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Prognostic factors in oral cancer surgery - results from a UK tertiary centre

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ABSTRACT

Introduction: Oral cancer surgery is complicated by the diverse nature of clinical and histopathological presentations that occur. Current National guidance recognises the significant role that surgical margin status plays in the overall survival of patients. Many other histopathological factors influence patient survival, the importance of which varies between the literature.

Materials and methods: In this prospective longitudinal study, all patients diagnosed with squamous cell carcinoma who had primary surgical treatment under general anaesthesia were included. Surgery was performed by one surgical team within this tertiary referral centre. Patients were followed up for a maximum of 7 years following their surgery.

Results: A total of 250 patients were included from 2015 to 2022. Patients were 61.44 years old (SD 13.23) at diagnosis, and 56.4% were male (n = 141). Pathology was mainly pT1 (39.1%) and the most common sites were the border of tongue (31.2%) and floor of mouth (18.8%). 43.4% of patients had clear surgical margins, with overall survival being significantly associated with margin status (p = 0.0079). Extra-capsular spread was significantly associated with higher risk of death from metastatic head and neck cancer (p = 0.014), whereas presence of high-grade dysplasia at surgical margins and depth of invasion of tumour were not.

Conclusion: This study has reinforced the importance of surgical margin clearance and as such the development of intra-operative techniques to ensure this is imperative. The significance of extra-capsular spread in survival has also been demonstrated. Discussion regarding the current deficiency in accurate pre-operative diagnostic methods for extra capsular spread is covered.

1. Introduction

Surgical approaches to oral cancer resection and reconstruction are continuously evolving and the evidence base for novel surgical techniques expanding. Tumour resection is considered 'complete' if there is a margin of at least 5.0 mm uninterrupted normal tissue on histological assessment. 'Close' margins measure between 1.0 and 4.9 mm and 'involved' margins <1.0 mm. Local or regional recurrence and overall survival outcomes have been shown to be significantly worse in those with 'involved' or 'close' margins following resection [1,2].

Current United Kingdom (UK) guidance for the management of oral cancer reinforces the requirement for tumour resection with adequate surgical margins and recommends 1 cm as the optimum clearance [3]. Whilst resection can be curative, extensive removal of tissue and vital structures can have dramatic impacts on form, function, and resultant quality of life [4,5]. Bearing this in mind, the balance between surgical approach and eventual morbidity/mortality must be considered by the surgical team.

Margins are not the only factors contributing to survival [6,7], as evidence demonstrates key histological tumour features such as perineural spread, lymphovascular spread, and grading scores to be significantly prognostic [6–10]. Extra-capsular spread (ECS) of

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nodal metastasis are also associated with locoregional recurrence, distant metastasis and overall worsened survival [11].

Depth of tumour invasion (DOI) is a histopathological measurement following surgical resection of the tumour below the basement membrane. The impact of tumour DOI on survival is a growing area of research interest, and its importance in overall patient survival has been contested. Whilst some authors propose it to be directly correlated with survival, others have proposed it may not be an independent prognostic factor and in fact predicts other markers of extensive disease and as such is linked to poorer outcomes [12,13]. The use of tumour DOI measurements has resulted in changes to the newest globally accepted TNM system [14] which now consider both DOI and radiologically assessed tumour thickness to stage primary tumours.

Within our tertiary referral unit, our standard care for oral cancer management involves radical primary surgery with free tissue transfer reconstruction when indicated. A selective neck dissection is performed when depth of tumour invasion exceeds 1.5 mm. Surgery is performed with curative intent aiming for a ≥5 mm margin of normal tissue.

The aims and objectives of this study were to use data from a UK tertiary referral centre cohort to analyse the relationship between histological features, including surgical margin status, and overall survival outcomes. We aimed to establish whether any histological features proved prognostic in our sample and the degree of importance of these findings. This information is vital in ensuring the most robust and up to date evidence can be utilised in the planning of patient care within our service.

2. Material and methods

Clinical data collection was designed prospectively. Basic sociodemographic details were extracted from the hospital database. All patients diagnosed with squamous cell carcinoma who had primary surgical treatment under general anaesthesia from 2015 to 2022 were included. All patients were operated on by the senior clinicians (AK,GF) in Leeds General Infirmary and represent approximately half of the total number of patients treated by all teams in the unit within this time frame.

2.1. Statistical analysis

Descriptive statistics were used to summarise patient characteristics. The mean (standard deviation) was reported for continuous variables, and frequency (percentage) was reported for categorical variables. Kaplan-Meier curves were produced to assess the impact on survival time for site, gender, TNM status, surgical margins, and depth of invasion. The Log-rank test was used to evaluate the difference between survival curves. Furthermore, Cox proportional hazard regression models were carried out to investigate the effect of involved margins and depth of invasion on all causes and disease-specific mortality. Crude and adjusted hazard ratios with 95% confidence intervals were reported respectively. The data were analysed using the software R version 4.0.3. The significance level was set as p-value <0.05.

Ethical approval

Data was collected as part of the clinical audit process and this part of data was approved by Leeds Teaching Hospitals Audit Department (Reference number: LOC0209).

3. Results

A total of 250 patients were included from 2015, with a maximum follow up period of 7 years. The average age at diagnosis was 61.44 years old (SD 13.23), and 56.4% (n = 141) were male. Most patients (39.1%) were diagnosed with pT1 pathology. The most prevalent tumour sites were the border of the tongue (31.2%) and floor of mouth (18.8%). Full demographic characteristics are summarised in Table 1.

Overall survival was significantly associated with pT staging (p value < 0.0001), see Fig. 1. Following primary surgery, 43.4% had clear surgical margins, 18% had involved margins and the remainder had close margins (38.5%). Overall survival was significantly associated with margin status (p = 0.0079); see Fig. 2. Patients with involved margins were significantly more likely to have shorter survival than those with close or clear margins. A total of 82 patients died during the follow up period; 39% (n = 32) died from head and neck cancer and 61% (n = 50) died from other causes. Fig. 3 demonstrates survival from head and neck cancer by margin status.

The presence of high-grade dysplasia at the surgical margin had no significant relationship to resultant death from metastatic head and neck cancer (p value = 0.732). A total of 29 patients (11.6%) had histological evidence of high-grade dysplasia at their surgical margins, of whom 3 (10.3%) died from metastatic head and neck cancer.

Extra-capsular spread (ECS) was significantly associated with a higher risk of death from metastatic head and neck cancer (p value = 0.014). A total of 20.5% (n = 8) of patients with ECS died from metastatic head and neck cancer, in comparison to 7.1% (n = 15) of those without ECS.

Table 1
Characteristics for the included oral cancer patients.

	Overall
Number of patients	250
Age in years, mean (SD)	61.44 (13.23)
Male	141 (56.4)
pT stage	
1	97 (39.1)
2	69 (27.8)
3	28 (11.3)
4	54 (21.8)
pN stage	
0	151 (60.9)
1	31 (12.5)
2	52 (21.0)
3	14 (5.6)
Post-operative radiotherapy	114 (45.6)
Free flap reconstruction	111 (45.5)
Margin status	
Clear	106 (43.4)
Close	94 (38.5)
Involved	44 (18.0)
Depth of invasion ≥ 4 mm	150 (71.8)
Tumour site	
Base of tongue	4 (1.6)
Border of tongue	78 (31.2)
Buccal mucosa	24 (9.6)
Cervical lymph nodes	3 (1.2)
Floor of mouth	47 (18.8)
Hard palate	8 (3.2)
Lower alveolar ridge	20 (8.0)
Lip (mucosal)	10 (4.0)
Maxillary sinus	3 (1.2)
Nasal cavity	4 (1.6)
Other	5 (2.0)
Retromolar pad	11 (4.4)
Soft palate	2 (0.8)
Submandibular gland	2 (0.8)
Tonsil	9 (3.6)
Upper gum	8 (3.2)
Ventral tongue	12 (4.8)

Data is presented as frequency (%) unless specified. % was calculated for completed cases only.

The depth of tumour invasion (DOI) was ≥4 mm in 71.8% (n = 150) of patients. Tables 2 and 3 demonstrate the specific deaths by margin status and DOI, including crude and hazard adjusted ratio modelling. The DOI did not specifically impact cause of death if the margin was considered clear or close. Patients with involved surgical margins had higher mortality, and few of these demonstrated a DOI of <4 mm. In Table 3 the margin status and DOI were included in the Cox regression model separately due to the high collinearity between margin status and DOI.

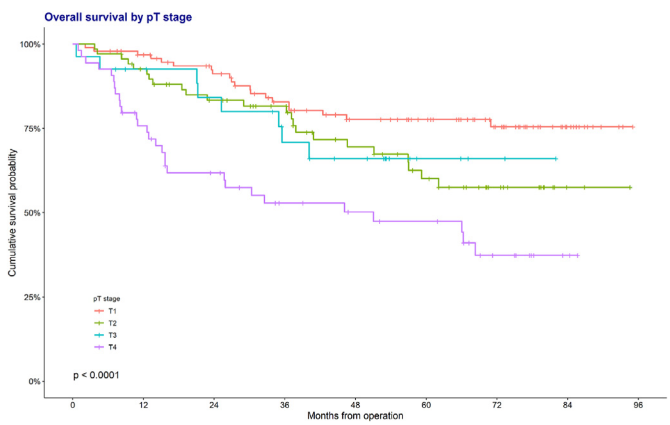

Fig. 1. Overall survival based on pT stage.

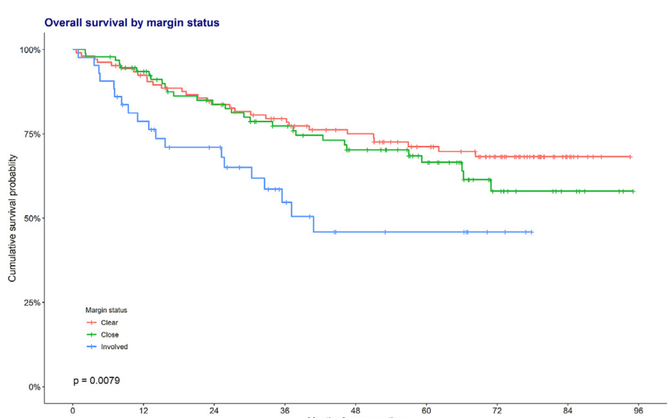

Fig. 2. Overall survival by margin status.

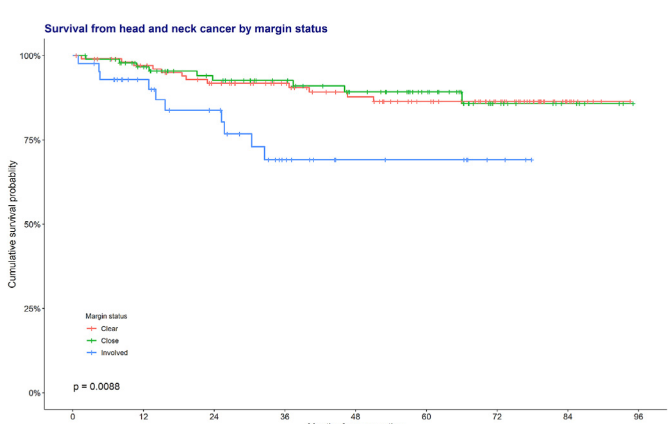

Fig. 3. Survival from head and neck cancer by margin status.

Patients who received adjuvant radiotherapy were more likely to die in comparison to those patients who did not (p value < 0.001). 43.9% (n = 60) of those having adjuvant radiotherapy died during the follow up period, compared to 23.5% (n = 32) patients without. This result should be considered with the knowledge that patients receiving post-operative radiotherapy were being treated for more advanced disease in the first instance, as adjuvant radiotherapy use increased with pT stage (p value < 0.001). In total, 79.6% (n = 43/54) of pT4 tumours received radiotherapy, in comparison to 78.6% (n = 22/28) of pT3, 56.5% (n = 39/69) of pT2 and 9.3% (n = 9/97) of pT1.

Contralateral neck recurrence was more common in those with pT3/T4 pathology. Only 1.2% (n = 2/166) patients with pT1/2 tumours present with contralateral neck recurrence during the follow up period, in comparison to 7.3% (n = 6/82) of patients with pT3/T4 tumours.

4. Discussion

This study has reinforced the importance of surgical margin clearance in oral cancer resection. Patients with involved margins (<1.0 mm) had demonstrably worse survival outcomes. Whilst 1 cm surgical margin clearance would be optimum as per UK guidance [3], often vital structures do not anatomically allow this. Surgeons are increasingly interested in intra-operative techniques to ensure marginal clearance [15–17]. These techniqques can provide real time reassurance that maximum pathology removal has occurred in an anatomically complex surgical field. There are a large assortment of techniques currently utilised within the UK, including Lugol's iodine [18,19], fluorescence molecular imaging and molecular margin analysis [20,21], Raman spectroscopy [22], narrow band imaging [23], optical coherence tomography [24], laser C02 piecemeal resection [25] and cytological bone margin analysis [15,26]. The intelligent knife (iKnife) is already utilised in other oncological surgical fields [27,28], utilising rapid evaporative ionisation mass spectrometry (REIMS) to discriminate between healthy, preinvasive and invasive carcinoma tissue. The results of this technique within oral cancer are currently unknown and being researched within the UK [29], with great anticipation.

Whilst these techniques are being researched and technological advances are maturing, there is no clear answer as to which ultimately provides the most accurate and effective answer to improving intraoperative marginal clearance. It is clear this is a growing field of research in oral cancer surgery, and it is imperative we are surgeons engage with and encourage research in this field to ultimately improve survival statistics.

Analysis of our patient cohort also demonstrated the significant importance of ECS in overall survival of oral cancer patients. The relationship between ECS and poor survival has been reported before within the literature [3,11,30,31], with independent predictors of ECS recorded as increased age (>75 years), smoking and high alcohol intake [11]. Depth of tumour invasion (>5 mm) and nodal metastasis size (>15 mm) have also been recognised as significant predictors of ECS presence [30]. This highlights that preoperative identification of ECS presence and severity (i.e. macroscopic or microscopic) is important in the overall treatment strategy for patients with oral cancer.

Currently utilised pre-operative diagnostic methods for ECS include computer tomography (CT), magnetic resonance imaging (MRI), ultrasound (US) and positron emission tomography (PET/CT). A 2015 systematic review and meta-analysis found CT to have relatively low sensitivity when diagnosing ECS, however MRI and CT had similar diagnostic efficacy. The review summarised that PET/CT and US had no evidence for use in the diagnosis of ECS [32]. Frood et al. found contrast-enhanced T1-weighted MRI imaging

Table 2
All causes and disease-specific deaths by both margin status and depth of invasion.

		Causes of death		
Margin status	Depth of invasion	All causes	Head and neck cancer	Metastatic head and neck cancer
Clear	<4 mm	8/36 (22.2%)	2/36 (5.6%)	1/36 (2.8%)
	≥ 4 mm	16/55 (29.1%)	8/55 (14.5%)	3/55 (5.5%)
Close	<4 mm	6/21 (28.6%)	1/21 (4.8%)	0/21 (0%)
	≥ 4 mm	22/67 (32.8%)	7/67 (10.4%)	6/67 (9.0%)
Involved	<4 mm	0/2 (0%)	0/2 (0%)	0/2 (0%)
	≥ 4 mm	14/26 (53.8%)	7/26 (26.9%)	5/26 (19.2%)

Note: data is presented as frequency (%) by each category.

Table 3
Crude and adjusted hazard ratio for all causes and disease-specific mortality.

	Hazard ratio (95% confidence interval)[a]					
	All causes		Head and neck cancer		Metastatic head and neck cancer	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Margin Status						
Clear	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Close	1.23 (0.74–2.05)	1.15 (0.69–1.94)	0.93 (0.39–2.21)	0.82 (0.34–1.98)	1.08 (0.39–2.99)	1.07 (0.39–2.99)
Involved	2.45 (1.38–4.34)	2.00 (1.09–3.68)	2.88 (1.23–6.70)	1.77 (0.72–4.38)	2.50 (0.86–7.27)	1.60 (0.52–4.98)
Depth of invasion						
<4 mm	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
≥ 4 mm	1.53 (0.85–2.76)	1.36 (0.74–2.49)	2.95 (0.88–9.86)	3.02 (0.89–10.28)	6.01 (0.79–45.48)	6.49 (0.84–50.09)

[a] Hazard ratios were estimated from Cox proportional hazard regression model for each cause of death separately. Crude hazard ratios were estimated by including margin status or depth of invasion alone in the Cox model. Adjusted hazard ratios were estimated by adjusting for confounding factors such as age, sex and pT stage in the Cox model.

features (including nodal entropy and irregular contour) significantly predicted ECS presence ($p = 0.018$) [33]. It is evidence that current imaging modalities are unpredictable in their ability to diagnose ECS pre-operatively. Neck dissection is often the only effective diagnostic option with histological confirmation remaining gold standard. As this research emphasises the critical importance ECS has on survival, we believe research efforts should be focussed into improving the pre-operative diagnostic tools available.

The authors acknowledge there are weaknesses to this study, including it being a single centre experience by one of the head and neck cancer surgical teams within the unit. We have previously published our overall 30-year head and neck cancer surgery experience prior to this patient cohort, and reported the relationship between surgical margins and survival [9]. The difference with this study is the analysis including the DOI.

Study participants were representative of known oral cancer demographics in terms of gender and age demographics. This study has many strengths including being prospective in nature, with a recorded depth of tumour invasion available for all patient specimens. This allowed for investigation into associations with surgical margins and overall survival. The study also followed-up patients over a significant period, up to 7 years.

5. Conclusions

The surgical outcomes from this large cohort of oral cancer patients are comparable with, or better than, data from other UK and international units. This is one of the largest studies involving patients with oral cancer in the UK examining the relationship between surgical margin status and depth of tumour invasion. This works supports the view that clear margins alone will improve overall survival from oral cancer. ECS is also an important prognostic factor which warrants focussed surgical planning. Further work should focus on the development of techniques for better pre-surgical ECS evaluation and intra-operative margins assessment.

Conflict of interest

RE: **Prognostic factors in oral cancer surgery - results from a UK tertiary centre**.

The authors have no conflict of interest to declare.

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