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**THE AMERICAN JOINT COMMITTEE ON CANCER STAGING FOR
METASTATIC HEAD AND NECK CUTANEOUS SQUAMOUS CELL
CARCINOMA: A MULTI-INSTITUTIONAL STUDY OF WITHIN-STAGE
HETEROGENEITY AND IMPACT ON PROGNOSTIC PERFORMANCE**

Running title: Prognostic heterogeneity in head and neck cSCC staging

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Author Contributions

Ardalan Ebrahimi: study design, data collection, statistical analysis, writing article, review and edits. Peter P Luk: data collection, reviewed and edited article. Hubert Low: reviewed and edited the article. Lachlan McDowell: data collection, reviewed and edited article. Matthew Magarey: reviewed and edited article. Paul N Smith: reviewed and edited article. Diana M Perriman: reviewed and edited article. Bruce Shadbolt: reviewed and edited article. Michael Veness: data collection, reviewed and edited article. Ruta Gupta: study design, data collection, reviewed and edited article. Jonathan Clark: study design, data collection, reviewed and edited article.

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ABSTRACT

Background: The American Joint Committee on Cancer (AJCC) staging for head and neck cutaneous squamous cell carcinoma (HNCSCC) stratifies risk poorly. We hypothesized that this results from prognostic heterogeneity within N and TNM groups.

Methods: Retrospective analysis of disease-specific survival (DSS) in a multicenter study of 1146 patients with nodal metastases from HNCSCC.

Results: The majority of patients were classified as pN2a or pN3b (83.1%) and TNM Stage IV (90.6%). On multivariate analysis, there was statistically significant prognostic heterogeneity within these groups based on the number and size of nodal metastases, immunosuppression and perineural invasion. When Stage IV patients were categorized into low, moderate and high-risk groups based on adverse features, there was wide variation in prognosis with 5-year DSS ranging from 90% to 60% ($p<0.001$).

Conclusions: The AJCC staging system stratifies risk poorly in HNCSCC due to significant prognostic heterogeneity within pN2a, pN3b and Stage IV groups.

Keywords: cutaneous squamous cell carcinoma; lymph node metastasis; cancer staging; prognosis; head and neck cancer

INTRODUCTION

The American Joint Committee on Cancer (AJCC) nodal (N) classification system for head and neck cutaneous squamous cell carcinoma (HNeSCC), which is based on mucosal head and neck cancer, introduced extranodal extension (ENE) in the recent 8th edition revision of the Staging Manual.[1] Under the new system, a single node ≤ 3 cm in size with ENE is upstaged from pN1 in the 7th edition to pN2a. All other ENE positive nodal metastases (single nodal metastasis > 3 cm in size or multiple nodes) are classified in the new pN3b category, effectively upstaging 7th edition pN2 and pN3 disease to pN3b in the 8th edition (Table 1). Several studies have shown that this results in the majority of patients being classified as Stage IV, even when the cancer is highly curable, leading to poor prognostic model performance based on objective measures.[2, 3]

An ideal staging system should provide homogeneity of prognosis within the same stage, good discrimination (or distinctiveness) between the different stages, and monotonic decreasing survival with increasing cancer stage.[4] Given the vast majority of patients appear to be classified as pN2a, pN3b, and TNM Stage IV in the 8th edition AJCC HNeSCC staging, we hypothesized that the poor performance may largely reflect within-stage heterogeneity due to grouping of patients with widely disparate prognoses into the same risk group. The aim of this study was to investigate for sources of within-stage prognostic heterogeneity in the 8th edition N and TNM

staging based on established clinicopathological prognostic factors in a large multicenter Australian cohort with nodal metastases from HNCSCC.

METHODS

Study Population

The study cohort was derived from a multi-institutional collaboration including four Australian centres: Chris O'Brien Lifehouse/Royal Prince Alfred Hospital, Westmead Hospital, Peter MacCallum Cancer Centre and Liverpool Hospital. We identified 1309 patients with HNCSCC metastatic to parotid and/or cervical nodes treated with curative intent by surgery $\pm$ adjuvant therapy, as candidates for inclusion. After excluding cases with missing data on the 8th edition AJCC pN or TNM stage, follow-up or peri-operative mortality, the final study population consisted of 1146 patients treated between 1980 and 2017. Demographic, clinicopathological, treatment and follow-up data were obtained for all patients. Ethics approval was obtained from the institutional research ethics committees of participating centers.

Statistical Analysis

Statistical analysis was performed using Stata version 12.0 SE (Stata Corporation, College Station, Texas). All statistics were two sided, and a p value <0.05 was considered statistically significant. The end point of interest was disease-specific survival (DSS), calculated from the date of surgery to the date of death or last follow-up visit. Patients who died from causes other than HNCSCC were censored at the time

of death. Differences in survival were determined using univariate Cox regression analysis, adjusted for treatment (surgery, surgery + adjuvant radiotherapy [RT], surgery + adjuvant chemoradiotherapy [CRT]) and stratified by institution to account for presumed heterogeneity between centres. Survival curves were generated using the Kaplan-Meier method. Within each pathological Nodal (pN) and TNM category, we explored for prognostic heterogeneity based on the following covariates of interest: age at diagnosis (continuous, years), sex, immunosuppression (absent, present), differentiation (well-moderate, poor), maximum nodal size, number of nodal metastases (1-2, 3-4, ≥ 5), perineural invasion [PNI (absent, present)], surgical margin status (clear-close, involved) and ENE (absent, present).

RESULTS

Study Population

The study cohort included 1146 patients, with 972 men and 174 women, and a median age at diagnosis of 73.0 years (range: 18.0-100.1 years). The median follow-up time was 3.4 years. Relevant demographic, clinicopathological and treatment details are summarized in Table 2. For reference, Kaplan-Meier curves for disease-specific survival based on N and TNM stage are shown in Figure 1.

pN1 Nodal Category

There were 108 (9.4%) patients classified as pN1 (metastasis in a single ipsilateral lymph node ≤ 3 cm in size without ENE), of which 9 (8.3%) died from HNCSCC with

a 5-year DSS of 86.1% (95% CI: 74.5%-92.7%). The cohort was treated with surgery alone in 38 (35.2%), surgery + RT in 67 (62.0%) and surgery + CRT in 3 (2.8%). There was a non-significant trend towards reduced DSS in the presence of involved margins (HR 9.00; 95% CI: 0.61-133.77; $p=0.110$). Interestingly, immunosuppression was rare in pN1 disease, present in only 2.8% of the group, with no deaths from HNCSCC.

pN2a Nodal Category

The pN2a category included 367 (32.0%) patients, 25 (6.8%) of whom had nodal metastases >3 to 6cm in size without ENE, and 342 (93.2%) which had nodes ≤ 3 cm in size with ENE. Hence, the majority of these patients were upstaged to pN2a based on the presence of ENE. There were 47 deaths from HNCSCC, with a 5-year DSS of 82.0% (95% CI: 76.2%-86.5%), which was similar to pN1 disease. Treatment consisted of surgery alone in 64 (17.5%), surgery + RT in 286 (77.9%) and surgery + CRT in 17 (4.6%). Surprisingly, despite the wide range of nodal metastasis size present in the pN2a category, size was not associated with within-stage heterogeneity ($p=0.893$). There was also no difference in survival based on ENE ($p=0.996$). PNI and immunosuppression were present in 30.0% and 9.0% of pN2a patients, respectively, and were significant predictors of DSS [PNI (HR, 2.09; 95% CI: 1.12-3.90; $p=0.021$) and immunosuppression (HR, 2.91; 95% CI: 1.26-6.74; $p=0.012$)]. In the absence of PNI or immunosuppression, pN2a patients had a 5-year DSS of 87.1% compared to 69.9% in the presence of one or both factors ($p=0.001$).

pN2b Nodal Category

There were only 74 (6.5%) patients in this nodal category, with the remaining 417 patients classified as pN2b in the 7th edition AJCC upstaged to pN3b based on the presence of ENE. There were 9 deaths from HNCSCC with 5-year DSS of 84.3%, (95% CI: 71.7%-91.6%) which was similar to the pN1 and pN2a subgroups. Treatment consisted of surgery alone in 12 (16.2%), surgery + RT in 57 (77.0%) and surgery + CRT in 5 (6.8%) patients. Despite limited statistical power in this subgroup, we observed trends for reduced DSS based on nodal size >3-6cm (HR, 5.36; 95% CI: 0.89-32.40; $p=0.068$) and immunosuppression (HR, 3.55; 95% CI: 0.61-20.79; $p=0.160$). In contrast to pN1 and pN2a disease, there was a marked survival advantage with administration of adjuvant therapy (RT or CRT) in pN2b disease (HR, 0.10; 95% CI: 0.01-0.92; $p=0.042$).

pN2c Nodal Category

There were only 8 (0.7%) patients with pN2c disease, with 1 death from HNCSCC and 5-year estimated 5-year DSS of 83.3%. The single disease-specific mortality occurred in a 71 year old male with a single 1.2cm nodal metastasis with clear margins treated with surgery alone.

pN3a Nodal Category

There were only 4 patients in this category reflecting the rarity of nodal metastases >6cm in size without ENE in HNCSCC. A single disease-specific death was noted in a 50 year old male with three nodal metastases, the largest being 6.5cm in size with poor differentiation. This patient was treated with surgery alone after declining radiotherapy and recurred in regional nodes.

pN3b Nodal Category

This subgroup accounted for 51% (N=585) of all patients, with patients upstaged from AJCC 7 based on the presence of ENE as follows: 110 were pN2a; 418 were pN2b; 28 were pN2c; and 29 were pN3. There were 139 deaths from HNCSCC with a 5-year DSS of 71.2% (95% CI: 66.4-75.4%). Treatment consisted of surgery alone in 75 (12.8%), surgery + RT in 462 (79.0%) and surgery + CRT in 48 (8.2%) patients. Significant predictors of DSS within the pN3b subgroup included immunosuppression (HR, 2.15; 95% CI: 1.36-3.38; $p=0.001$), nodal size >6cm [compared to ≤ 3 cm (HR, 3.56; 95% CI: 1.92-6.58; $p<0.001$) and compared to >3-6cm (HR, 3.03; 95% CI: 1.63-5.64; $p<0.001$)], number of nodal metastases [3-4 nodes vs 1-2 (HR, 1.43; 95% CI: 0.94-2.19; $p=0.094$), ≥ 5 nodes vs 1-2 (HR, 2.09; 95% CI: 1.39-3.13; $p<0.001$) and PNI (HR, 1.56; 95% CI: 1.10-2.21; $p=0.012$). As shown in Table 3, these were all statistically significant predictors of DSS on multivariate analysis after adjusting for adjuvant radiotherapy, time period of treatment and institution.

TNM Stage III

The 108 patients with pN1a disease were classified as TNM Stage III, accounting for 9.4% of the cohort. The findings in the pN1 nodal category above apply to this TNM cohort.

TNM Stage IV

The remaining 1038 (90.6%) patients with pN2-3 disease were classified as TNM Stage IV. There were 197 deaths from HNCSCC, with a 5-year DSS of 76.1% (95% CI: 72.8%-79.1%). Treatment consisted of surgery alone in 155 (14.9%), surgery + RT in 812 (78.2%) and surgery + CRT in 71 (6.8%). Significant predictors of DSS within this cohort included PNI (HR, 1.69; 95% CI: 1.25-2.27; $p=0.001$), immunosuppression (HR, 2.44; 95% CI: 1.66-3.57; $p<0.001$), nodal maximum diameter [$>6\text{cm}$ versus $>3\text{-}6\text{cm}$] (HR, 1.49; 95% CI: 1.07-2.08; $p=0.019$) and number of nodal metastases (HR, 1.03; 95% CI: 1.01-1.04; $p<0.001$). ENE failed to reach statistical significance (HR, 1.69; 95% CI: 0.98-2.92; $p=0.059$). All predictors on univariate analysis remained significant in the multivariate model shown in Table 4, which included ENE, adjusted for treatment and time period and stratified by institution.

Exploratory Risk Reclassification of TNM Stage IV

As an exploratory analysis to demonstrate prognostic heterogeneity, we assigned a cumulative risk score to TNM Stage IV patients based on the results of multivariate analysis. The risk score included PNI, immunosuppression, number and size of nodal

metastases as well as ENE (ENE was included despite the non-significant P value based on clinical considerations). Each variable was weighted based on the hazard ratios seen in Table 4.

The median risk score was 2.99 (mean 3.17, range 0-11.59). We split the cohort based on an *a priori* decision into low, moderate and high-risk groups based on tertiles of the risk score. After adjusting for treatment, institution and time period, we noted a progressive statistically significant decrease in disease-specific survival with increasing risk score (Figure 2). Of note, the low-risk TNM Stage IV patients appear to have a prognosis similar to pN1 and Stage III disease with 5-year DSS of 90%, whilst the high-risk patients had a far worse prognosis than the 8th edition TNM Stage IV cohort with only 60% 5-year DSS. A sensitivity analysis confirmed the results were robust to restriction of the analysis to patients treated from the year 2000 onwards.

DISCUSSION

As a result of the introduction of ENE into the 8th edition AJCC N categories for HNSCC, the majority of patients with nodal metastases are now classified as pN2a and pN3b and hence TNM Stage IV. In this large multicentre study we showed there is significant within-stage heterogeneity in DSS for both N and TNM stages based on the established prognostic factors of immunosuppression, PNI and the number and size of nodal metastases. This grouping of patients with widely disparate prognoses

into the same risk category by the AJCC staging system, largely based on the presence of ENE which is present in most patients, likely explains its poor prognostic performance.

The 8th edition AJCC pN1 category (single node ≤ 3 cm without ENE) accounted for 9.4% of the study cohort and represented the only node positive patients that are classified as TNM Stage III. They had a relatively favourable 5-year DSS of 86.1%. Interestingly, immunosuppression was rare in this subset of patients suggesting immunosuppressed patients typically present with more advanced disease. There was a trend towards reduced survival in the presence of involved margins ($p=0.110$) but otherwise this appeared to be a relatively homogeneous group of patients in terms of prognosis.

The pN2a category accounted for 32% of patients, with the majority (93%) having 7th edition pN1 disease being upstaged due to ENE. Although the 5-year DSS was only slightly lower than pN1 disease (82% versus 86%, respectively), a higher proportion received adjuvant RT to achieve this (83% versus 65%; $p<0.001$). Interestingly, the AJCC decision to combine nodal metastases 3-6cm in size without ENE with nodes ≤ 3 cm in size with ENE appears reasonable given we found no within-stage heterogeneity based on size ($p=0.893$) or ENE ($p=0.996$). There was however statistically significant heterogeneity based on PNI and immunosuppression. Within the pN2a cohort, 5-year DSS was 87.1% in the absence of PNI or immunosuppression

compared with 69.9% in the presence of either adverse feature ($p=0.001$). Hence, the low-risk pN2a patients appear to have a similar prognosis to patients staged pN1 by the 8th edition AJCC.

The pN2b subset accounted for only 6.5% of the study cohort, with their 5-year DSS of 84.3% similar to pN1 and pN2a disease. Despite limited statistical power in this subgroup, we observed trends for reduced DSS based on nodal size $>3-6\text{cm}$ ($p=0.068$) and immunosuppression ($p=0.160$). There were very few patients in the pN2c (0.7%) and pN3a (0.3%) nodal categories precluding analysis for heterogeneity. We believe the pN2c and pN3a categories may be redundant for HNCSCC, since contralateral disease is relatively rare and may reflect lymphatic drainage patterns from midline primaries and nodal metastases $>6\text{cm}$ in size without ENE are rare. Consideration should be given to reclassifying these patients based on other features such as the size and number of nodal metastases.

The new pN3b category accounted for 51% of all patients, with the majority having AJCC 7th edition pN2 disease upstaged based on ENE. Adjuvant therapy was administered in 87% of this cohort and the 5-year DSS was 71.2%. On multivariate analysis, immunosuppression, nodal size $>6\text{cm}$, number of nodal metastases and PNI were all statistically significant predictors of DSS in pN3b patients.

Similar results were found for TNM Stage IV disease, which accounted for 91% of the study cohort and had an unusually favourable 5-year DSS of 76.1%. Again, immunosuppression ($p<0.001$), nodal size ($p<0.001$) number of nodal metastases ($p<0.001$) and PNI ($p<0.001$) were all statistically significant predictors of DSS on multivariate analysis. ENE was present in 89% of Stage IV patients but not a significant prognostic factor ($p=0.281$). We hypothesised that ENE failed to reach significance because it was present in the vast majority of TNM Stage IV patients and that the ENE negative subset were not truly low risk patients due to the presence of factors such as multiple nodal metastases or nodal size 3-6cm.

After stratifying TNM Stage IV patients into low, moderate and high-risk subsets based on these prognostic factors using a weighted risk score, the 5-year DSS ranged from 90% in low-risk to 60% in high-risk patients ($p<0.001$). This analysis was exploratory but it demonstrates the issue with the current staging where patients with a 400% difference in disease-specific mortality risk are classified together. Importantly, the low-risk subset had a prognosis similar to pN1 and TNM Stage III disease, whilst the high-risk subset had a worse prognosis than the 8th edition Stage IV cohort (60% versus 76%). This further confirmed significant prognostic heterogeneity in the 8th edition TNM Stage IV cohort with a 30% difference in absolute risk and 400% difference in relative risk between subgroups.

Several study limitations need to be acknowledged. Firstly, our cohort consisted only of patients with HNCSCC and nodal metastases treated with curative intent. There are of course a subset of patients that present with either unresectable or distant metastatic disease which are also classified by the AJCC as Stage IV. Given these patients tend to have a very poor prognosis, their exclusion presumably resulted in this study underestimating the prognostic heterogeneity in AJCC Stage IV disease. The second consideration is the retrospective study design, which may lead to bias in the results since higher stage disease may have been treated more aggressively. Again, this may have led to an underestimate of the true heterogeneity within each AJCC stage. Also, all analyses were adjusted for adjuvant therapy administration. Finally, we were lacking data on the primary HNCSCC in a large proportion of patients and elected to assign stage based on nodal factors alone. This was based on evidence that suggests nodal factors are the main determinant of prognosis in patients with HNCSCC and lymph node metastases.[5, 6] In addition, the only patients where the T category can alter the TNM designation is the 9.4% of patients classified as pN1, who would be upstaged from Stage III to IV in the presence of T4 disease. However, T4 disease due to gross bone invasion or skull base foramen involvement is rare in most cohorts, accounting for <0.3% of patients with HNCSCC, and therefore highly unlikely to influence our results.[7, 8]

CONCLUSION

In this large multicenter study of HNCSCC with lymph node metastases we found that the majority of patients are classified as pN2a and pN3b and hence Stage IV based on the 8th edition AJCC staging manual. The prognosis of pN1, pN2a, pN2b and pN2c groups were similar, providing complexity with little risk stratification. Very few patients were designated as pN2c and pN3a suggesting that these nodal categories may be redundant in HNCSCC and consideration should be given to removing them. There was a wide variation in DSS noted in pN2a, pN3b and TNM Stage IV disease based on the well-established prognostic factors immunosuppression, size and number of nodal metastases and PNI. This within-stage heterogeneity may be the key reason that the current AJCC staging performs poorly in predicting prognosis. We believe a key issue is the inclusion of ENE in the staging system since it is very common in HNCSCC and leads to the vast majority of patients being classified as pN2a or pN3b and hence Stage IV. ENE does not appear to be as important a predictor of survival in HNCSCC compared to mucosal SCC and it's inclusion in the staging system needs to be reconsidered. Future staging systems may also be improved by inclusion of immunosuppression and perineural invasion as well as further risk stratification based on the number of nodal metastases. This study highlights the need to develop and validate a staging system specific to HNCSCC that reflects its distinct tumor biology and provides clinicians with a more accurate tool to risk stratify patients.

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FIGURE LEGENDS

Figure 1. Kaplan-Meier curves for disease-specific survival based on the American Joint Committee on Cancer 8th edition N category (A) and TNM Stage (B).

Figure 2. Disease-specific survival in TNM Stage IV patients stratified as low, moderate and high-risk based on a weighted risk score comprised of immunosuppression, number of nodal metastases, nodal size, perineural invasion and extranodal extension.

HED_26369_Figure 1a KM pN8 DSS B&W tif.tif

HED_26369_Figure 1b KM TNM stage DSS B&W tif.tif

HED_26369_Figure 2 DSS by risk score.tif

Table 1. American Joint Committee on Cancer 8th edition N and TNM Staging of head and neck cutaneous squamous cell carcinoma

AJCC N Category			
pN0	No regional lymph node metastasis.		
pN1	Single ipsilateral lymph node metastasis ≤ 3 cm, ENE(-).		
pN2a	Single ipsilateral or contralateral lymph node ≤ 3 cm, ENE(+) <i>or</i> single ipsilateral lymph node >3 cm but ≤ 6 cm and ENE (-).		
pN2b	Multiple ipsilateral lymph node metastases ≤ 6 cm and ENE(-).		
pN2c	Bilateral or contralateral lymph node metastases ≤ 6 cm in greatest dimension and ENE(-).		
pN3a	Lymph node metastasis >6 cm in greatest dimension, ENE(-).		
pN3b	Single ipsilateral lymph node metastasis >3 cm in greatest dimension and ENE(+) <i>or</i> multiple ipsilateral, contralateral or bilateral lymph nodes metastases, any with ENE(+).		
AJCC TNM Groups			
T	N	M	Stage
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1-T3	N1	M0	III
T1-T3	N2	M0	IV
Any of T4 or N3 or M1			IV

Abbreviations: AJCC, American Joint Committee on Cancer; ENE, extranodal extension

Table 2. Patient demographic, clinicopathological and treatment details.

Variable	N.	%
Age, years		
≤60	192	16.7
>60 - 80	661	57.7
>80	293	25.6
Sex		
Male	972	84.8
Female	174	15.2
Immunosuppression		
Absent	1038	90.6
Present	108	9.4
Institution		
Chris O'Brien Lifehouse/RPAH	443	38.7
Westmead Hospital	410	35.8
Peter MacCallum Cancer Centre	197	17.2
Liverpool Hospital	96	8.4
Time period of treatment		
1980-1999	239	20.9
2000-2017	907	79.1
Treatment		
Surgery alone	193	16.8
Surgery + adjuvant RT	879	76.7
Surgery + adjuvant CRT	74	6.5
Extent of Surgery		
Parotidectomy alone	152	13.2
Parotidectomy + SND	478	41.7
Parotidectomy + CND	242	21.1
SND alone	166	14.5
CND alone	97	8.5
Other	11	1.0
Extranodal extension		
Absent	219	19.1
Present	927	80.9
Pathological N Stage		
pN1	108	9.4
pN2a	367	32.0
pN2b	74	6.5

pN2c	8	0.7
pN3a	4	0.3
pN3b	585	51.1
TNM Stage		
III	108	9.4
IV	1038	90.6

Abbreviations: Royal Prince Alfred Hospital; RT, radiotherapy; CRT, chemoradiotherapy; SND, selective neck dissection; CND, comprehensive neck dissection.

Table 3. Multivariate analysis of disease-specific survival in patients with pN3b disease *

Variable	Disease-Specific Survival	
	HR (95% CI)	p value
Immunosuppression	2.04 (1.22-3.43)	0.007
Nodal size		
>3-6cm vs ≤3cm	1.27 (0.85-1.90)	0.248
>6cm vs ≤3cm	4.35 (2.37-7.96)	<0.001
Number of nodal metastases		
3-4 vs 1-2	1.61 (0.98-2.65)	0.062
≥5 vs 1-2	2.90 (1.84-4.57)	<0.001
Perineural invasion	1.74 (1.19-2.55)	0.004
Adjuvant therapy		
RT vs nil	1.28 (0.65-2.49)	0.475
CRT vs nil	0.79 (0.32-1.93)	0.603
Time period		
2000-2017 vs 1980-1999	0.47 (0.28-0.79)	0.004

* Multivariate analysis stratified by institution to account for heterogeneity between centres.

Abbreviations: HR, hazard ratio, CI, confidence interval; vs, versus; RT, radiotherapy; CRT, chemoradiotherapy.

Table 4. Multivariate analysis of disease-specific survival in patients with TNM Stage IV disease *

Variable	Disease-Specific Survival	
	HR (95% CI)	<i>p</i> value
Immunosuppression	2.24 (1.46-3.45)	<0.001
Nodal size		
>3-6cm vs ≤3cm	1.42 (1.02-1.98)	0.036
>6cm vs ≤3cm	5.14 (2.98-8.85)	<0.001
Number of nodal metastases		
3-4 vs 1-2	1.62 (1.05-2.48)	0.028
≥5 vs 1-2	2.84 (1.94-4.16)	<0.001
Perineural invasion	1.77 (1.29-2.43)	<0.001
Extranodal extension	1.37 (0.77-2.44)	0.281
Adjuvant therapy		
RT vs nil	0.77 (0.49-1.20)	0.250
CRT vs nil	0.57 (0.28-1.16)	0.120
Time period		
2000-2017 vs 1980-1999	0.51 (0.34-0.75)	0.001

* Multivariate analysis stratified by institution to account for heterogeneity between centres.

Abbreviations: vs, versus; RT, radiotherapy; CRT, chemoradiotherapy.

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