outcomes by stage, there is no justification for using a different staging system for GBCSCC.

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Conflict of interest
None.

Keywords

Gingivobuccal; Tongue; Squamous Cell; Staging; AJCC; Prognosis; Retrospective Studies; Oral Cancer; Head and Neck Cancer; Survival

INTRODUCTION

Oral cavity squamous cell cancer (OCSCC) accounts for 3.8% of all cancer cases and is responsible for 3.6% of cancer deaths worldwide [1]. A unique characteristic of the oral cavity is the presence of multiple subsites within it. Though anatomically congruent, these sites have specific characteristics as far as potentially malignant disorders and tumor spread are concerned [2]. The two most commonly involved subsites of the oral cavity are the oral tongue, more common in North America and Europe, and the lower gingivobuccal complex, more common in Southeast Asia [3]. Lower gingivobuccal complex SCC (GBCSCC) are those arising from the buccal mucosa, lower gum, and the retromolar trigone [4].

In Southeast Asia, GBCSCC are thought to have different etiological and clinicopathological characteristics when compared to oral tongue squamous cell cancer (TSCC) [3, 5], raising the argument that these cancers should have a different staging system compared to other oral cavity cancers. However, there has been no single study that has compared the survival data between GBCSCC and TSCC with stage-wise comparisons. Therefore, we present our own single-center experience with these two entities to determine if there is a need for a separate staging system for GBCSCC.

PATIENTS AND METHODS

We carried out a retrospective analysis of our oral cavity cancer patient database. The patient records were accessed after the study protocol was approved by the Institutional Review Board (IRB). All patients with biopsy-proven SCC either from the oral tongue or GBC who had received primary surgical treatment at Memorial Sloan Kettering Cancer Center from 1985 to 2012 were included in the study. Surgical treatment was defined as excision of the primary tumor with adequate margins with or without neck dissection. The patients also received adjuvant treatment based on current National Comprehensive Cancer Network guidelines or, in some cases, after multidisciplinary team consultations. Patients who had distant metastatic disease at the time of initial presentation or had received non-surgical therapy as neo-adjuvant or primary treatment were excluded.

The demographic profiles of the patients were evaluated to identify differences in age, smoking status, alcohol exposure, and comorbidities. The histopathology reports were analyzed to identify the tumor characteristics. The patients were staged as per the American Joint Committee on Cancer (AJCC) 7th edition. We did not use the AJCC 8th staging system for this cohort of patients as DOI was not reported regularly as a pathological tumor variable prior to 2002 and thus in our patient cohort from 1985 – 2012 there were lot of patients that could not be staged according to the new guidelines. Overall survival (OS) was calculated from the date of surgery to either the last date the patient was known to be alive, regardless of disease status, or death date. An OS event was defined as death from any cause. Disease-

specific survival (DSS) was calculated from the date of surgery to last date of disease assessment or death date. A patient was only considered to have a DSS event if he/she died of disease or if the patient had active disease at the date of last disease assessment. All other patients were censored for DSS at the last date of disease assessment by a medical professional. Recurrence-free survival (RFS) was calculated from the date of surgery to date of recurrence or date of last disease assessment. A RFS event was defined as any local, regional, or distant recurrence. If the patient did not recur, he/she was censored at the date of last disease assessment. Recurrences were considered local if occurring within the same site as the primary tumor, regional if occurring within the regional lymph nodes, and distant if occurring outside of the local and regional areas. Second primary cancer of the same histologic type was defined as any tumor more than 2 cm away from the index tumor, or at least 3 years after the diagnosis of the first tumor. Further second primary cancer of a different histologic type was identified without the 2-cm requirement. A detailed definition of second primary cancer was published by Hong et al., in 1990 [6].

Statistical analysis was performed using the SPSS Statistics Software for Windows, V24.0 (IBM, Armonk, NY). Patient and tumor characteristics were compared between the GBCSCC and TSCC groups using the Chi-squared test. Potential variables assessed were age, sex, pathological stage, nodal status, margin status, depth of invasion, lympho-vascular invasion (LVI), and peri-neural invasion (PNI). A multivariate Cox regression model was used to determine if subsite was an independent predictor for OS, DSS, and RFS, adjusting for other variables. The survival outcomes were compared using the log-rank and the Gehan-Breslow-Wilcoxon methods (mentioned separately), and p-value of less than 0.05 was considered statistically significant for the study.

RESULTS

From our database of 1,866 patients with OCSCT treated with surgery at Memorial Sloan Kettering Cancer Center from 1985 to 2012, there were 936 patients with TSCC and 486 with GBCSCC tumors (119 buccal mucosa, 258 lower gum, and 109 retromolar trigone).

Clinical characteristics

Clinical characteristics are shown in Table 1. Patients with GBCSCC were more likely to be older (age ≥ 60 years: 64% vs. 48%, $p < 0.001$), more likely to smoke (70% vs. 59%, $p < 0.001$), and more likely to have comorbidities (30.9% vs. 23.6%, $p = 0.003$) compared to patients with TSCC. Patients with GBCSCC presented with more advanced disease compared to patients with TSCC, with more advanced T stage (cT3 and cT4 tumors: 41.3% GBCSCC vs 14.1% TSCC, $p < 0.001$) and higher burden of positive nodal disease (cN+: 36.6% GBCSCC vs 26.2% TSCC $p < 0.001$).

Treatment characteristics and histopathological analysis

Of 486 GBCSCC patients, 400 (82%) underwent neck dissection with either elective (46.5%) or therapeutic intent (35.8%). Of 936 TSCC patients, 708 (75.6%) had neck dissections with either elective (49.8%) or therapeutic intent (25.9%).

On histopathological analysis of the surgical specimen, the GBCSCC group had more advanced T stage (pT3 and pT4 tumors: 38% GBCSCC vs 13% TSCC, $p < 0.001$), and were more likely to have positive margins (20% GBCSCC vs. 10.3% TSCC, $p < 0.001$). However, it was noted that the TSCC group showed higher PNI compared to the GBCSCC group (34.9% TSCC vs. 25.1% GBCSCC, $p = 0.001$), indicating a greater propensity of TSCC for perineural spread. There was no difference for LVI (13.6% GBCSCC vs 15.3% TSCC, $p = 0.46$).

Adjuvant therapy

All margin-positive and margin-close patients and patients with positive nodal disease received postoperative radiotherapy. In a few select cases, postoperative radiotherapy plus chemotherapy was given. One patient in the TSCC cohort received chemotherapy only. As expected, more GBCSCC patients received adjuvant therapy (45.9% GBCSCC vs 30.6% TSCC, $p < 0.01$) than did patients with TSCC. The number of GBCSCC patients that received adjuvant treatment for advanced disease (T3 or T4 tumors) was not statistically different from the TSCC group (69.7% GBCSCC vs 68.7% TSCC, $p = 0.86$).

Follow-up and outcome data

With a median follow-up of 78 months (interquartile range: 48–129 months), 170 and 310 patients developed recurrences in the GBCSCC group and TSCC group, respectively, as seen in Figure 1. The recurrence pattern was different in the GBCSCC and TSCC groups (Figure 1). GBCSCC had a higher incidence of local recurrence compared to the TSCC group (5-year local RFS: GBCSCC 71.7 % vs. TSCC 79.5%, p [Breslow] = 0.002), whereas TSCC had a higher incidence of regional recurrence (5-year regional RFS: GBCSCC 85.5% vs. TSCC 80%, p [Breslow] = 0.042). Second primary cancers at 5 years from the date of surgery occurred in 7.9% patients in the GBCSCC group compared to only 4.3% in the TSCC group (p [Breslow] = 0.004).

The OS for the GBCSCC group was significantly lower than the TSCC group (Table 2) (Figure 2A: 5-year OS 61.0% GBCSCC vs. 67.8% TSCC, $p < 0.01$). However, there was no difference in DSS (77.8% GBCSCC vs 80.0% TSCC, $p = 0.24$) [Figure 2B] or RFS (61.1% GBCSCC vs. 65.1% TSCC, $p = 0.14$) [Figure 2C].

When we compared survival outcomes between GBCSCC and TSCC by stage, we found that stage-specific OS at 5 years among patients with GBCSCC was similar to that of patients with TSCC (Figure 3A–3D). The stage IV GBCSCC group had a superior OS for early events compared to the stage IV TSCC group, which however, did not reach significance for non-time-weighted events, as noted by the log-rank test (36.4% GBCSCC vs 28.8% TSCC, $p = 0.02$ [Breslow], $p = 0.067$ [log-rank]). To address the issue of over-staging of small (Thickness < 2 cm) T4 GBCSCC tumors, we further identified that no difference exists in OS between small and large T4 GBCSCC tumors ($p = 0.769$).

A multivariate Cox regression model (Table 3A) was done to determine if subsite was an independent predictor for OS. The unadjusted HR suggested GBCSCC had poorer OS. However, after adjusting for other variables, the difference in OS was not significant.

Similarly, subsite (GBCSCC vs. TSCC) was not a significant predictor for DSS (Table 3B) or RFS (Table 3C).

DISCUSSION

OCSCC commonly affects the tongue and the lower gingivobuccal complex. SCC from these subsites present differently and have varied outcomes, which has led to the suggestion that GBCSCCs have a different clinicopathological profile when compared to TSCC and may need to have a different TNM staging system.

In our study, GBCSCC presented more frequently in older patients with more comorbidities, advanced T stage, and positive nodal disease compared to patients with TSCC. In a study of 1,400 patients, Nair et al. noted similar results: GBCSCC was observed in older patients (51 years vs. 48 years) and had more advanced T stage at presentation (82% vs. 40%) when compared to patients with TSCC [3]. Histopathological analysis showed that GBCSCC was noted to have higher pathological T stage and positive margins. In one of the early series that studied 2,268 patients with oral cavity cancers from 1935 to 1959, the authors concluded that gingiva, buccal mucosa, and palate presented with advanced disease compared to the rest of the oral cavity and had poorer survival [7, 8]. Pathak et al. studied a cohort of advanced GBCSCC and noted that patients with pT3/T4 disease and margin-positive disease had uniformly poorer outcomes [4]. A recent study from the Surveillance, Epidemiology, and End Results (SEER) database reported a 5-year relative survival of 65% for tongue cancer and 59.1% for cancers of the gum and other parts of the mouth (excluding lips, oropharynx, and tonsil) [9]. These data suggest poorer outcomes in GBCSCC compared to TSCC.

These differences in clinicopathologic and survival characteristics have prompted genomic studies that have shown a difference in the mutational landscape of GBCSCC in comparison to TSCC. The Notch signaling, and chromatin remodeling pathways had higher mutations, with little or no evidence of a genomic tobacco signature (C nucleotide to G nucleotide [C > G] transversions) in the TSCC patients compared to unique USP9X, MLL4, ARID2, UNC13C, TRPM3 mutations with increased C > G transversions in the GBCSCC [10, 11].

Therefore, it is evident that GBCSCC is a different disease, clinically, and pathologically when compared to TSCC. Should a different staging system be applied for such tumors? To answer this question, one must recognize the purpose of the TNM staging system.

The most important purpose of the TNM staging system is to predict prognosis. Patients are grouped into stages from I to IV, which describe the anatomical extent of cancer based on three variables: local tumor extent (T), nodal disease (N), and distant metastases (M). Each stage describes tumors with a similar prognosis. By grouping patients in a similar stage, we can compare outcomes of patients treated with different therapeutic modalities, in different countries, and determine the efficacy of new treatments using a common language.

The initial observation that patients with GBCSCC have poorer OS than those with TSCC was not supported after controlling for age, comorbidities, depth of invasion, margins, PNI, LVI, pathological T stage, and pathological N stage using a multivariate regression model

for OS. A stage-stratified analysis comparing OS, RFS, and DSS in these two sets failed to show any statistical difference. Therefore, there appears to be no data that would justify a change in the TNM staging system for GBCSCC. Comparable results of a stage-stratified analysis were reported in a study from Germany that showed that buccal mucosa SCC behaves similarly to other subsites in the oral cavity [12].

Should a different staging system be used for patients for GBCSCC in Southeast Asia? Is it possible that GBCSCC in the United States is different than those in Southeast Asia? In a study published by Pathak et al. comparing outcomes of patients with BMSCC from Canada and India, they found no difference in outcomes in terms of 10-year OS, RFS, and DSS when adjusted for age and stage at presentation [13]. A study by Walvekar et al. reported the 2-year and 5-year loco-regional RFS as 63.8% and 53.3%, respectively, for advanced disease (stage III/stage IV) in Southeast Asia [14]. This is similar to the 2-year and 5-year RFS of our cohort of stage III/IV GBCSCC, which is 59.8% and 50.7%, respectively. Thus, there are no data to support a different staging system for Southeast Asia for GBCSCC.

There are some limitations in our study that should be acknowledged. First, our study is subject to the bias inherent to a retrospective study design. Second, we have not staged the patients based on the AJCC 8th edition, due to lack of prospectively collected data to classify all the patients in terms of tumor thickness and presence or absence of extranodal extension; therefore, the effect of the new staging system remains to be seen in this population [15, 16].

CONCLUSION

The current TNM staging system adequately categorizes Oral Tongue and Gingivobuccal complex SCC into stage I to stage IV patients who have worsening survival trends with increasing stage. Further, no difference in survival outcomes is noted in either of the subgroups when compared stage for stage. Thus, there is no justification for using a different staging system for GBCSCC and TSCC.

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Highlights

- GBCSCC has a different clinicopathological profile than TSCC
- GBCSCC tends to present in older patients with advanced stage compared to TSCC
- Consistent decline in 5-year OS with worsening stages for either subgroups
- Multivariate analysis -Subsite is not an independent predictor of outcome
- No justification to have a different staging system for GBCSCC

GBCSCC^a Group (n = 486) (Total recurrences = 170)

TSCC^b Group (n = 936) (Total recurrences = 310)

5-year RFS ^c	GBCSCC ^a	TSCC ^b	p-value (Breslow) ^d	p-value (Log-Rank)
Local	71.7%	79.5%	0.002	0.001
Regional	85.5%	80.0%	0.042	0.073
Distant	88.3%	90.1%	0.438	0.295

Recurrence patterns in GBCSCC^a and TSCC^b cohorts

a- GBCSCC, Gingivobuccal complex squamous cell cancer; b- TSCC, Oral tongue squamous cell cancer; c- RFS, Recurrence Free Survival; d - Gehan-Breslow-Wilcoxon method ; *(n (%)) = number of recurrences [percentage from total recurrences]

A

B

C

Comparison of survival outcomes for GBCSCC^a and TSCC^b for overall survival (Figure 2A), disease-specific survival (Figure 2B), and recurrence-free survival (Figure 2C)

a- GBCSCC, Gingivobuccal complex squamous cell cancer; b- TSCC, Oral tongue squamous cell cancer, *p-values - log-rank test.

A

B

C

D

Stage-stratified comparison for overall survival of GBCSCC^a and TSCC^b

a- GBCSCC, Gingivobuccal complex squamous cell cancer; b- TSCC, Oral tongue squamous cell cancer

Table 1

Clinical characteristics

Variable		GBCSCC ^a N ^b (%)	TSCC ^c N (%)	p-Value
Total No. Of Cases		486	936	
Sex	Female	219 (45.1)	415 (44.0)	0.707
	Male	267 (54.9)	524 (56.0)	
Age	< 60	177 (36.4)	491 (52.5)	< 0.001
	> 60	309 (63.6)	445 (47.5)	
Alcohol	Never	139 (28.8)	308 (33.0)	0.109
	Ever	343 (71.2)	625 (67.0)	
Smoking	Never	146 (30.2)	387 (41.4)	< 0.001
	Ever	338 (69.8)	548 (58.6)	
Comorbidities	No	336 (69.1)	715 (76.4)	0.003
	Yes	150 (30.9)	221 (23.6)	
Clinical T Stage	T1	101 (20.8)	402 (42.9)	< 0.001 [*]
	T2	172 (35.4)	392 (41.9)	
	T3	42 (8.6)	94 (10.0)	
	T4	159 (32.7)	38 (4.1)	
	Tx	12 (2.5)	10 (1.1)	
Clinical N Stage	N0	308 (63.4)	691 (73.8)	
	N+	178 (36.6)	245 (26.2)	< 0.001
	N1	92 (18.9)	107 (11.4)	
	N2	84 (17.3)	133 (14.2)	
	N3	2 (0.4)	5 (0.5)	
Neck Dissection	No	86 (17.7)	228 (24.4)	< 0.001
	Elective	226 (46.5)	466 (49.8)	
	Therapeutic	174 (35.8)	242 (25.9)	
LVI ^d	No	310 (86.4)	585 (84.7)	0.464
	Yes	49 (13.6)	106 (15.3)	
PNI ^e	No	269 (74.9)	450 (65.1)	0.001
	Yes	90 (25.1)	241 (34.9)	
Margin	Negative	280 (57.8)	646 (69.1)	< 0.001
	Close	107 (22.1)	193 (20.6)	
	Positive	97 (20.0)	96 (10.3)	
Pathological T Stage	T1	166 (36.2)	555 (63.2)	< 0.001 ^{**}
	T2	118 (25.7)	211 (24.0)	
	T3	24 (5.2)	47 (5.4)	
	T4	151 (32.9)	65 (7.4)	

Variable		GBCSCC ^a N ^b (%)	TSCC ^c N (%)	p-Value
Pathological N Stage	N0	296 (60.9)	643 (68.7)	0.003
	N+	190 (39.1)	293 (31.3)	
Adjuvant Therapy	None	263 (54.1)	649 (69.4)	< 0.001 ***
	PORT ^f	190 (39.1)	240 (25.7)	
	PORT + chemotherapy	33 (6.8)	46 (4.9)	

^a - GBCSCC, gingivobuccal complex squamous cell cancer;

^b - N, number;

^c - TSCC, tongue squamous cell cancer;

^d -LVI, lympho-vascular invasion;

^e -PNI, peri-neural invasion;

^f - PORT, post-operative radiotherapy.

* Tx not included in p-value for clinical T stage

** Pathological T staging- Data of 85 patients missing

*** Patient had Chemotherapy only

Table 2

5-year overall survival in TSCC^a and GBCSCC^b cohorts.

Stage	TSCC ^a	GBCSCC ^b	p-value (Breslow)	p-value (Log Rank)
Overall Survival	67.8%	61.0%	< 0.01	<0.01
Stage I	82.8%	82.2%	0.712	0.039
Stage II	69.0%	74.4%	0.863	0.298
Stage III	66.7%	76.1%	0.467	0.952
Stage IV	28.8%	36.4%	0.020	0.067

^a - tongue squamous cell cancer;

^b - gingivobuccal complex squamous cell cancer

Table 3

A. Unadjusted and adjusted HR^a for tumor site for OS^b					
Variables		Unadjusted HR (CI)^c	p-value	Adjusted HR (CI)	p-value
Site	Gingivobuccal	Reference	< 0.001	Reference	0.281
	Tongue	0.72 (0.62–0.83)		1.13 (0.91–1.39)	
Sex	Female	Reference	0.1	Reference	0.987
	Male	1.13 (0.98–1.30)		1.00 (0.83–1.21)	
Age	< 60 years	Reference	< 0.001	Reference	< 0.001
	60 years	2.14 (1.84–2.49)		2.24 (1.83–2.73)	
DOI ^d	0–5 mm	Reference	< 0.001	Reference	0.334
	5.01–10 mm	1.60 (1.31–1.95)		1.13 (0.86–1.48)	
	>10 mm	2.81 (2.34–3.38)		1.26 (0.93–1.71)	
Margins	Negative	Reference	< 0.001	Reference	0.195
	Close/Positive	1.68 (1.45–1.95)		1.14 (0.93–1.40)	
Pathological T stage	T1	Reference	< 0.001	Reference	< 0.001
	T2	1.71 (1.43–2.06)		1.12 (0.86–1.45)	
	T3	2.93 (2.18–3.92)		1.79 (1.21–2.63)	
	T4	3.74 (3.09–4.52)		2.43 (1.76–3.36)	
Pathological N stage	N0	Reference	< 0.001	Reference	< 0.001
	N+	2.54 (2.20–2.93)		1.89 (1.54–2.32)	
LVI ^e	No	Reference	< 0.001	Reference	0.007
	Yes	2.32 (1.86–2.89)		1.41 (1.10–1.82)	
PNI ^f	No	Reference	< 0.001	Reference	0.015
	Yes	2.00 (1.67–2.39)		1.30 (1.05–1.60)	

B. Unadjusted and adjusted HR^a for tumor site for DSS^b					
Variables		Unadjusted HR(CI)^c	p-value	Adjusted HR (CI)	p-value
Site	Gingivobuccal	Reference	0.246	Reference	0.713
	Tongue	0.86 (0.67–1.11)		1.06 (0.76–1.48)	
Sex	Female	Reference	0.995	Reference	0.61
	Male	1.00 (0.79–1.28)		0.93 (0.70–1.24)	
Age	< 60 years	Reference	0.063	Reference	0.164
	60 years	1.26 (0.99–1.61)		1.23 (0.92–1.64)	
DOI ^d	0–5 mm	Reference	< 0.001	Reference	0.025
	5.01–10 mm	2.46 (1.67–3.61)		1.31 (0.81–2.14)	
	>10 mm	5.84 (4.15–8.23)		1.94 (1.16–3.25)	
Margins	Negative	Reference	< 0.001	Reference	0.144
	Close/Positive	2.22 (1.74–2.83)		1.25 (0.93–1.69)	
Pathological T stage	T1	Reference	< 0.001	Reference	0.001

B. Unadjusted and adjusted HR ^a for tumor site for DSS ^b					
Variables		Unadjusted HR(CI ^c)	p-value	Adjusted HR (CI)	p-value
	T2	2.37 (1.73–3.25)		0.99 (0.65–1.51)	
	T3	4.10 (2.54–6.63)		1.76 (0.98–3.15)	
	T4	5.72 (4.18–7.82)		2.09 (1.30–3.36)	
Pathological N stage	N0	Reference	< 0.001	Reference	< 0.001
	N+	5.68 (4.39–7.35)		3.46 (2.45–4.90)	
LVI ^e	No	Reference	< 0.001	Reference	0.014
	Yes	3.06 (2.25–4.17)		1.53 (1.09–2.14)	
PNI ^f	No	Reference	< 0.001	Reference	0.087
	Yes	2.93 (2.23–3.85)		1.33 (0.96–1.83)	

C. Unadjusted and adjusted hazard ratio for tumor site for RFS ^a					
Variables		Unadjusted HR ^b (CI ^c)	p-value	Adjusted HR (CI)	p-value
Site	Gingivobuccal	Reference	0.139	Reference	0.593
	Tongue	0.67 (0.72–1.05)		1.07 (0.83–1.39)	
Sex	Female	Reference	0.861	Reference	0.74
	Male	1.02 (1.22)		0.96 (0.77–1.2)	
Age	< 60 years	Reference	0.051	Reference	0.176
	60 years	1.20 (1.00–1.43)		1.17 (0.93–1.46)	
DOI ^d	0–5 mm	Reference	< 0.001	Reference	0.413
	5.01–10 mm	1.42 (1.11–1.82)		0.96 (0.7–1.33)	
	>10 mm	2.26 (1.81–2.83)		1.18 (0.82–1.69)	
Margins	Negative	Reference	< 0.001	Reference	0.001
	Close/Positive	1.88 (1.57–2.26)		1.5 (1.19–1.89)	
Pathological T stage	T1	Reference	< 0.001	Reference	0.001
	T2	1.41 (1.12–1.77)		0.91 (0.66–1.25)	
	T3	2.10 (1.41–3.14)		1.46 (0.9–2.39)	
	T4	2.84 (2.24–0.361)		1.76 (1.23–2.53)	
Pathological N stage	N0	Reference	< 0.001	Reference	<0.001
	N+	2.21 (1.85–2.65)		1.84 (1.43–2.37)	
LVI ^e	No	Reference	< 0.001	Reference	0.045
	Yes	2.07 (1.60–2.68)		1.35 (1.01–1.81)	
PNI ^f	No	Reference	< 0.001	Reference	0.048
	Yes	1.90 (1.53–2.35)		1.29 (1–1.65)	

^a - HR, hazard ratio;

^b - OS, overall survival;

^c - CI, confidence interval;

^d - DOI, Depth of Invasion;

^e - LVI, lympho-vascular invasion;

^f - PNI, peri-neural invasion

^a - HR, hazard ratio;

^b - DSS, disease specific survival;

^c - CI, confidence interval;

^d - DOI, Depth of Invasion;

^e - LVI, lympho-vascular invasion;

^f - PNI, peri-neural invasion

^a - RFS, recurrence-free survival;

^b - HR, hazard ratio;

^c - CI, confidence interval;

^d - DOI, Depth of Invasion;

^e - LVI, lympho-vascular invasion;

^f - PNI, peri-neural invasion