Oral Oncology 127 (2022) 105797

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Comparison of royal college of pathologists and college of american pathologists definition for positive margins in oral cavity squamous cell carcinoma

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ARTICLE INFO

Keywords:
Oral cavity
Head and neck cancer
Squamous cell carcinoma
Margins
College of American Pathologists
Royal College of Pathologists
Recurrence
Survival

ABSTRACT

Background: Pathological margin assessment is an essential component of surgical management of oral cavity squamous cell carcinoma (OCSCC), however, in many studies, variable definitions of involved margins have been used. The purpose of the present study was to compare the prognostic ability of involved margins according to Royal College of Pathologists (RCPath) and College of American Pathologists (CAP) guidance.
Methods: Retrospective study of 300 patients with previously untreated OCSCC undergoing definitive surgical management. Main specimen margin status was defined according to RCPath guidance and CAP guidance. "Final margin status", incorporated the results of frozen sections and extra tumour bed resections. The prognostic impact of each margin definition was studied using univariate analysis, and in multivariate models including T-stage (AJCC 8th edition), nodal status (pN+), extranodal extension (ENE), and use of adjuvant radiotherapy.
Results: Both RCPath and CAP positive margins were associated with local recurrence (LR), disease-specific survival (DSS), and overall survival (OS) on univariate analysis, while final margin status was associated with LR and DSS, but not OS. On multivariate analysis, only CAP positive main specimen margin status was independently associated with LR (odds ratio 2.44, 95% CI 1.37, 4.34), DSS (odds ratio 2.28, 95% CI 1.31, 3.82), and OS (odds ratio 1.59, 95% CI 1.04, 2.42).
Conclusions: Involved main specimen margin as defined by CAP guidance has the advantage of being an independent prognosticator of LR and survival in our cohort.

Introduction

Fundamental to the successful surgical management of oral cavity squamous cell carcinoma (OCSCC) is complete resection of the primary tumour, along with neck dissection and postoperative radiotherapy (RT) as appropriate. An essential component of this process is the pathological reporting of surgical margins. The goals of pathological surgical margin reporting are to provide a measure of completeness of primary tumour excision, to provide prognostic information, and to serve as an indicator for adjuvant treatment. However, not all studies have shown a clear independent correlation between margin status and outcome [1–4]. The reasons for this are likely multifactorial, with one important consideration being the impact of other established adverse prognosticators, such as tumour size, depth of invasion, nodal involvement, and extranodal extension (ENE) [2,5]. However, a further factor may be the variable definitions of margin status used in different studies.

The ideal definition used for margin status in OCSCC should have an independent impact on risk of local recurrence (LR) and / or survival. Two of the most established and widely used definitions for reporting surgical margins are those of the Royal College of Pathologists (RCPath) and the College of American Pathologists (CAP). According to RCPath guidance, the presence of invasive cancer within 1 mm of the margin is considered to constitute a positive margin [6]. In contrast, the CAP definition of an involved margin is the presence of invasive cancer or

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https://doi.org/10.1016/j.oraloncology.2022.105797
Received 29 December 2021; Received in revised form 13 February 2022; Accepted 24 February 2022
Available online 7 March 2022

high grade dysplasia at the margin [7]. In addition, the CAP recommends consideration of use of "final margin status", based on multidisciplinary integration of main specimen and separately submitted tumour bed margins [7]. However, final margin status determined by incorporating results of extra tumour bed resections has been shown to be inferior to margin status based on the main tumour specimen as a prognosticator of recurrence and survival [8–10].

The purpose of the present study was to compare the prognostic impact of margins defined according to RCPath and CAP guidance in our cohort of patients with OCSCC.

Methods

This study was a retrospective review of patients undergoing primary radical surgery for OCSCC at our institution (South Infirmary Victoria University Hospital), between 2007 and 2020 inclusive. Exclusion criteria were patients with previous Head and Neck mucosal SCC, patients with distant metastatic disease, patients not undergoing surgery with curative intent, and patients with <6 months of clinical follow up postoperatively. Ethical approval was obtained from the Cork Clinical Research Ethics Committee.

Patients were identified by review of the Head and Neck Cancer database. Clinical data were extracted from the database and from review of patients' case notes. Surgical pathology of patients with OCSCC was generally reported at our institution according to RCPath proforma, including recording of maximum tumour size and depth of invasion, distance to closest mucosal and deep margins, presence of severe dysplasia at margin, status of bony margins, number of positive lymph nodes, and presence of ENE. A database containing pathological details of all patients with oral SCC was created by extraction of data from pathology reports, with re-review of original slides in case of missing information. In addition, slides of all cases prior to 2017 were re-reviewed for remeasurement of depth of invasion according to the 8th edition AJCC TNM staging manual. For later cases, reporting was performed according to the updated 8th edition staging. Finally, all cases were re-staged according to AJCC TNM 8th edition.

Surgical management of OCSCC in our institution generally encompassed wide en-bloc resection of the primary tumour, with the intention of achieving 10 mm gross clearance around the tumour, and 5 mm microscopic margins. Unilateral or bilateral neck dissections were performed as appropriate. Frozen sections were performed selectively. When performed, these were taken from the tumour bed. In cases where gross inspection of the specimen raised concerns about a close or involved margin, a further wide resection of tissue from the corresponding area in the tumour bed was undertaken, with or without further frozen sections or tumour bed resections from the resulting additional defect. All postoperative histology was discussed at Head and Neck multidisciplinary team (MDT) meetings. Postoperative radiotherapy was generally recommended for patients with large (T3/4) primary tumours, involved (<1mm) margins, or metastatic nodal disease, taking into consideration the patient's overall performance status and social support. Additional relative indicators for radiotherapy were perineural invasion and lymphovascular invasion. Postoperative concurrent chemoradiotherapy was used selectively in young patients with extensively involved margins where there was concern about significant residual microscopic disease (based on MDT discussion) and/or ENE. Postoperatively, patients were generally followed at 3 monthly intervals for the first year, at 4 monthly intervals for the second year, and thereafter at 6 monthly intervals. In addition, patients were able to request immediate review in case of any new symptoms or concerns.

Definitions

Margin status according to RCPath and CAP guidance was determined based solely on the main resection specimen, and not taking into consideration frozen sections or extra tumour bed resections. Positive margin according to RCPath was defined as invasive cancer <1 mm from the closest mucosal or deep inked margin. Positive margin according to CAP was defined as presence of invasive cancer or severe dysplasia/carcinoma-in-situ at the inked margin. Final margin status was an integrated classification based on the main specimen and intraoperative frozen sections or extra tumour bed resections, taking into consideration the spatial correlation of the latter with any positive margins on the main specimen. Any case with negative mucosal and soft tissue margins but involved bony margins was considered to have involved margins according to all definitions (RCPath, CAP, and final margin status). Finally, we classified all cases as <3 mm or ≥3 mm margins, based on distance to the closest main specimen margin (mucosal, deep or bony).

All patients commencing prescribed postoperative radiotherapy (RT) were considered to have received postoperative RT, regardless of whether they had completed the course. Local recurrence (LR) was considered to be present in any patient with persistent, recurrent, or new SCC in the same or contiguous oral subsite as the index primary tumour, regardless of the time interval postoperatively. New SCCs arising in non-contiguous subsites within the oral cavity or oropharynx were considered to be second primary cancers. Patients were censored for LR at time of LR, last follow-up, or date of diagnosis of second primary cancer. Patients were censored for death at date of death or last follow-up. Disease specific survival (DSS) was calculated based on death from index cancer. Patients who died who were known to have cancer recurrence at time of last follow-up were considered as having died from the index OCSCC. In addition, any patient dying within 30 days of surgery was considered to have died due to cancer [11,12]. Overall survival (OS) was calculated based on death due to any cause, including second primary cancers.

Statistical analysis

Statistical analysis was performed by XLSTAT (Addinsoft, France, version 2015.1.03). Comparisons on 2 × 2 contingency tables were performed using Fisher's exact test. Comparisons of normally distributed data were performed using Students *t*-test. Kaplan-Meier method was used for survival analysis. Univariate hazard ratios (HR) were calculated using Cox proportional hazards modelling. Following univariate analysis, margin status according to each of the definitions (RCPath, CAP, and final margin status) was entered individually into multivariate models, along with T-stage, nodal status, ENE, and administration of postoperative radiotherapy (RT), to test for independent effect using Cox proportional hazards modelling. We also tested the impact of <3 mm main specimen margin, which we previously reported to have an independent impact on recurrence and survival in oral SCC [13]. Finally, multivariate analysis including all study variables was performed using backwards Cox proportional hazards modelling.

Results

The final study population consisted of 300 patients. Clinical and demographic details are given in Table 1.

Eighty-six patients (28.7%) had involved main specimen margins according to RCPath definition, including 83 with involved mucosal/soft tissue margins and 3 additional patients with involved bony margins. 50 patients (16.7%) had main specimen positive margins according to CAP definition, including 41 with invasive carcinoma present at margins, 7 with severe dysplasia at margins, and 2 further patients with positive bony margins. 147 patients (49%) had extra tumour bed resections performed (38 frozen sections, 78 permanent sections, 31 both). Sixteen patients (32%) with positive main specimen margins had clearance of positive margins based on negative frozen sections (2), negative extra permanent tumour bed resections (9), or both (5), and were thus considered to have negative final margin status. 7 further patients had additional tumour bed resections which contained cancer (5) or had clearance of positive mucosal/soft tissue margins, but positive

Table 1
Clinical and demographic features of study population.

		Number	%
Sex	Male	199	66.3
	Female	101	33.7
Primary site	Tongue	124	41.3
	Floor of mouth	85	28.3
	Buccal	25	8.3
	Alveolus / RMT / palate	54	18.0
	Lip	12	4.0
Extra tumour bed resections	Frozen section	69	23.0
	Permanent resections	109	36.3
Neck dissection	None	68	22.7
	Unilateral	167	55.7
	Bilateral	65	21.7
T-classification (8th edition)	T1	75	25.0
	T2	107	35.7
	T3	47	15.7
	T4	71	23.7
N-classification	N0	126	42.0
	N1	34	11.3
	N2a	9	3.0
	N2b	17	5.7
	N2c	3	1.0
	N3b	43	14.3
	cN0 (no ND)	68	22.7
Stage grouping (TNM8)	I	69	23.0
	II	75	25.0
	III	48	16.0
	IVA	64	21.3
	IVB	44	14.7
Extranodal extension (ENE)	Yes	52	17.3
	No	248	82.7
Postoperative radiotherapy (RT)	No	162	54.0
	RT alone	115	38.3
	Chemoradiotherapy	23	7.7
Positive margin, main specimen, RPCath definition (<1mm)	Yes	86	28.7
Positive margin, main specimen, CAP definition	Yes	50	16.7
Close margin (<3mm), main specimen	Yes	168	56.0
Positive 'final margin status' (including extra tumour bed resections)	Yes	34	11.3

bony margins (2), and were considered as having positive final margin status. Thus, 34 patients (11.3%) in total were regarded as having positive final margin status.

Involved margins by all definitions were significantly more frequent in patients with advanced (T3/4) primary tumours, non-tongue subsites, and in those who received adjuvant treatment. In addition, involved margins according to RCPath definition was significantly associated with positive nodal disease and ENE (Table 2).

Mean (median) follow-up for all patients was 49 (37) months (range 0–168 months), and for surviving patients, 64 (60) months (range 6–168 months). Ninety-nine patients (33.0%) developed recurrent disease, of whom 65 (21.7%) had local recurrence. Seventy-five patients (25.0%) died from cancer, and 80 patients (26.7%) died from other causes.

Univariate analysis of impact on LR, DSS, and OS of margin status according to each of the 4 different definitions, as well as other clinicopathological variables is shown in Table 3. On univariate analysis, RCPath margin status, CAP margin status, and <3 mm margins were all significantly associated with LR, DSS and OS. Final margin status was significantly associated with LR and DSS, but not OS.

Each margin definition was then entered individually into multivariate analysis including T-classification, nodal status, ENE, and postoperative RT. Positive margins according to CAP definition was an independent predictor of LR, DSS, and OS (Table 4). In contrast, neither positive margins according to RCPath definition (Table 5), nor final margin status (Table 6), was found to be independently predictive of LR or any of the survival outcomes. <3 mm margin was significantly predictive of LR and OS, and just outside significance for DSS (Table 7).

Finally, stepwise backward multivariate analysis including all margin definitions was performed. Independent predictors of LR on overall multivariate analysis were CAP margins (odds ratio (OR) 1.86; 95% confidence interval (CI) 1.02, 3.48), and T3/4 classification (OR 2.80; 95% CI 1.53, 5.13). For DSS, independent predictors were CAP margins (OR 2.28; 95% CI 1.31, 3.97), T3/4 classification (OR 2.92. 95% CI 1.60, 5.34), N + status (OR 3.93; 95% CI 1.98, 7.79), ENE (OR 2.05; 95% CI 1.10, 3.82) and postoperative RT (OR 0.35; 95% CI 0.20, 0.60). For OS, independent predictors were <3 mm margin (OR 1.58; 95% CI 1.06, 2.35), T3/4 classification (OR 2.38; 95% CI 1.57, 3.62), N + status (OR 2.79; 95% CI 1.74, 4.48), ENE (OR 1.68; 95% CI 1.03, 2.74) and postoperative RT (OR 0.29; 95% CI 0.20, 0.43). CAP margin status (OR 1.65; 95% CI 0.99, 2.75) was just outside significance. Tabulated results of overall multivariate analysis are given in Tables 8–10 in Supplementary materials.

Discussion

In the present study, involved main specimen margins in OCSCC as defined by both RCPath and CAP were significantly associated with LR and survival on univariate analysis. However, only the CAP definition was an independent predictor on multivariate analysis including other established prognosticators of advanced T-stage, metastatic nodes, and ENE. These findings would suggest that the CAP definition of positive margins may be superior to the RCPath definition as an independent

Table 2
Risk factors for positive margins.

Margin definition		RCPath		CAP		Final margin status		<3 mm	
T-stage	T1/2	33 (18%)	**<0.0001**	16 (9%)	**<0.0001**	8 (4%)	**<0.0001**	102 (44%)	**<0.0001**
	T3/4	53 (45%)		34 (29%)		26 (22%)		88 (75%)	
Primary site	Tongue	21 (17%)	**0.0002**	9 (7%)	**0.0002**	6 (5%)	**0.003**	52 (42%)	**<0.0001**
	Non-tongue	65 (37%)		41 (23%)		28 (16%)		116 (66%)	
	T1/2 tongue	7 (8%)		2 (2%)		2 (2%)		24 (28%)	
N-status	N0	68 (32%)	**0.046**	86 (34%)	0.52	93 (35%)	0.71	102 (53%)	0.11
	N+	38 (44%)		20 (40%)		13 (38%)		66 (62%)	
ENE	Absent	29 (14%)	**0.01**	40 (16%)	0.22	43 (16%)	0.15	132 (53%)	**0.045**
	Present	23 (27%)		12 (24%)		9 (26%)		36 (69%)	
Adjuvant Rx	None	36 (42%)	**0.01**	108 (43%)	**0.04**	119 (45%)	0.27	76 (47%)	**0.0007**
	RT / CRT	50 (58%)		30 (60%)		19 (56%)		92 (67%)	

Table 3
Univariate analysis of risk factors for LR, DSS, and OS.

	LR		DSS		OS	
CAP	2.84 (1.65, 4.88)	**<0.001**	2.23 (1.31, 3.78)	**0.003**	1.51 (1.01, 2.26)	**0.04**
Final margin	2.39 (1.27, 4.49)	**0.007**	2.12 (1.16, 3.88)	**0.02**	1.27 (0.89, 1.79)	0.19
RCPath	1.82 (1.09, 3.03)	**0.022**	1.92 (1.19, 3.11)	**0.008**	1.69 (1.07, 2.66)	**0.02**
<3mm margin	2.20 (1.28, 3.77)	**0.004**	2.05 (1.23, 3.42)	**0.006**	1.55 (1.11, 2.16)	**0.01**
T3/4	2.80 (1.69, 4.63)	**<0.0001**	4.74 (2.85, 7.89)	**<0.0001**	2.62 (1.89, 3.64)	**<0.0001**
N+	1.60 (0.96, 2.67)	0.07	5.04 (3.05, 8.39)	**<0.0001**	2.63 (1.89, 3.66)	**<0.0001**
ENE	2.01 (1.08, 3.72)	**0.027**	5.63 (3.45, 9.20)	**<0.0001**	3.28 (2.24, 4.80)	**<0.0001**
RT	1.27 (0.77, 2.09)	0.35	1.25 (0.78, 2.00)	0.36	0.77 (0.56, 1.08)	0.13

Table 4
Multivariate analysis using CAP definition of positive main specimen margins.

	LR		DSS		OS	
CAP	2.44 (1.37, 4.34)	**0.002**	2.28 (1.31, 3.82)	**0.004**	1.59 (1.04, 2.42)	**0.03**
T3/4	2.60 (1.38, 4.90)	**0.003**	2.92 (1.60, 5.34)	**<0.001**	2.44 (1.63, 3.65)	**<0.0001**
N+	1.28 (0.64, 2.57)	0.49	3.93 (1.98, 7.79)	**<0.0001**	2.70 (1.70, 4.30)	**<0.0001**
ENE	1.24 (0.56, 2.75)	0.60	2.05 (1.10, 3.82)	**0.02**	1.65 (1.01, 2.70)	**0.05**
RT	0.61 (0.33, 1.12)	0.11	0.35 (0.20, 0.60)	**<0.001**	0.30 (0.21, 0.44)	**<0.0001**

Table 5
Multivariate analysis using RCPath definition of positive main specimen margins.

	LR		DSS		OS	
RCPath	1.49 (0.87, 2.54)	0.15	1.41 (0.86, 2.34)	0.17	1.11 (0.78, 1.60)	0.56
T3/4	2.85 (1.53, 2.85)	**0.001**	3.09 (1.68, 5.70)	**<0.001**	2.59 (1.71, 3.90)	**<0.0001**
N+	1.14 (0.57, 2,28)	0.71	3.41 (1.73, 6.70)	**<0.001**	2.49 (1.58, 3.94)	**<0.0001**
ENE	1.19 (0.53, 2.64)	0.67	2.00 (1.07, 3.73)	**0.03**	1.62 (0.99, 2.65)	0.05
RT	0.66 (0.36, 1.19)	0.17	0.38 (0.22, 0.64)	**<0.001**	0.31 (0.21, 0.46)	**<0.0001**

Table 6
Multivariate analysis using final margin status to define positive margins.

	LR		DSS		OS	
Final margin status	1.80 (0.92, 3.53)	0.09	1.83 (0.97, 3.49)	0.06	1.53 (0.95, 2.47)	0.08
T3/4	2.77 (1.46, 5.26)	**0.002**	3.05 (1.66, 5.60)	**<0.001**	2.45 (1.63, 3.69)	**<0.0001**
N+	1.20 (0.59, 2.41)	0.62	3.75 (1.88, 7.47)	**<0.001**	2.67 (1.67, 4.27)	**<0.0001**
ENE	1.22 (0.55, 2.70)	0.62	1.99 (1.07, 3.70)	**0.03**	1.62 (0.99, 2.65)	0.06
RT	0.65 (0.35, 1.19)	0.17	0.36 (0.21, 0.62)	**<0.001**	0.31 (0.21, 0.45)	**<0.0001**

Table 7
Multivariate analysis using <3 mm margin.

	LR		DSS		OS	
<3 mm margin	1.89 (1.08, 3.30)	**0.03**	1.70 (0.99, 2.90)	0.05	1.50 (1.06, 2.13)	**0.02**
T3/4	2.75 (1.47, 5.15)	**0.002**	2.92 (1.57, 5.42)	**0.001**	2.39 (1.58, 3.59)	**<0.0001**
N+	1.14 (0.57, 2.28)	0.72	3.47 (1.75, 6.89)	**<0.001**	2.60 (1.64, 4.14)	**<0.0001**
ENE	1.22 (0.55, 2.69)	0.63	2.09 (1.12, 3.88)	**0.02**	1.65 (1.01, 2.70)	**0.05**
RT	0.63 (0.35, 1.15)	0.14	0.35 (0.21, 0.61)	**<0.001**	0.30 (0.20, 0.44)	**<0.0001**

prognosticator. It is notable that in the present dataset there was a significant association between involved margins using RCPath definition, and metastatic nodal disease, and ENE, whereas the association between these adverse prognosticators and positive margins by CAP definition, and final margin status, was not significant. This finding may explain the superior independent prognostic ability of CAP margin status over RCPath in our cohort and is consistent with that of previous studies, which concluded that other histological risk factors are more important than margin status in predicting outcome [1–3].

Whilst to our knowledge, there are no previously published direct comparisons between the RCPath and CAP definitions for involved margins, a number of authors have published on OCSCC margins, with differentiation between cases with cancer present at the margin, very close (<1mm) margins, and close/clear margins. Hakim et al reported a divergence of survival curves between cases with tumour present at the margin (R1), and <1 mm from margin (R0hr), and concluded outcomes were similar between R1 and R0hr, but substantially poorer than those seen in patients with clear (R0) or with 1–4 mm (R0cm) margins [5]. Among a series of clinically early OCSCC, Bajwa reported that cases with involved but not cut-through (INC-T) margins had similar LR to patients with close or clear margins, whereas patients with cut-through (C-T) margins had significantly worse LR. Both INC-T and C-T had worse disease-free survival than patients with close margins. Differences in DSS and OS were not significant [14] Buchakjian reported cases with positive margins to have worse LR and OS than cases with either very close (<1mm) margins or carcinoma-in-situ (CIS) present at margins. On multivariate analysis, both positive and very close/CIS margins were independently predictive of LR, but only positive margins were an independent predictor of OS [15]. A further paper by the same group reported a higher LR for cases with tumour present at margin versus with tumour <1 mm from inked margin, which in turn had higher LR than tumours 1 mm from the margin, although with overlapping confidence intervals [16].

An important point from these studies is that while tumour at margins may represent a higher risk situation than <1 mm margins, the latter still represents a high-risk group, with worse survival outcomes

than patients with 1–5 mm margins. Therefore, while the CAP definition of positive margins may have advantages over the RCPath definition in being an independent prognosticator for oncological outcomes based on the data presented in this paper, this does not imply that very close margins are not high-risk cases. Currently, the optimum cut-off between low-risk and high-risk margins in OCSCC remains unresolved. The RCPath utilizes 5 mm as the cut-off between close and clear margins [6]. However, many authors have questioned the significance of close margins by this definition [1,14,16–18] and the CAP acknowledges that values ranging from 3 mm to 7 mm have been used successfully [7]. In a previous study, we reported 3 mm as a better cut-off between low-risk and high-risk margins [13]. Other authors have also reported margin cut-offs of between 2 mm and 3 mm to better differentiate low-risk and high-risk cases than 5 mm [18–22]. Of note, in the present study, a <3 mm margin was once again confirmed to have independent impact on LR and OS, and was just outside significance ($p = 0.05$) for DSS, while in the overall multivariate analysis, including alternate margin definitions, it retained independent predictive effect for OS along with positive margins according to CAP definition.

The use of frozen sections or extra tumour bed resections to determine final margin status is commonplace [23]. However, the benefits of this practice are disputed [8,24,25]. While a worse survival for patients with involved frozen sections is reported [26], intraoperative clearance of positive margins to negative has not been shown to confer a survival benefit [9,10,27]. Among the difficulties with reliance on frozen sections and extra tumour bed resections are difficulties in establishing the exact spatial relationship between the compromised margin on the main specimen and tumour bed, along with the effects of tissue shrinkage. There is likely also variation between units in degree of gross tumour clearance, frequency of use of frozen section, technique in taking extra resections [23], and interpretation of same. In the present series, while final margin status was associated with LR and DSS on univariate analysis, it did not have an independent effect when included with other adverse prognosticators in a multivariate model. This finding is consistent with that of other authors, suggesting that final margin status is a less reliable predictor of outcome than main specimen margin involvement as defined by CAP, but in the present series this should be interpreted in the light of the selective use of extra tumour bed resections.

Limitations of the present study include the retrospective nature. In addition, there are possible differences between our cohort and that of others, including distribution of tumour subsites, T- and N-stages, surgical techniques, and patient risk factors and performance status. Thus, our series may not be directly comparable to those of patients with clinically early OCSCC, or composed primarily or exclusively of patients with tongue cancer, which are associated with lower incidence of positive margins [5,16,21,28,29]. Furthermore, frozen sections were used selectively, therefore this study was not adequately designed to compare final margin status incorporating results of frozen section and extra tumour bed resections to main specimen margin status. Finally, while most patients with positive margins received postoperative radiotherapy, concurrent chemoradiotherapy was used very selectively in young patients. On the other hand, major advantages include the full pathological dataset available for nearly all patients, including remeasurement of depth of invasion of all cases prior to 2017 to conform with the 8th edition TNM staging manual, and re-staging of all cases according to the 8th edition TNM staging.

Conclusion

The findings of the present study would suggest that involved main specimen margins as defined by the CAP guidelines has better prognostic ability for survival outcomes in OCSCC than the RCPath definition. The CAP margin definition may offer advantages in terms of more consistent prognostication, and as a definition for studies regarding prescription of adjuvant treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by the Head and Neck Oncology Fund, South Infirmary Victoria University Hospital (payment of salary of Research Assistant)

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2022.105797.

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